



Chemoselective Hydrogenation Of Fragrance Precursor Using H-Cube® Continuous Flow Reactor

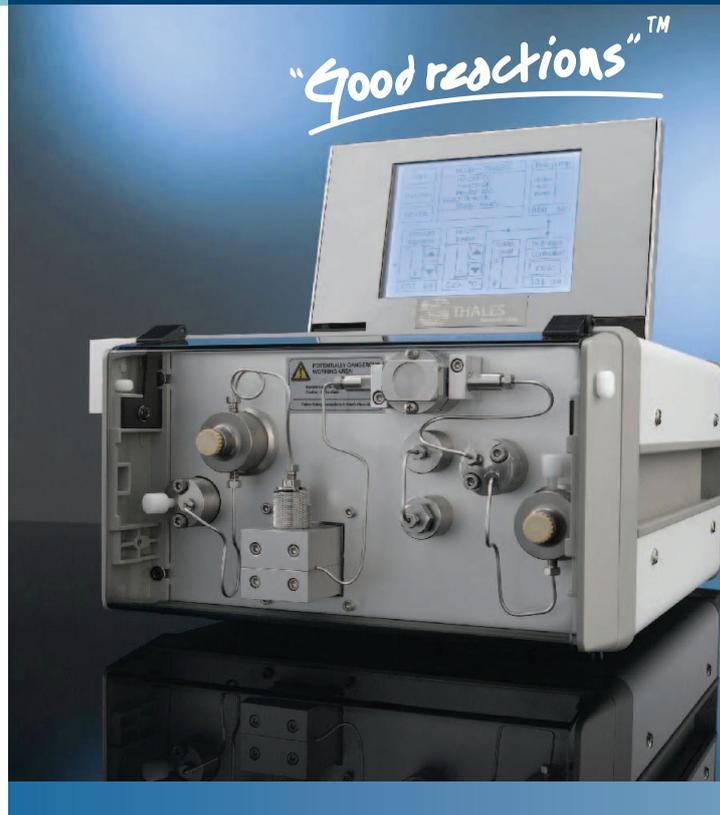
The following application note demonstrates how ThalesNano's H-Cube® flow reactor proved to be a paradigm change for safe, fast, and easy to use hydrogen catalyst screening for Givaudan.

INTRODUCTION

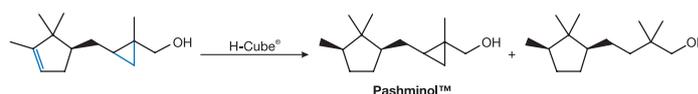
Chemoselective hydrogenation of fragrance precursors opens up the way to a vast variety of new candidates for olfactory screening. Their chemical syntheses are not only making them cheaper but they are also saving the natural resources of such compounds. Using this method, novel, unique odor characteristics can be made that are not synthesized in nature. In the following application note we will introduce selective hydrogenation reactions that were in Givaudan's research scope. Each of the presented molecules hereby fall under the groups of such odor substances that are of great importance from fragrance industrial perspectives. The studied compounds are mainly alkenols; unsaturated and cyclopropanated carbonyls (e.g. derivatives and precursors of Pashminol™, cis-Javanol, Melonal™ etc).

Alkenyl – Cyclopropanecarbinols

'Substantivity' is of great importance in fragrance chemistry. The term refers to the perfume materials' persistence capability on the intended field of application such as skin, hair, garment, etc. One method of increasing substantivity of a certain fragrance compound is to increase its molar mass in such a way that the transformation does not



have a major impact on the molecule's conformation. Therefore, the shape of the molecule, a factor of key importance for odor sensation, remains similar and its vapor pressure is decreased due to the elevated molar mass. Modified new substances may result in a longer lasting effect with similar odor characteristics. A well tried method for increasing substantivity is the cyclopropanation of alkene related fragrance precursors. This type of transformation does not modify the conformation of the unsaturated functionalized terpenes that much as long as they are synthesized under stereospecific Simons-Smith conditions. Chemoselective hydrogenation of a partially cyclopropanated diene or polyene may pose a challenging task due to possible cyclopropane cleavage side reactions. This is what Givaudan's chemists were faced with during Pashminol™ synthesis.



Entry	CatCart®	T/p	Occurance in product		
			Substrate (1)	Cyclopropane cleavage (2)	Pashminol™
1	10% Pd/C	25 °C/1 bar	3 %	5 %	73 %
2	5% Pd/Al ₂ O ₃	25 °C/1 bar	17 %	15 %	53 %
3	5% Pt/C	25 °C/1 bar	1 %	0 %	84 %
4	Raney Nickel	80 °C/1 bar	2 %	1 %	87 %
5	5% Pd/CaCO ₃	25 °C/1 bar	1 %	1 %	83 %

Table 1: Selected examples of catalyst screening in Pashminol™ synthesis

Table 1. demonstrates some selected results of catalyst screening in the selective hydrogenation of a Pashmino™ precursor. Schröder et al. found that, even though Raney Nickel and Pd/CaCO₃ proved to be very efficient catalysts with a nearly quantitative substrate conversion and minor cyclopropane cleavage, the 5% Pt/C catalyst gave the best results for leaving the cyclopropyl moiety untouched.

Other substrates were also screened with similar catalysts and the most effective catalyst for a given substrate is listed in Table 2. Entry 7 was also tested with Pd/CaCO₃ and Pt/C catalysts, but it was only Raney Nickel that left the hydroxyl group untouched, avoiding deoxygenation.

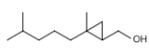
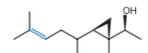
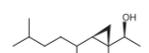
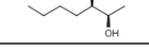
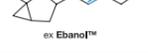
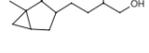
Entry	Substrate	Catalyst	Product
1		Pd/CaCO ₃	
2			
3			
4			
5			
6			
7		Raney Nickel	
8		Pt/C	

Table 2: Selective hydrogenation of alkenes in the presence of cyclopropylcarbinols or allyl alcohols.

Unsaturated Aldehydes

In case of unsaturated aldehydes, displayed in Table 3, Pt/CaCO₃ and Pd/CaCO₃ left the aldehyde function untouched. Raney Nickel caused a selective aldehyde function reduction under mild reaction conditions. However, at elevated pressures and temperatures the same catalyst ceased being selective anymore and triggered further saturation in the screened substance. Pd/C had a relatively unselective and drastic saturating effect on the dienal substrate (entry 4). During the hydrogenation of conjugated aldehydes in the H-Cube® flow reactor, Pd/CaCO₃ proved to be an effective catalyst for selectively saturating the carbon-carbon double bond. Ru/C had an unselective hydrogenation effect (entry 4). See below in Table 4.

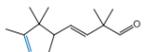
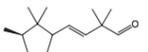
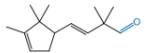
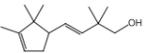
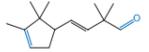
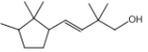
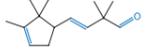
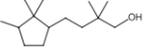
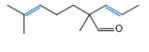
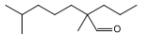
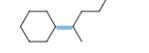
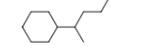
Entry	Substrate	Catalyst	Product
1		Pt/CaCO ₃	
2		Raney Nickel	
3		Raney Nickel (Higher T and p)	
4		Pd/C	
5		Pd/CaCO ₃	
6		Pd/C	

Table 3: Selective hydrogenation of unsaturated aldehydes.

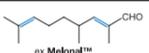
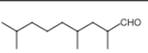
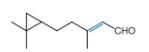
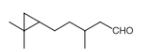
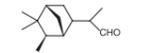
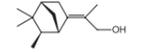
Entry	Substrate	Catalyst	Product
1		Pt/CaCO ₃ (100 °C)	
2		Pt/CaCO ₃	
3		Pt/CaCO ₃	
4		Ru/C (90 °C/90 bar)	

Table 4: Selective hydrogenation of conjugated aldehydes.

Unsaturated Ketones

In case of using Pd/CaCO₃ for the presented cyclopropylketone hydrogenation in Table 5 (entry 1) a cyclopropyl cleavage occurs first due to the neighboring group effect of the alkene, then the resulting alkene is reduced giving the saturated ketone. However in case of using Raney Nickel with the same substrate (entry 2), the alkene hydrogenation occurs first, which makes the possible cyclopropylketone relatively inert against cleavage.

Quantitative Raney Nickel hydrogenation of cyclododeca-4,8-dienone gave the monoalkene with 46% selectivity, against 25% of substrate and 26% of cyclododecanone. Pd/C and Lindlar's catalyst tested on the same substrate gave exclusively cyclododecanone. Reducing raspberry ketone's benzene ring to the cyclohexanone moiety was achieved using Pd(OH)₂/C (entry 5). Rh/Al₂O₃ yielded a complex product composition with the same substrate (entry 6).

Alkenols

With alkenols, only Pd/C catalyst effected a complete conversion on the studied substrates using H-Cube®. It is worth noting that Pd/C did not trigger deoxygenation in the sensitive tertiary alcohols displayed in Table 6.



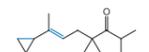
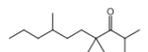
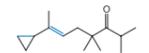
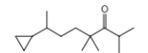
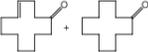
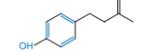
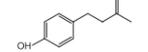
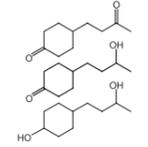
Entry	Substrate	Catalyst	Product
1		Pd/CaCO ₃	
2		Raney Nickel	
3		Raney Nickel	
4		Pd/C Lindlar	
5		Pd(OH) ₂ 90 °C	
6		Rh/Al ₂ O ₃	

Table 5: Selective hydrogenation of unsaturated ketones.

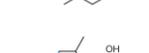
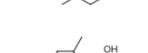
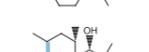
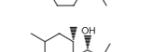
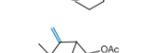
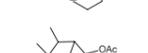
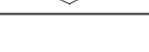
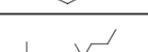
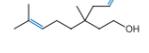
Entry	Substrate	Catalyst	Product
1		Pd/C	
2			
3			
4			
5		Pd/CaCO ₃	
6			

Table 6: Selective hydrogenation of alkenols.



SUMMARY

It was demonstrated that the H-Cube[®] flow reactor along with a wide range of supplemental CatCart[®]s proved to be a paradigm change for safe, fast and easy catalyst screening for the Flavour & Fragrance chemistry and facilitated Givaudan's research challenges to be addressed. As a result of their efforts they have successfully developed a vast number of selective hydrogenation reactions, whose products are of great importance from commercial aspects. In this demonstration the first generation hydrogenation apparatus of ThalesNano, the H-Cube[®], was used. The new generation version of this device, the H-Cube Pro, could also be used for this purpose. The Phoenix Flow Reactor, the new, high temperature flow reactor is also very useful for similar catalyst screening processes.

ACKNOWLEDGEMENTS

We would like to thank Dr. Fridtjof Schröder for presenting at our user group meeting, his constant help in our work and his friendship. Your contribution is highly valued!

REFERENCE

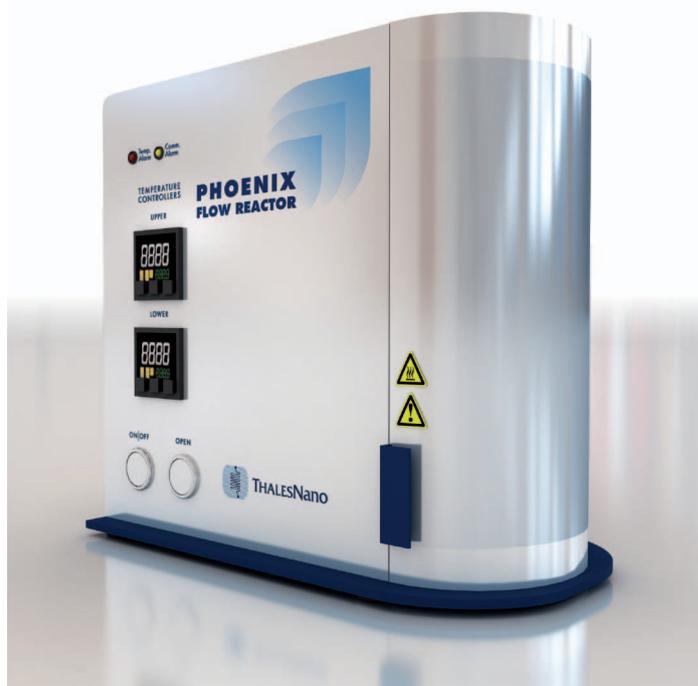
Brunner, G; Elmer, S; Schröder, F; Transition-Metal-Catalyzed Cyclopropanation of Nonactivated Alkenes in Dibromomethane with Triisobutylaluminium; *Eur. J. Org. Chem* ; **2011**; 4623-4633

LEGAL

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H-Cube Pro™



Phoenix Flow Reactor

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