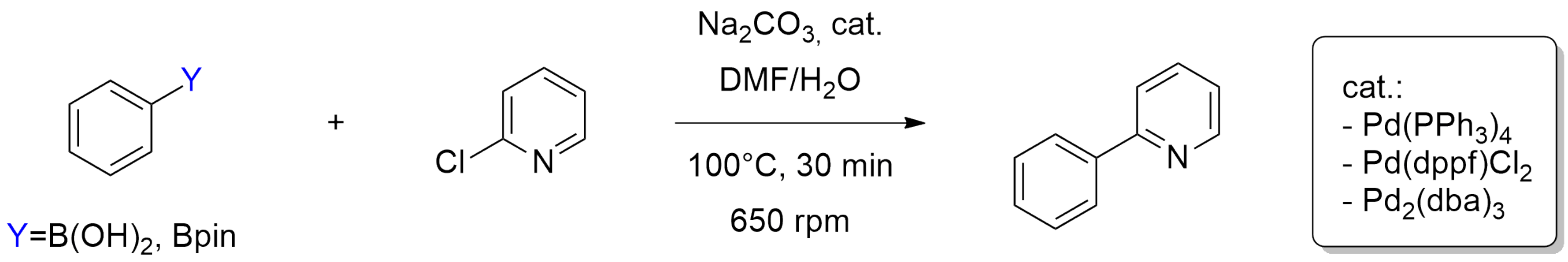
SYNLOCK

SUZUKI CROSS-COUPLING:
VARIATION OF REACTION CONDITIONS

SUMMARY

This application note describes the implementation on the Cheminizer platform of an evaluation study of different boronic compounds and catalysts for a Suzuki coupling.

REAGENTS



Volumes mentioned for one synthesis. Reagent B must be used within 24h after preparation.

Reagent A: boronic compound (1M) and 2-Cl-pyridine (0.65M) were dissolved in DMF (1.5 mL).
n(boronic) = 1.5 mmol, n(2-Cl-pyridine) = 0.98 mmol.
Reagent B: catalyst (0.005M) was dissolved in DMF (1.0 mL) (concentration can be changed to modify the catalyst loading).
n(catalyst) = 0.005 mmol (if 0.005M solution is used).
Reagent C: sodium carbonate (0.8M) was dissolved in HPLC water (2.5 mL).
n(Na_2CO_3) = 2.0 mmol.
Solvent D: DMF (10 mL) to rinse fluidic path.
Solvent E: H_2O/Acetone (10 mL,1/1 v/v) for the rinse of the crude mixture to the final vial.
Solvent F: aqueous HNO_3 10% (2x10 mL) to clean the reaction vessel.
Solvent G: acetone technical grade (2 x 10 mL) to clean the reaction vessel.

HARDWARE SETUP

Reagents A, B and **C** are connected to *ChemiDISP* (port 2, 1 and 3 respectively). **Solvents D, E** and **F** are used to clean and rinse the **Cheminizer** and are then positioned to *ChemiSOLV* (port 1, 7 and 4 respectively). To help the catalyst for dissolving, **Reagent B** is sonicated and stored under nitrogen and protected from light with an aluminum foil.
Two waste bottles are linked to the **Cheminizer**, one on *ChemiDISP* (port 8) for priming solutions and rinsing the fluidic backbone. The other one is placed on *ChemiREAC* (port 7) to collect the waste generated for the cleanup process at the end of one experiment. The final vials are placed on *ChemiREAC* (ports 1 to 6 available).

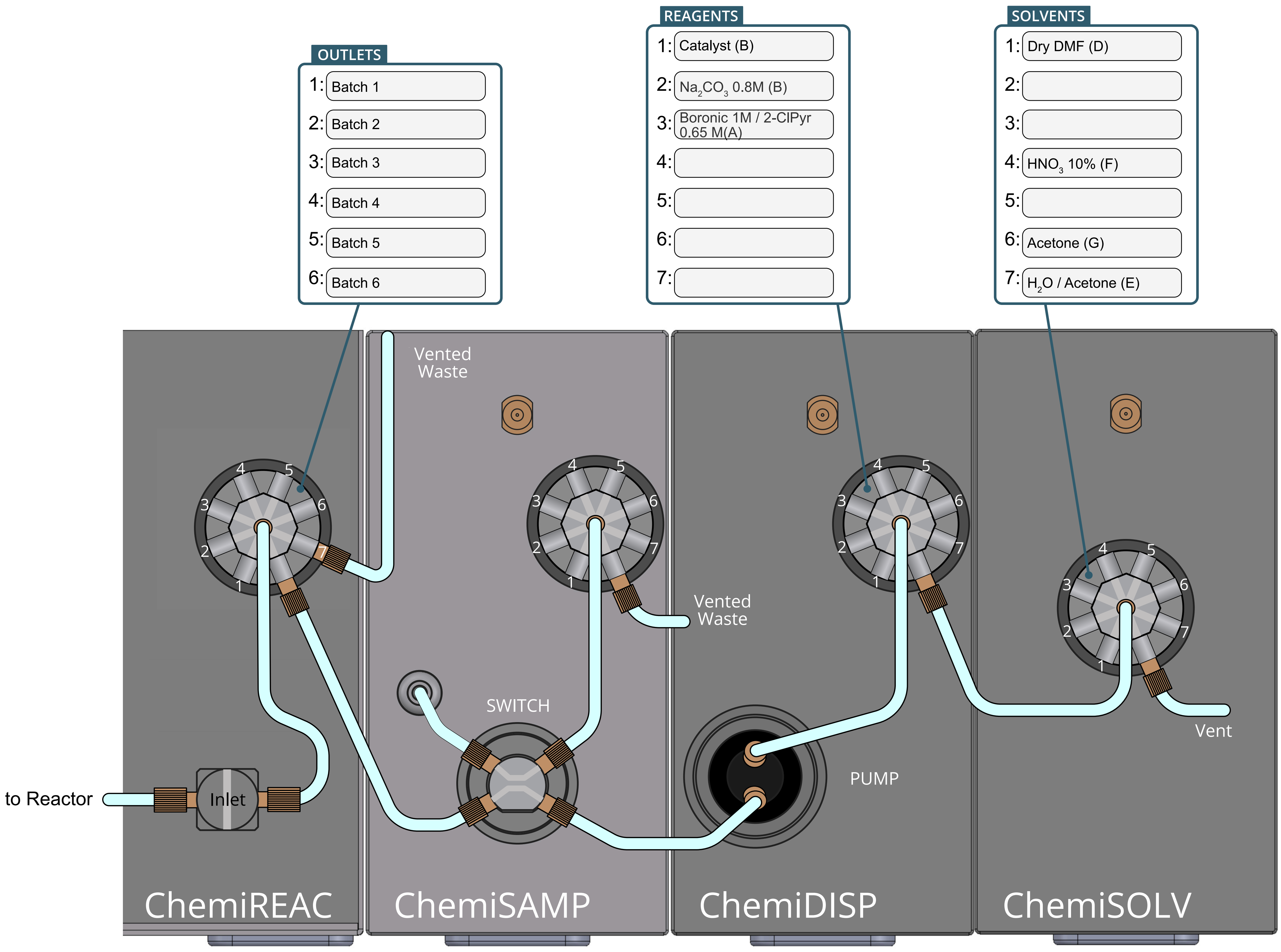


Figure 1. *Reagents configuration on the Cheminizer*

EXPERIMENT

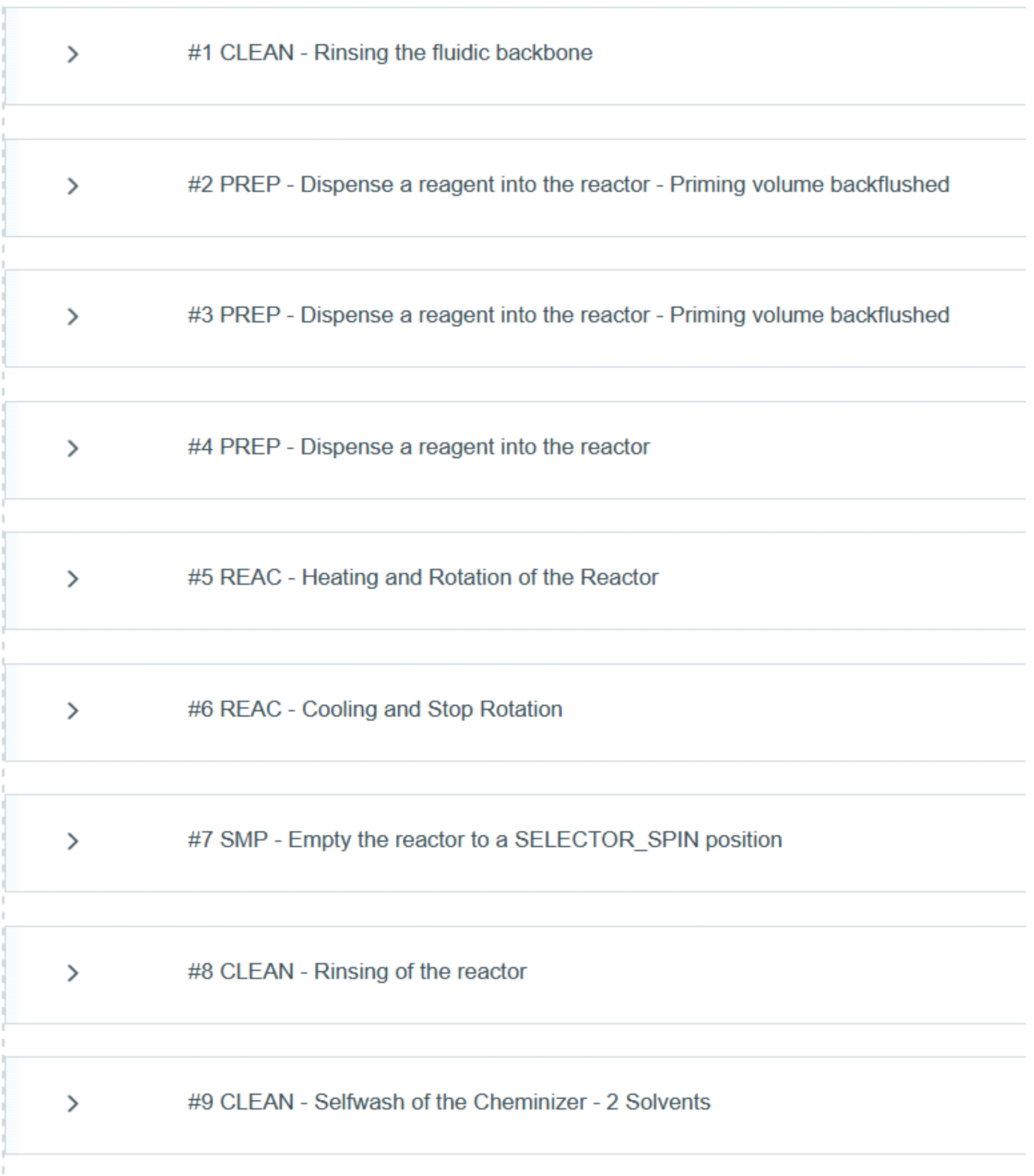


Figure 2. *Reaction sequence on the Protocol Automator*

First, the fluidic backbone from the dispensing unit to *ChemiREAC* is rinsed with 10 mL of DMF (#1). Then **Reagent B** (1.0 mL) is added (#2), followed by **Reagent A** (1.5 mL) and **Reagent C** (2.5 mL) (#3 & #4). Priming volumes of solution **A** and **B** are partially back-flushed to the stock solution vials. The reaction vessel start to rotate at 650 rpm and heating at 100°C is carried out with reactor closed, for 30 min (#5). The reaction vessel is cooled with compressed air at 45°C and rotation is stopped (#6). The crude mixture is transferred to a collected vial by pressurization with a positive nitrogen pressure (#7). The reaction vessel is rinsed with **solvent E** and wash solution is sent to the same collected vial as step #7 (#8).
At the end of the experiment (#9), *ChemiREAC* is cleaned with a nitric aqueous solution (10%, 2 x 10 mL) to efficiently remove palladium compounds. Reactions were conducted in duplicate or triplicate. For comparison same reaction conditions were replicated in seal vials. Yields were quantified by HPLC with the corresponding calibration curves of starting material 2-Cl-pyridine and final compound 2-phenylpyridine.

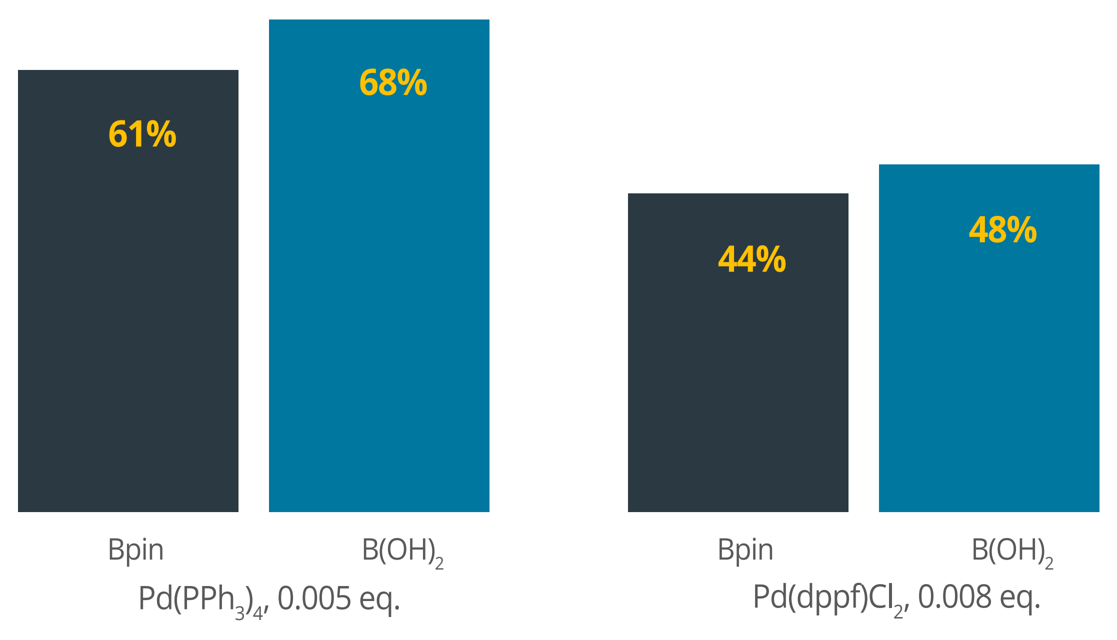
RESULTS

Mean values of the raw results are represented in the figures below.

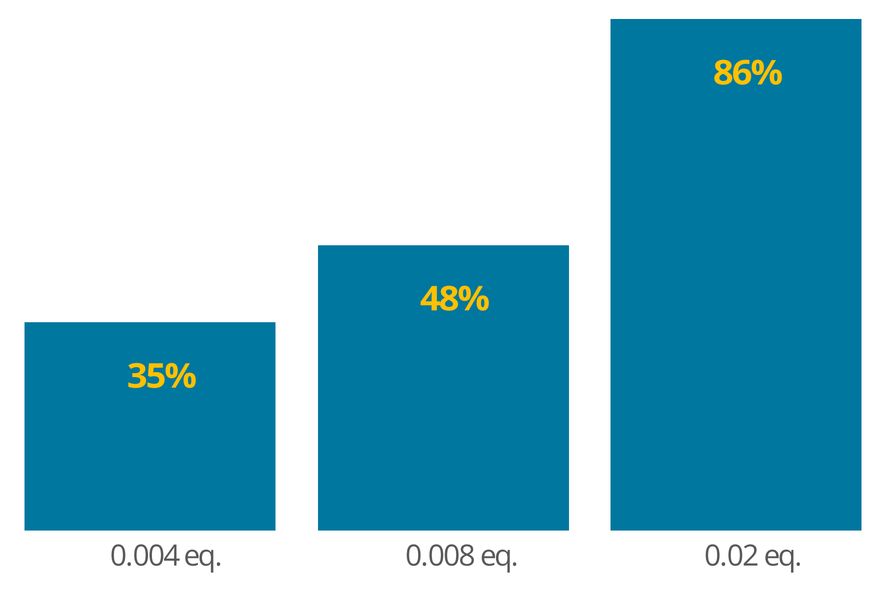
CONCLUSION

The evaluation study of Suzuki reaction on the **Cheminizer** platform provided key insights into performance of several reaction parameters: The platform demonstrated significantly superior yields, with a notable increase of 30-40% compared to conventional glassware setups. The boronic acid derivative consistently yielded marginally higher product quantities. Among the catalysts tested, $Pd(PPh_3)_4$ proved to be the most effective, producing the highest yields. As anticipated, a direct positive correlation was observed between the catalyst concentration and the reaction yield. This analysis confirms the **Cheminizer**'s capability to enhance reaction efficiency and provides specific guidance for optimizing synthetic protocols using this system.

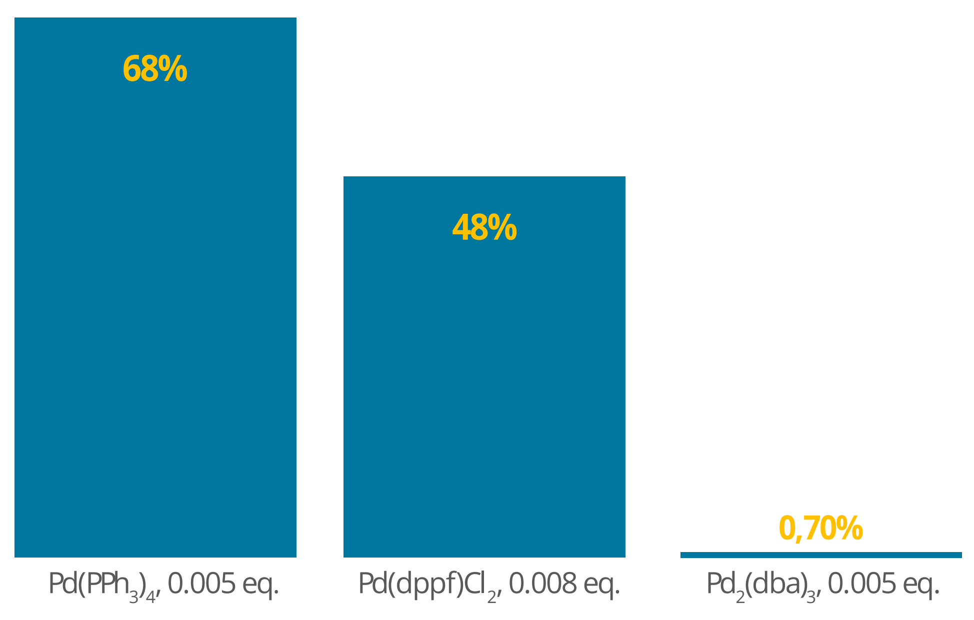
Coupling yields depending on the catalyst and the boronic compound



Catalyst loading $Pd(dppf)Cl_2$ on the coupling yield with boronic acid



Coupling yields depending on catalyst with boronic acid starting material



Yields of the Suzuki cross coupling: Cheminizer *vs* conventional glassware