# Interesting applications on a novel high pressure high temperature microfluidic-based flow reactor

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## ABSTRACT

Recently, a novel high-pressure, high-temperature, microfluidic-based benchtop reactor was developed by ThalesNano Inc. as a result of the need for performing hazardous organic chemical reactions under harsh conditions in a safe and fast manner. Wide variety of organic chemical reactions including alkylation, esterification, nitration, hydrosylilation, bromination, different C-C-, C-N cross coupling reactions have been successfully performed on the instrument and presented here. As difficult to perform reactions, isonitrile synthesis as well as azide formation have been targeted, tested and resulted in a complete conversion of the reagents. The instrument was designed with an external gas introduction possibility to run triphasic reactions using reactive and sometime hazardous gases/mixtures like carbon monoxide used in carbonylation. Furthermore, as interesting application nanoparticle synthesis was also targeted and the first results are demonstrated here as well.

***Keywords***: flow reactor, microfluidics, carbonylation, nanoparticles, heterogeneous catalysts

## 1 INTRODUCTION

Investigating organic chemical reactions in the high pressure, high temperature regime by using highly efficient heterogeneous catalysts is a challenging opportunity offering radical shortening of reaction time combined with higher yield and higher purity of the products than that normal batch reactor could provide. Meso- and microfluidic-based flow reactors filled with active catalysts are suitable for this purpose, as the experience with Thales Cube Reactors™ filled mostly with nanostructured catalysts demonstrates [1-5]. Cube Reactors™ are belonging to the family of „mesofluidic" reactors, i.e. reactors which operating with reactions lines having larger inner diameters (100 to 300 micron) than in usual microfluidic reactors. Here we demonstrate the use of the last member of the Cube Reactor™ series, called the X-Cube™, first of all for general organic chemical reactions and difficult to perform reactions, while at the end we will discuss about new applications towards inorganic nanoparticle synthesis within the instrument.

## 2 EXPERIMENTAL

### 2.1 The X-Cube™ reactor

The newest member of the Thales Cube™ micro-flow reactor series (see Fig. 1) used for carrying out organic and inorganic synthetic reactions consists of three main units: 1) the built-in dual HPLC pump system for solute delivery allowing 0.1-3 ml/min flow rates; 2) the actual reactor box which contains two heating units with temperatures up to 200°C and encapsulating the so called CatCart™ systems packed with either heterogeneous catalysts/immobilized reagents on different supports or scavengers. Furthermore the whole reaction line can be pressurized up to 150 bar by a back pressure regulator as well.; 3) and last but not least the touch screen panel which allows us to have full control over the reaction conditions allowing us to change the reaction parameters on-the-fly mode resulting the fine tuning of the conversion and the selectivity of the chemical transformations.

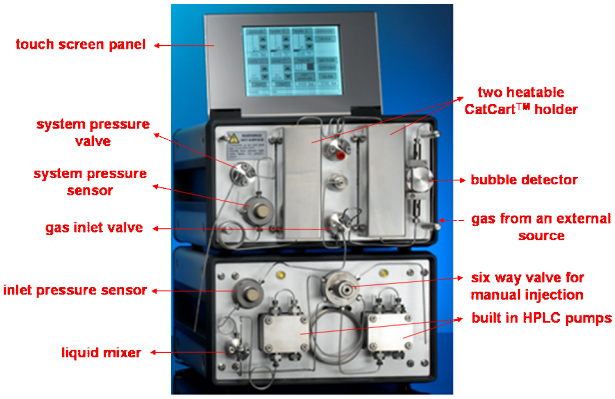


Figure 1: The X-Cube™ high-temperature, high-pressure flow reactor.

### 2.2 General organic chemistry performed on the novel X-Cube™ flow reactor

Below are listed (Fig. 2) validation reactions carried out on the X-Cube™ catalytic flow reactor using different heterogeneous catalysts/immobilized reagents embedded in the CatCart™ system. All the reactions were carried out at flow rates between 0,2-2 ml/min, and under one flow which

means second scale reaction times. In this manner, using the Cube series allows us to optimize diverse reactions and to synthesize compound libraries in a short period of time. Nonetheless, the short reaction time results in high product purities as shown. Two carbonylation type reactions have been carried out by using an external carbon monoxide gas source and introducing the gas into the instrument through a series of valves. With this option triphasic reactions can be performed under pressures up to 110 bar.

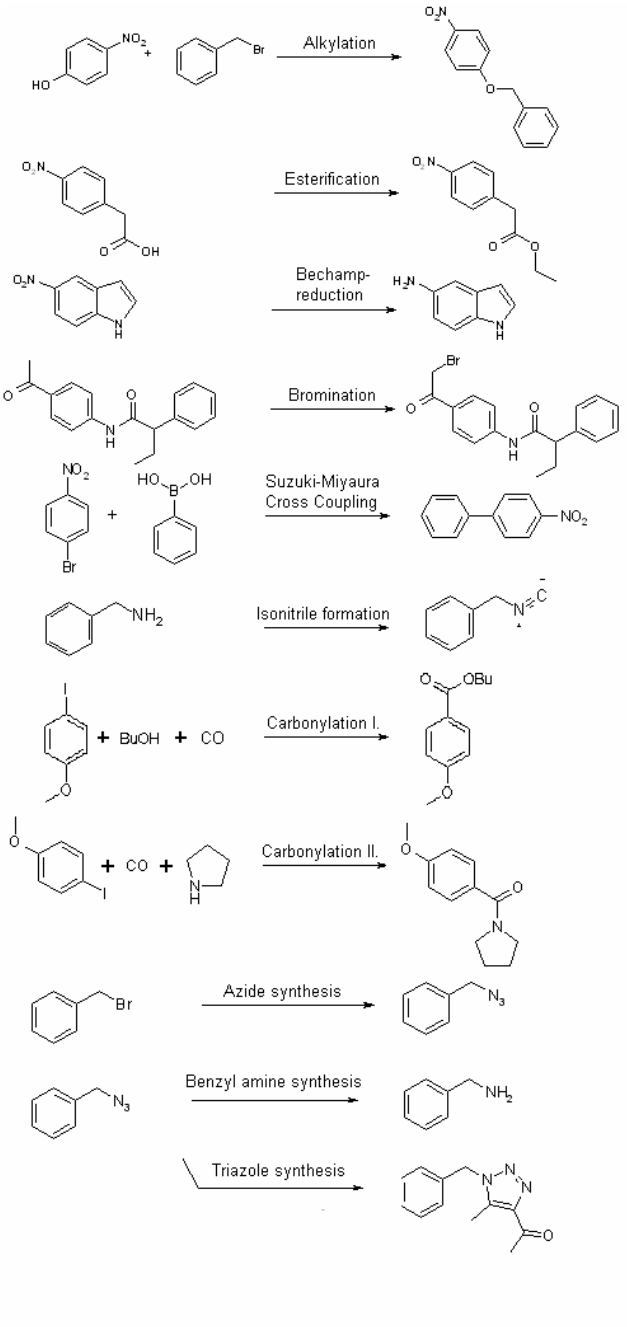


Figure 2: Organic chemical reactions performed on the X-Cube™.

## 2.3 Inorganic nanoparticle synthesis on the novel X-Cube™ flow reactor

Pt nanoparticles in the catalytically relevant 1-10 nm size regime have been synthesized on the X-Cube™ reactor using the advantages of the flow chemistry, namely the fast reaction time, and the quick, on-the-fly optimation [6]. The synthetic process is demonstrated on Fig. 3.

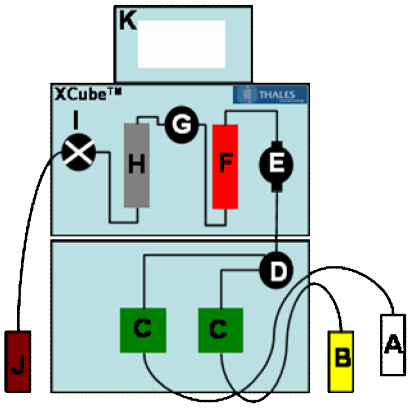


Figure 3: Reactor setup for nanoparticle synthesis.

6mM alcoholic solution of $H_2PtCl_6x6H_2O$ (Sigma-Aldrich) (from vial **B**) was directed through pump **C** into the mixer unit (**D**), where mixed with the 60 mM PVP (polyvinyl-pirrolidone (Sigma-Aldrich)) (from vial **A**) solution. During the nanoparticle formation PVP molecules act as protective agents. They stabilize the surface of Pt nanocrystals in order to prevent their aggregation. The nanoparticle formation (nucleation and growth) obtained in the CatCart™ (**F**), that was heated up to 150°C and pressurized to 50 bar. After the colloid solution passed through another mixer unit (**G**), it was cooled down to room temperature in the second CatCart™ holder (**H**), and left the instrument through the back-pressure regulator (**I**) into the collection vial (**J**). Since the nanoparticle synthesis does not require any special heterogeneous catalyst, the two CatCart™ systems were filled with inert quartz sand.

# 3 RESULTS AND DISCUSSION

## 3.1 General organic chemistry performed on the X-Cube™ flow reactor

The reactions performed on the instrument are collected in Table 1 with the appropriate references [7-15], and the respective results from batch technology. The data show us that we have successfully performed high-temperature, high pressure meso- and microfluidics-based catalytic flow reactions by using the Thales Cube reactor which, compared to the batch technology, offers radical shortening of reaction time in the second scale, combined with high

| Reaction | CatCart™ | T (oC) | P (bar) | solvent | conversion (%) | purity (%) | Lit. data Yield (%) | Ref. |
|---|---|---|---|---|---|---|---|---|
| *Alkylation* | $K_2CO_3$ | 150 | 50 | $CH_3CN$ | 100 | 95 | 94 | 7 |
| *Esterification* | $AlCl_3$ s. | 200 | 50 | EtOH | 100 | 98 | 90 | 8 |
| *Bechamp- reduction* | Fe powder | 200 | 50 | EtOH:$H_2O$ | 100 | 98 | 29 | 9 |
| *Bromination* | Tribromid s. | 100 | 40 | DCM | 100 | 85 | 89 | 10 |
| *Suzuki-Miyaura* | Pd EnCatTM | 80 | 20 | Isopropanol | 90-95 | 70 | 98 | 11 |
| *Isonitrile formation* | NaOH | 75 | 50 | DCE | 100 | 95 | - | - |
| *Carbonylation I.* | $Pd(TPP)_4$ s. | 80 | 30(CO) | BuOH | 100 | 95 | 99 | 12 |
| *Carbonylation II.* | $Pd(TPP)_4$ s. | 100 | 30(CO) | THF | 100 | 97 | 40 | 13 |
| *Azide formation* | Azide s. | 100 | 40 | $CH_3CN$ | 100 | 95-100 | 91 | 14 |
| *Triazole formation* | $K_2CO_3$ | 200 | 40 | $CH_3CN$ | 100 | 90 | 82 | 15 |

Table 1: General organic chemical reactions performed on the X-Cube™ flow reactor.

yield and high purity of the products. Furthermore the X-Cube™ flow reactor can offer the advantages of developing high-throughput and scalable technologies with short optimation time and that of running reactions in a safer, more controllable mode than normal batch reactors can provide.

### 3.2 Inorganic nanoparticle synthesis on the novel X-Cube™ flow reactor

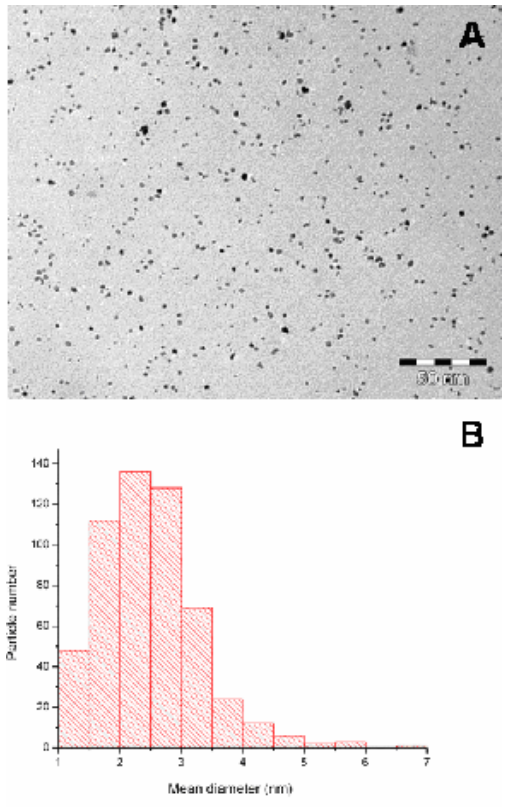


Figure 4: TEM image of Pt nanoparticles synthesized in the X-Cube™ reactor (A) with the respective particle size distribution (B).

Pt nanoparticles have been successfully synthesized on the novel high-pressure, high-temperature flow reactor developed by ThalesNano Inc. within only a few second reaction time as opposed to the general batch processes, where it can take several hours [16-19]. The nanoparticles formed exhibit monodispersed size distribution centered at 2 nm (Fig. 4). Furthermore they tend to keep their stability in colloid solution for several months.

## 4 CONCLUSION

Here we have presented successfully performed high-temperature, high-pressure continuously flow catalytic reactions carried out on the X-Cube™ system developed by ThalesNano Inc.. This novel device significantly reduce the reaction time and provide higher yields and product purities than commercial batch technologies. Nevertheless the reactor offer to combine it with automated liquid handlers to create high-throughput automated systems for faster optimation and compound library syntheses in a safer, more controllable mode. Wide range of organic chemical reactions has been carried out on different catalyst/reagents filled into the CatCart™ system. The reactions including general organic or hazardous/unpleasant chemical transformations such as alkylation, esterification, nitration, bromination, different C-C-, C-N cross coupling were optimized in a safe and quick way resulting in high yields and product purities. As difficult to perform reactions in batch reactors, isonitrile synthesis as well as azide formation have been targeted, tested and resulted in a complete conversion of reagents. Furthermore we have demonstrated the ability to run triphasic reactions with introducing reactive and sometime hazardous gases/mixtures like carbon monoxide into the reactor. Finally, as an interesting and relevant application inorganic nanoparticle (Pt) synthesis was discussed. The results showed that this novel reactor unit is capable to perform not only organic syntheses but can be used for inorganic synthetic approaches as well.

## Acknowledgements

We thank Zoltan Konya and Imre Kiricsi from the Applied and Environmental Chemistry Department of University of Szeged for the transmission electron microscopy measurements. The authors acknowledge Balint Piroth and Andor Juhasz from ThalesNano Inc. for providing the filled CatCarts™ for the experiments.

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