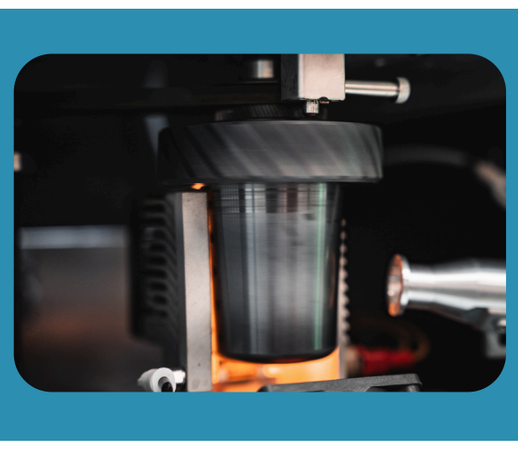
SYNLOCK

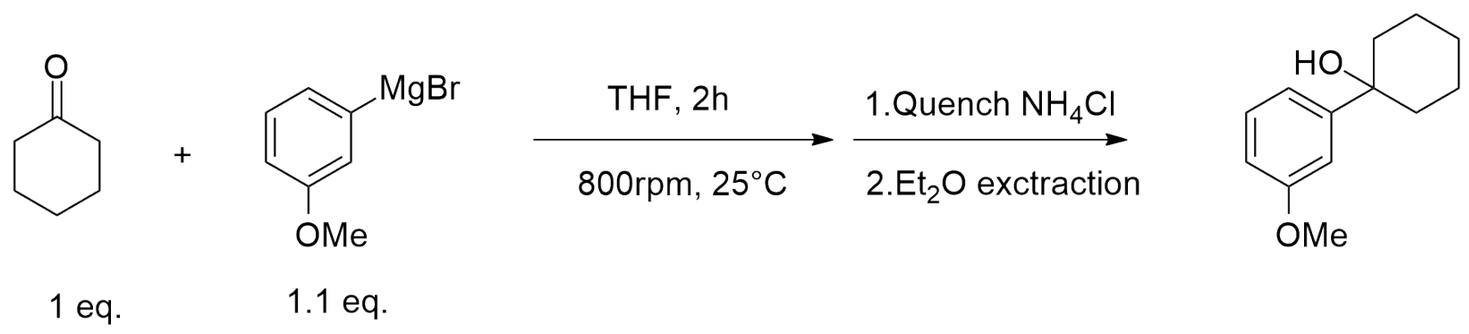
Cheminizer Application Note - N°1

Grignard addition



SUMMARY

This application note describes the addition of a Grignard reagent on cyclohexanone with the **Cheminizer** system. The device enables to store reagents and perform reaction under inert atmosphere and thus guarantees safe use, optimal and reproducible performances with moisture sensitive reagents, as described below.



REAGENT

Reagent A: Cyclohexanone (1.96 g, 20 mmol) was dissolved in 20 mL anhydrous THF to give a 1 M solution

Reagent B: 1 M 3-Methoxyphenyl magnesium bromide solution (Sigma-Aldrich, 100 mL)

Reagent C: Ammonium chloride (30.69 g, 0.57 mol) was dissolved in 100 mL of deionized water to obtained a 28% wt NH_4Cl solution

Solvent D: Anhydrous THF (ChemSolute, 100 mL)

HARDWARE SETUP

Prior to every experiments **Cheminizer** system was fully washed and dry with an automatic cleaning sequence. Silicon carbide reaction vessel was heated under vacuum and cooled under nitrogen flow.

Reagent A, B & C bottles were connected to the multi-position valve of the *ChemiDISP* module (Port 1, 2 & 3 respectively) and stored in the dedicated reagent rack support. Nitrogen feed line from the *ChemiDISP* module was connected the reagent storage split manifold. Two nitrogen feed lines from the split manifold were connected to the R**eagent A & B** bottles.

Solvent D & E were connected to the multi-position valve of the *ChemiSOLV* module (Port 1 & 2) and placed in the dedicated solvent rack support.

Waste bottle was connected to port 8 of the multi-position valve of the *ChemiSAMP* module and to port 7 of the multi-position valve of the *ChemiREAC* module.

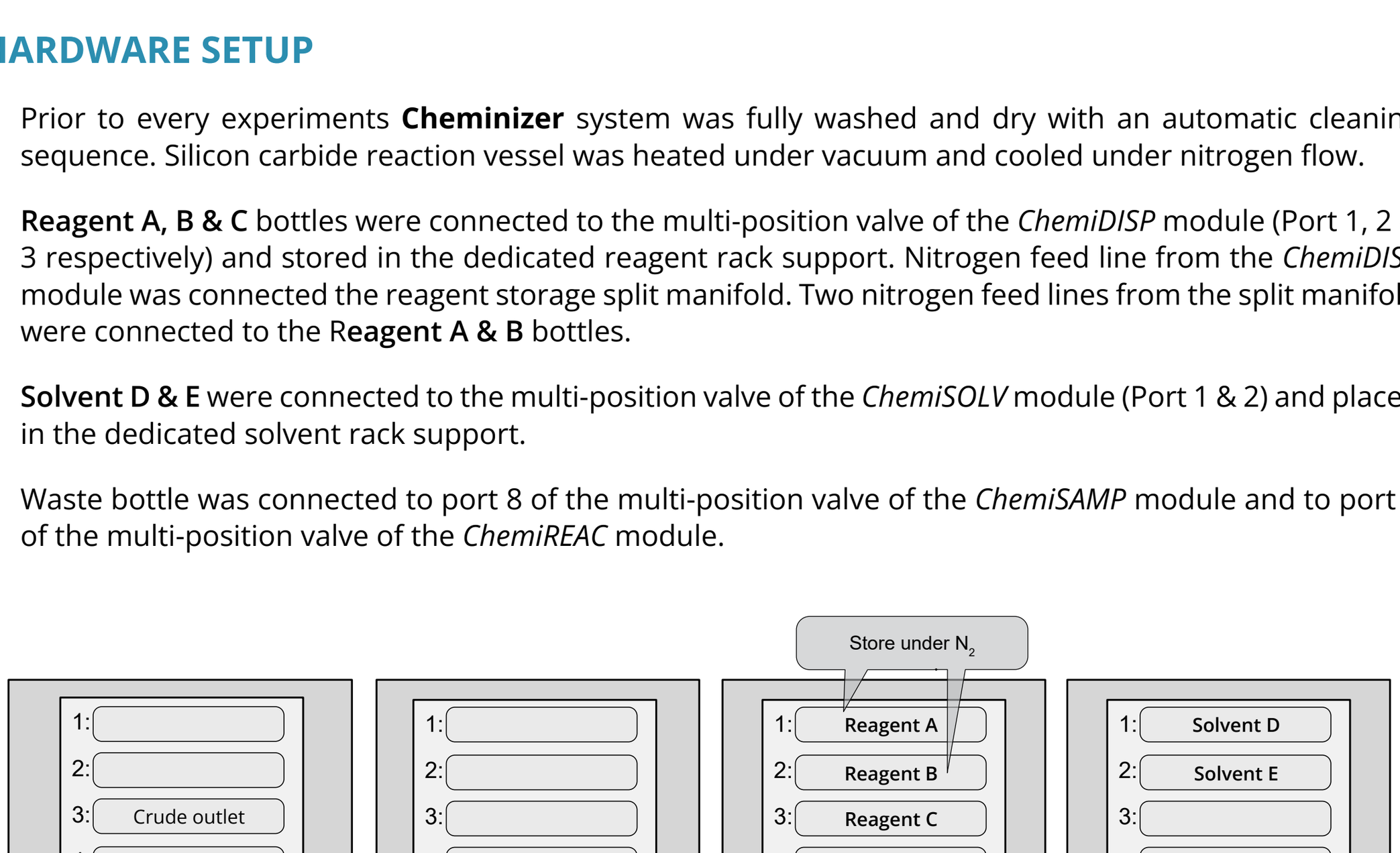


Figure 1. *Reagent configuration on the* ***Cheminizer***

SYNLOCK

EXPERIMENT

Reaction sequence is built using the **Protocol Automator** application. Reactions parameters such as reagent amount, reaction temperature, rotation speed rate are defined. The sequence is then saved and exported as an .xls file for importation in the **Cheminizer** control software (**Protocol Runner**).

To the dry and clean SSiC reaction vessel, in rotation at 650 rpm, was charged cyclohexanone (**Reagent A**, 2 mL, 2 mmol) in anhydrous THF. The fluidic backbone was rinsed with anhydrous THF (Solvent D, 10 mL). 3-Methoxyphenyl magnesium bromide (**Reagent B**, 2.2 mL, 2.2 mmol) was added at a constant flow rate of 7 mL/min. The rotation was maintained at 700 rpm for 5 min then mixture kept at 25°C for 2 h. Reaction rotation speed was reduced to 250 rpm and ammonium chloride solution (**Reagent C**, 3 mL) was added to the crude reaction media and the resulting biphasic mixture was transferred to a separator funnel by applying positive nitrogen pressure into the reactor. The silicon carbide reactor is rinsed with diethyl ether (**Solvent E**, 5 mL), and the resulting wash solution is subsequently transferred to the separator funnel. This operation is repeated twice.

Layer separation was performed manually and Combined organic phase was diluted to 10 mL in a volumetric flask with dichloromethane. The target compound and remaining cyclohexanone starting material were quantified by GC-FID using relevant calibration.

Experiment was carried out in 6 iterations.

RESULTS

Exothermicity associated with Grignard reagent addition is very well controlled (ΔT_{max} = 2°C, Figure 2).

Grignard reaction on **Cheminizer** afforded constant yield of 76% with minimal variations (Standard deviation: 2%). The same reaction was also run in a sealed vial (in triplicate) for comparison, leading to an average yield of 77% (SD = 4%).

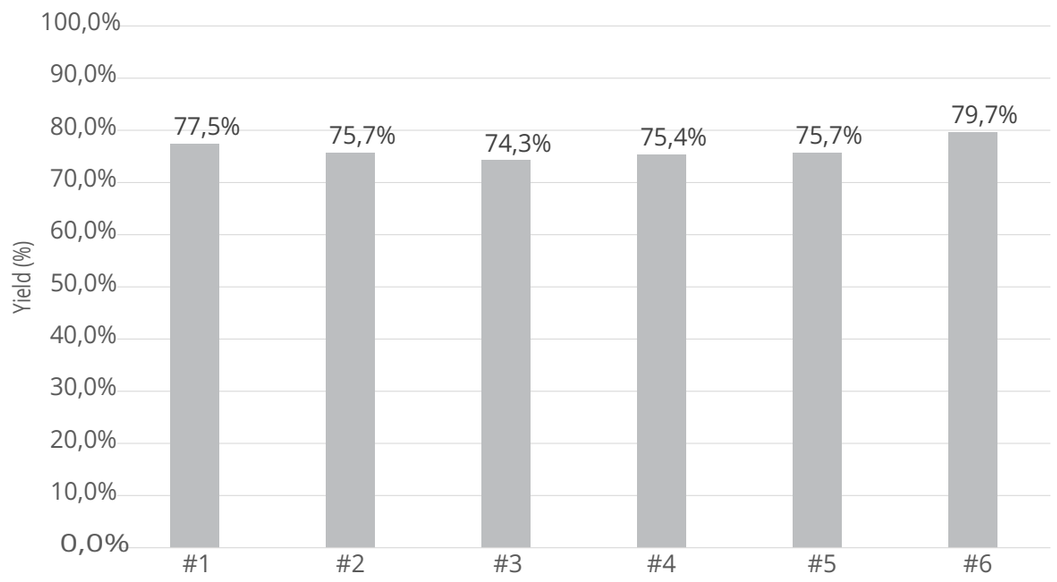


Figure 3. *Yield of Grignard reaction with the* ***Cheminizer***

CONCLUSION

The **Cheminizer** system, using its thin film technology, effectively controls the exothermicity of the Grignard reaction. This allows the reaction to be performed safely at room temperature, with a minimal temperature increase. The consistent yields over time demonstrate that the Grignard reagent, stored under an inert atmosphere, did not undergo premature degradation. The **Cheminizer** system provides a consistent and reproducible performance which demonstrate that it is a reliable and safe platform for performing reactions with moisture-sensitive reagents, with high control over the reaction parameters.

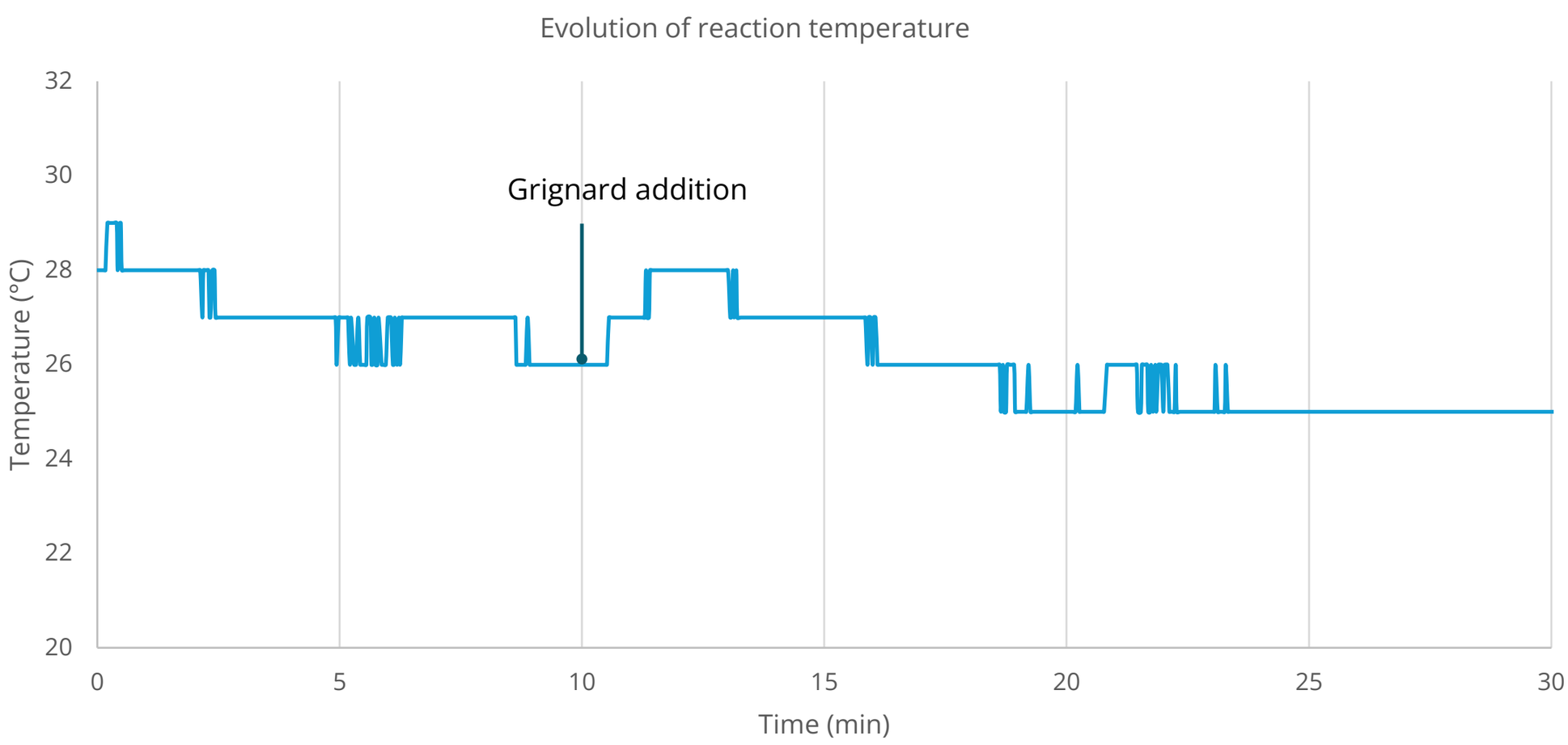


Figure 2. *Real time monitoring of exothermicity within the thin film during Grignard addition*

For further information please contact us at info@synlock.eu