

1000-fold Scale-up of Microwave Heated Reactions without Re-optimisation: Is it Possible?

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Introduction

Microwave assisted organic synthesis (MAOS) is now a commonly accepted technique, used to rapidly heat up chemical reactions and thus accelerate the reaction rates. Small scale microwave instruments dedicated to MAOS are available from several manufacturers and are present in many industrial organic chemistry and pharmaceutical laboratories. In these instruments, typically amounts of milligrams or a few grams can be processed. When it comes to the need for processing larger amounts, i.e. tens of grams up to a kilogram, no general technique or instrument is available due to inherent limitations (solid handling for flow reactors and limited microwave field penetration when enlarging the reaction vessels). These techniques require extensive and time consuming re-optimisation and modification of the conditions applied in the small scale instruments.

Biotage has now released a new version of the large scale microwave instrument, Advancer KiloBatch (**Picture 1**), that makes the processing of larger amounts of substances possible without any further re-optimisation. This means that the times and temperatures used in the small scale instrument, Initiator™, can be directly transferred to the Advancer KiloBatch. In order to examine the cycle-to-cycle and batch-to-batch reproducibility by transferring the parameters from the small scale to the large scale instrument, we here present the results of a Suzuki reaction (**Scheme 1**) and a Diels-Alder reaction (**Scheme 2**).

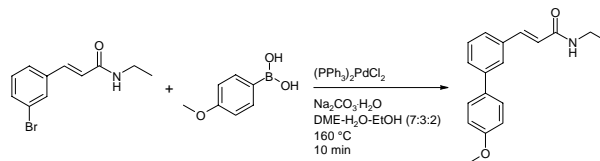


Picture 1.

Results and Discussion

Suzuki Reaction

Using the newly introduced carousel for addition of solids (**Picture 2**), four sequential cycles (scaled up 1000 times) as well as four individual batches were performed. The conversions were compared to that of the small scale reaction (**Chart 1**).



Scheme 1.

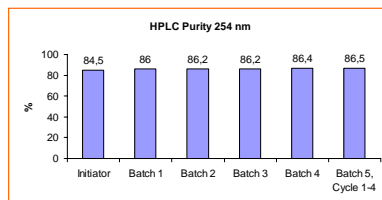


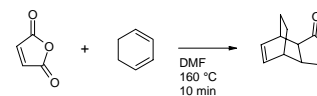
Chart 1.



Picture 2.

Diels-Alder Reaction

Using the syringe pump and allowing the instrument to run 56 cycles consecutively, 14 liters (scaled up 7000 times) of the reaction solution was processed within 14.5 hours. Thus 1.24 kg of the corresponding Diels-Alder adduct could be isolated after concentration of the reaction mixture. The purity and isolated yield were compared to the results obtained from the experiment performed in Initiator (**Chart 2**).



Scheme 2.

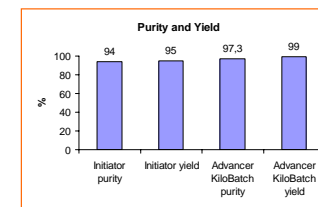


Chart 2.

General Experimental Procedure

Suzuki Reaction

Batch 1, Batch 2, Batch 3, Batch 4: These four batches were run and collected individually according to the procedure described below, in order to compare them to the outcome from the run on the Initiator, but also to examine the batch-to-batch reproducibility. The reaction mixtures from these batches were not worked up.

Batch 5, Cycle 1-4: This batch consists of four sequential cycles that were run and collected unattended as a single batch according to both the procedure and the work-up described below.

To each of the small compartments of the solid adding carousel was added 360 mg (0.51 mmol, 0.013 equiv) $(PPh_3)_2PdCl_2$, and to each of the large compartments was added 7.63 g (61.5 mmol, 1.5 equiv) $Na_2CO_3 \cdot H_2O$. With the syringe pump, 125 mL (0.328 M, 41.0 mmol) of the bromide solution and 125 mL (0.492 M, 61.5 mmol, 1.5 equiv) of the boronic acid solution were added. The resulting slurry was heated to 160 °C for 10 minutes. **Work up of Batch 5, Cycle 1-4:** After momentary flash cooling, filtration through Celite and evaporation, the residue was dissolved in CH_2Cl_2 and washed with 1 M NaOH and water. The organic layer was dried with Na_2SO_4 , concentrated, and the solid residue was re-crystallised from hot ethyl acetate yielding 32.3 g (70 %) of the product (purity: 97.2 % by HPLC-MS and >95 % by 1H NMR).

Diels-Alder Reaction

125 mL of a 1.0 M maleic anhydride solution (687 g, 7.00 mol in 7.0 L DMF) and 125 mL of a 1.5 M 1,3-cyclohexadiene solution (1.00 L, 10.5 mol in 7.0 L DMF, 1.5 equiv) were mixed and heated to 160 °C for 10 minutes and then flash cooled. This was repeated 55 times unattended over 14.5 hours. The resulting solution (13.5 L) was concentrated and dried under vacuum yielding 1.24 kg (99 %) of the product (purity: 97.3 % by HPLC-MS at 200 nm and >95 % by 1H NMR).

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