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Improvements for air sensive reactions by using a new developed inertizing manifold

For air sensitive reactions, such as most of the ubiquitous metal mediated cross-coupling reactions, the presence of oxygen traces is known to play a fundamental role in the reaction outcome.[1]

To assure reproducible performances at screening scale an Inertization Manifold was developed in collaboration with scientists of Boehringer Ingelheim. This manifold can be easily coupled with the XELSIUS Condensing Unit to provide excellent reproducibility for the chemistry performed in the XELSIUS reactor still maintaining high degree of flexibility, thus offering a significant improvement in data quality and laboratory efficiency.

The XELSIUS Inertization Manifold permits parallel inert gas purging of a variable (1 to 10) number of XELSIUS reaction vessels by applying vacuum/inert gas cycles under magnetic stirring, if desired.

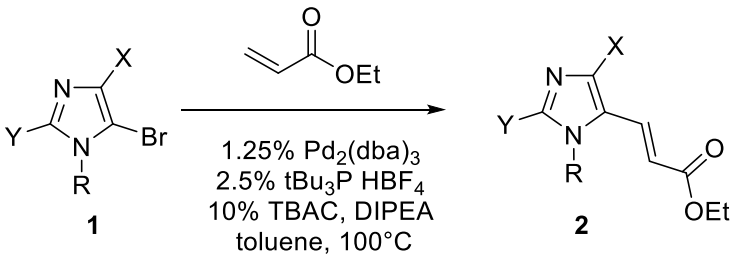
After complete inertization, the manifold with the reaction vessels is transferred to the XELSIUS reaction block where the desired chemistry is run at the programmed temperature.

A manometer is installed in-line to provide a more accurate control of the vacuum levels during the inertization operations.

Thanks to an addition port included in each vessel cap, the vessels can be accessed for sampling or reagent addition while reactions are running under inert conditions.

The efficiency of the Inertization Manifold was tested on a number of oxygen and moisture sensitive reactions in the laboratories of Boehringer Ingelheim.

The Heck cross-coupling of **1** with ethyl acrylate depicted below was shown to be very air sensitive as largely incomplete conversions were observed when the reaction was conducted under inert atmosphere with poor degassing before starting the reaction.



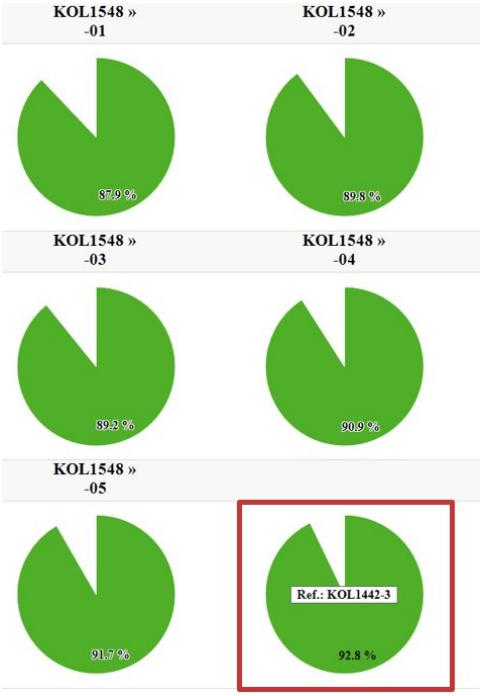
Initially, the oxygen sensitivity of this reaction was confirmed by running three reactions in parallel at 500 mg scale under a nitrogen atmosphere and using different degassing techniques. When the reaction mixture simply heated under a nitrogen blanket without previous inertization, about 45 % of starting material was left unreacted after overnight stirring. Argon bubbling through the reaction mixture before setting it to 100°C much improved the conversion, which was however still not complete (ca. 5% starting material remained). Finally, vacuum/argon cycles were effective and complete conversion was observed at this scale.

Oxygen sensitivity of the Heck cross-coupling

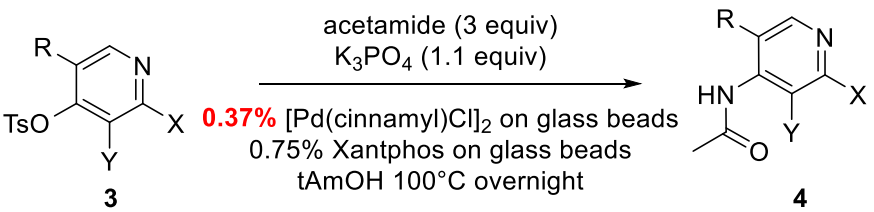
TIBCO Spotfire® pie charts displaying the assay yield of residual starting material **1** (yellow) and of the Heck product **2** (green) after overnight stirring under nitrogen atmosphere at 100°C using different degassing procedures. No degassing (left), degassing *via* argon bubbling (in the middle), degassing *via* vacuum/argon cycles (5x) (right).

The same reaction was evaluated in the Xelsius reactor at 150 mg scale using the Xelsius LV reaction vessels. The reaction mixtures were degassed by using vacuum/argon cycles (5x). Five replicates were run to assess the stability of the procedure. Results indicate very stable conversions in every case and assay yield completely comparable to the reference experiment run at 500 mg scale (red framed pie chart exp#KOL1442-3) and around 88-92%

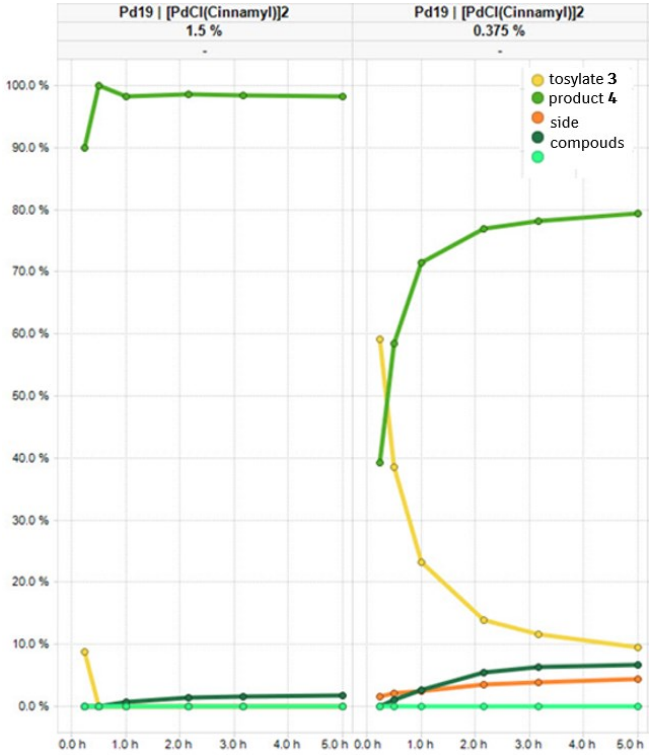
Results of the reaction run in the XELSIUS Reactor after degassing using the XELSIUS Inertization Manifold



A second example was provided by Boehringer Ingelheim and refers to the Buchwald-Hartwig amidation of the tosylate **3** with acetamide. This cross coupling was proved to run very stable at a relatively high palladium loading of 1.5% but lowering of the catalyst loading below 0.4% delivers instability to the system and in the presence of oxygen traces, as introduced by sampling, incomplete conversion and formation of important amounts of side compounds deriving from hydrolytic pathways were observed.



Oxygen/moisture sensitivity Buchwald-Hartwig amidation

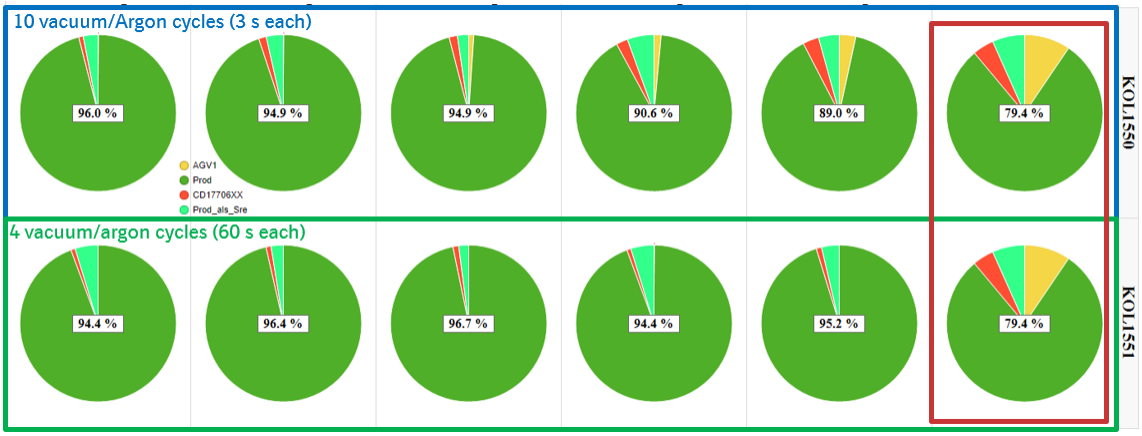


Kinetic profiling of the amidation of tosylate **3** at different palladium loadings with manual sampling: 1.5% palladium loading (left) and 0.37% palladium loading (right). The sampling introduces trace amounts of oxygen and moisture thus causing the coupling to prematurely stall with significant formation of side compounds. Interestingly, larger scale reactions at the same low palladium level of 0.37% sampled using an EasySampler probe deliver instead complete conversion (internal data).

The cross-coupling was evaluated in five replicates in the Xelsius reactor at 500 mg scale using the Xelsius LV reaction vessels at 0.37% palladium loading (0.9 mg $[Pd(cinnamyl)Cl]_2$). In order to assure reproducible catalyst dosing at this very low amounts, both the palladium precatalyst and the Xantphos ligand were added absorbed on glass beads, a technique recently disclosed by scientists at Abbvie.[2] The reaction mixtures were degassed at room temperature using vacuum/argon cycles prior to increasing the temperature to 100°C.

In this case, given the extreme oxygen sensitivity of this transformation the degassing time too plays an essential role. When the vacuum/argon cycles were quick (5 s) some instability was still observed. However, by increasing the degassing time to 60 s per cycle very stable results could be achieved with complete conversion and minimal and comparable amounts of side compounds in every case.

Results of the reaction run in the XELSIUS Reactor after degassing using the XELSIUS Inertization Manifold



TIBCO Spotfire® pie charts displaying the assay yield for residual starting material **3** (yellow) and for amidation product **4** (green) under argon atmosphere after overnight stirring at 100°C using different degassing times. Short degassing cycles of 5 s each (above Exp# KOL1550) and long (60 s) degassing cycles (below Exp# KOL1551). Side compounds are displayed in orange and light green. Reference experiment is red framed.

In conclusion, experimental data are provided in replicate which show that the Inertization Manifold allows very air/moisture sensitive reactions to run stable and reproducible thus offering a precious tool for screening exercise at low scale without sacrificing data quality and laboratory efficiency.

[1]Jeremy M. Merritt, Jonas Y. Buser, Alison N. Campbell, Jared W. Fennell, Neil J. Kallman, Thomas M. Koenig, Hossam Moursy, Mark A. Pietz, Norma Scully, Utpal K. Singh. *Use of Modeling and Process Analytical Technologies in the Design of a Catalytic Amination Reaction: Understanding Oxygen Sensitivity at the Lab and Manufacturing Scales.* Org. Process Res. Dev. **2014**, *18*, 1, 246–256

[2]M. Cynthia Martin, Gashaw M. Goshu, Jeffery R. Hartnell, Collin D. Morris, Ying Wang, Noah P. Tu. *Versatile Methods to Dispense Submilligram Quantities of Solids Using Chemical-Coated Beads for High-Throughput Experimentation.* Org. Process Res. Dev. **2019**, 23, 9, 1900–1907.