

Ionic Liquids as Phase-transfer Catalyst in Suzuki Cross-coupling Reactions in Continuous Flow

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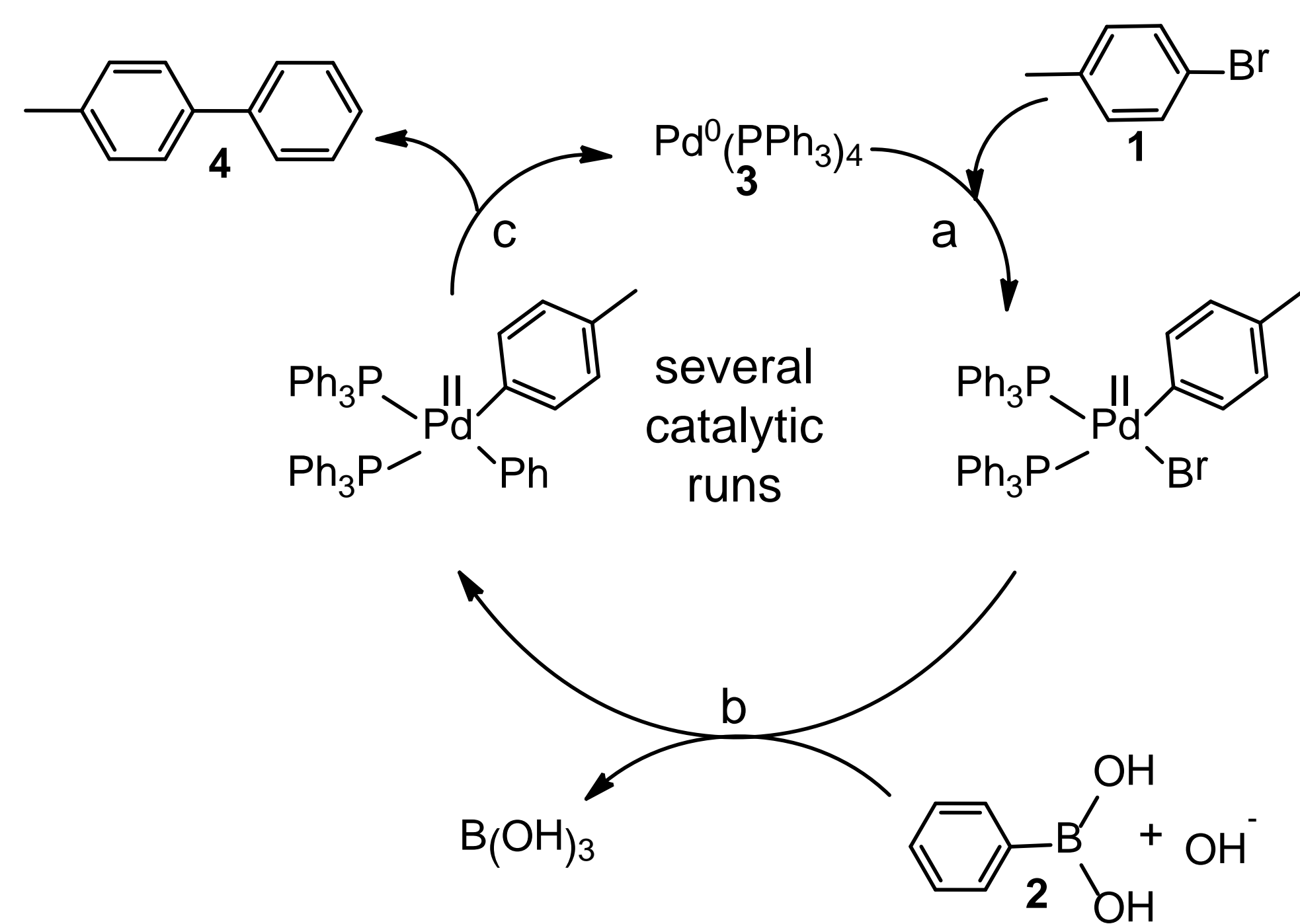
Introduction

The Suzuki cross-coupling reaction is widely used to generate carbon-carbon bonds from boronic acids and halides. It is successfully applied in homogeneous and heterogeneous synthesis of e.g. biaryls.^[1] The formation of two phases during the reaction requires an intensive mixing in batch.^[2] Transferred into a flow system a continuous mixing along the flow axis is required to stabilize the optimized interfacial area. Furthermore, to enable high temperatures above the boiling point in the capillaries or tubes pressurized systems are required. As literature known using [BMIM][BF₄] as phase-transfer catalyst under batch conditions yielded in 93 % in 10 minutes.^[3]

Based on the current state of research a retention mixing element (SIGRATHERM® Soft Felt, SGL CARBON SE, Germany) was applied to enlarge the interfacial surface and consequently increase the mass transfer by abiding the dispersion.

As a model substrate 4-bromotoluene **1** was chosen. It reacts conveniently with phenyl boronic acid **2** under catalysis of tetrakis(triphenylphosphine)palladium(0) **3** to 1-methyl-4-phenylbenzene **4**. Side products like biphenyl generated of two molecules phenyl boronic acid or benzene due to deboronation are easy to quantify.

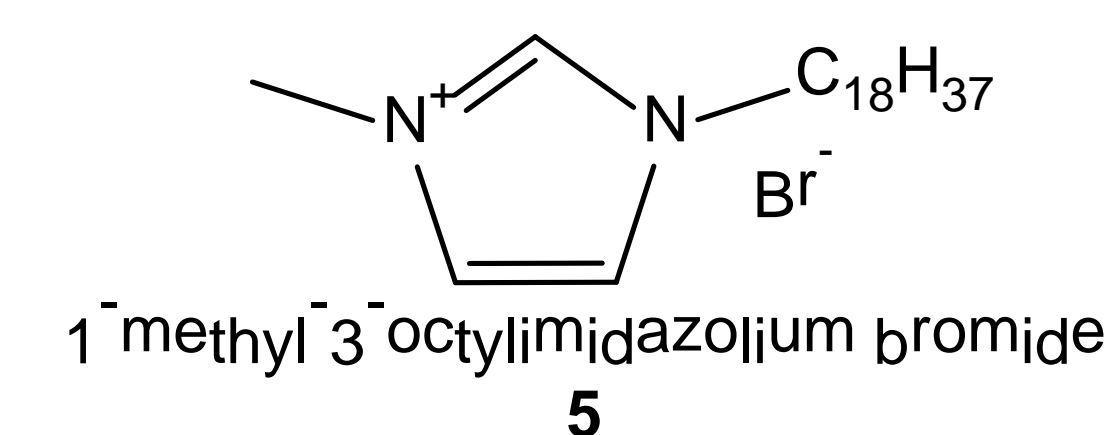
Suzuki-Reaction



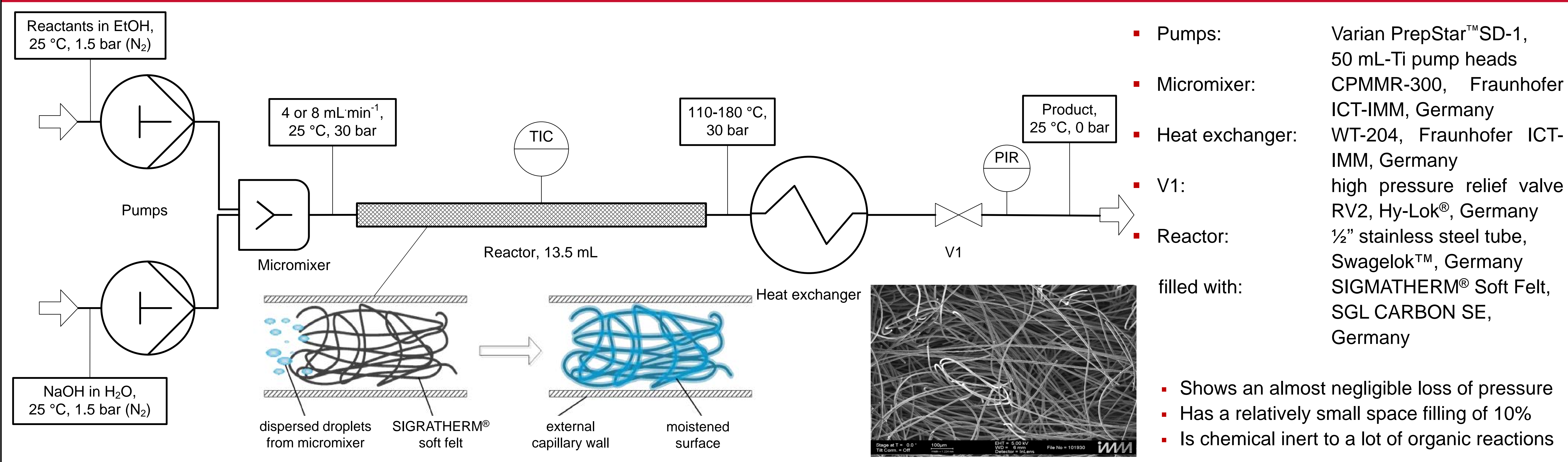
- Useful and most important synthesis to connect a C-C bond
- Catalytic cycle:
 - oxidative addition
 - transmetalation
 - reductive elimination
- Oxidative addition is the rate-determining step
- Turnover frequency (TOF):
 - Rate of reaction in catalysis
 - Highest TOF for this reaction: 100 s⁻¹

Ionic Liquids as phase-transfer catalyst

- Ionic Liquids (IL) are defined as salts with melting temperatures below 100 °C, evolved from traditional high temperature molten salts.
- Possibility of IL recycling
- Add-on of IL causes:
 - Stabilization of the aryl boronates
 - Generation of an educt-product-catalyst three-phase system
 - Acts as phase-transfer catalyst
- Choice of IL: [C₁₈MIM]Br **5**
 - Soluble in ethanol
 - Insoluble in water
- Adding 5% [C₁₈MIM]Br:
 - Reaction can be accelerated remarkably
 - IL contains the active catalyst which can be recycled several times



Flow-Scheme



Experimental

4-Bromotoluene **1** (98%, 0.25 mol), phenylboronic acid **2** (98%, 0.25 mol) and tetrakis(triphenyl-phosphine)palladium(0) **3** (99%, 0.25 mmol) were dissolved in ethanol (ad 250 mL). In a second solution sodium hydroxide was dissolved in water (ad 250 mL). Both solutions were filtered to remove possible impurities before they were combined at various temperatures in the system with a flow rate of 4 mL · min⁻¹ corresponding a reaction time of 202 seconds. The concentration of the palladium catalyst relating to phenylboronic acid **2** was 100 ppm (equates 0.01 mol%). In second series 1-methyl-3-octadecylimidazoliumbromid **5** (12.5 mmol) was added.

Additionally, with [C₁₈MIM]Br the coupling was performed at various temperatures in 101 seconds corresponding to a flow rate of 8 mL · min⁻¹. The concentration of the palladium catalyst relating to phenylboronic acid **2** was 100 ppm (equates 0.01 mol%).

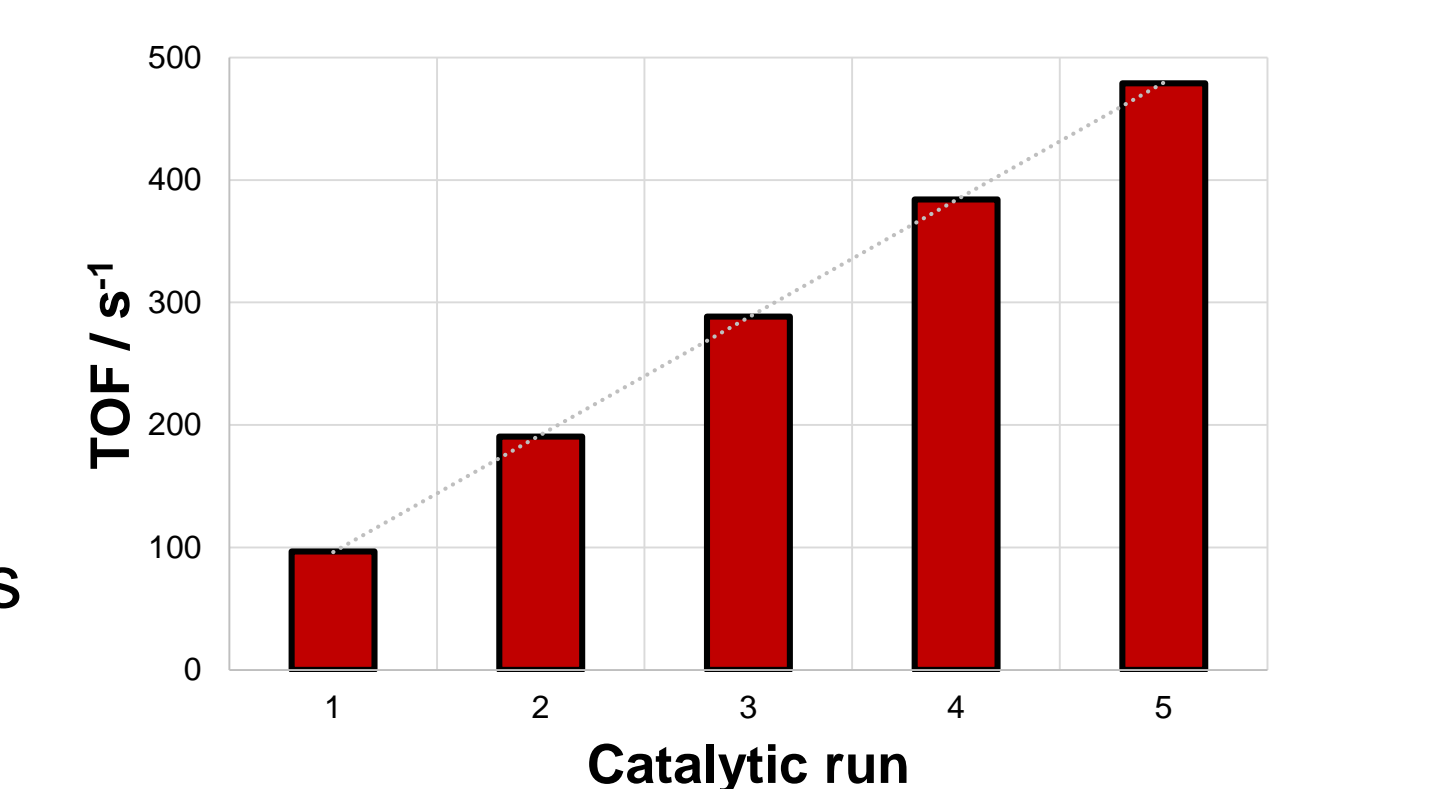
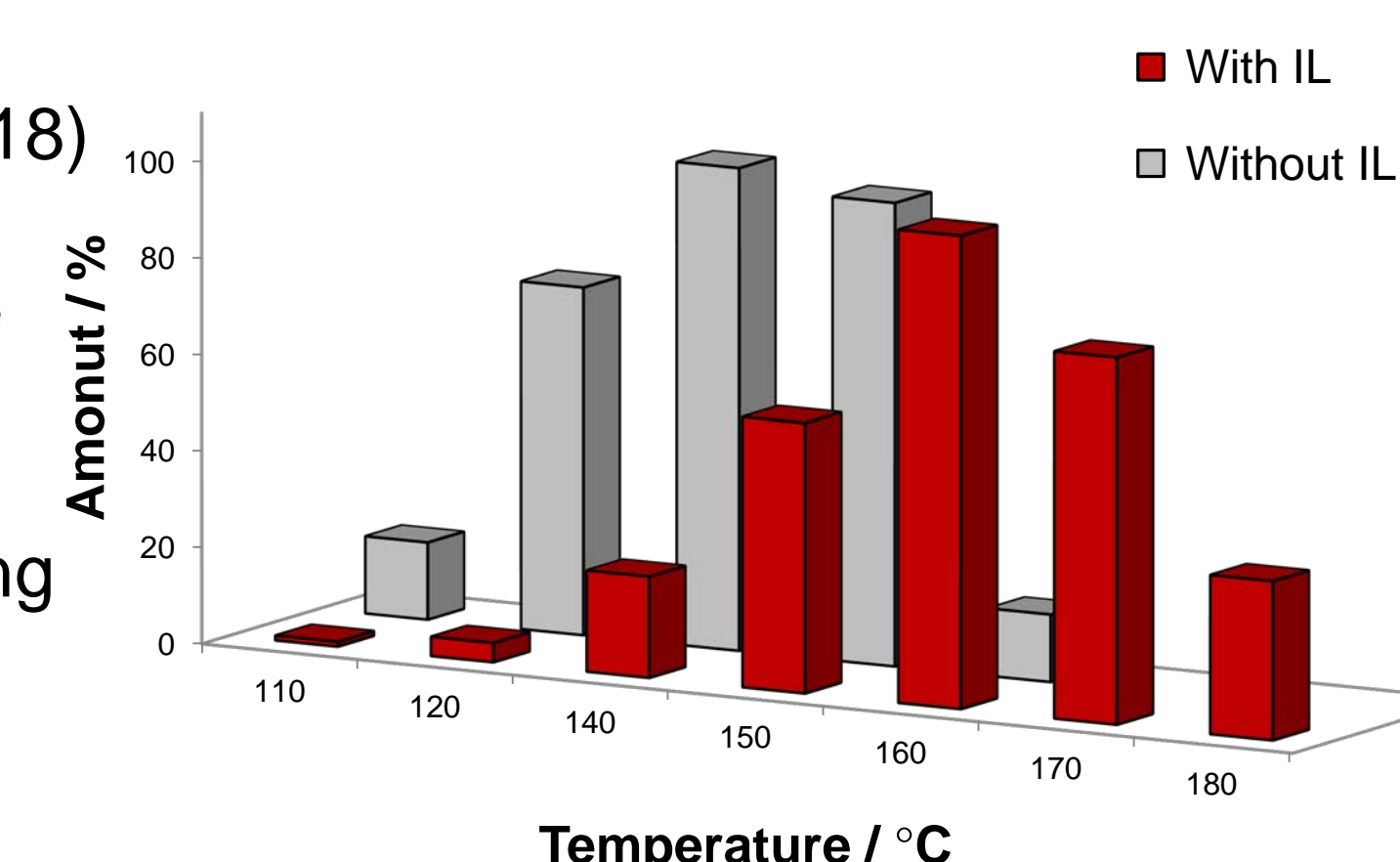
Advantage & Summary

- Reduced catalyst concentrations: 100 ppm Pd(PPh₃)₄
- No homo-coupled products
- Raw product with high purity: >99 % 1-methyl-4-phenylbenzene **4**
- Without IL:
 - In 202 seconds at 140 °C
 - TOF = 49.4 s⁻¹
- With [C₁₈MIM]Br **5**:
 - In 101 seconds at 160 °C
 - TOF = 96.8 s⁻¹
- The IL contains the activated catalyst which allows repetitive catalytic runs

Results

The obtained products were characterized by HPLC (Merck-Hitachi HPLC, A-4500 UV detector (250 nm), D-6000 PC-interface, Kromasil column 250 mm x 4 mm x 5 μm C18) with an isocratic method (34 % acetonitrile, 33 % methanol, 33 % water) and a flow rate of 1 mL · min⁻¹.

- Below 140 °C: residence time was not long enough for a completed cross coupling
- Above 140 °C: side reaction (terminal deboronation) increases
- No side product of homo coupling could be detected
- The catalytic solution including the IL was reused five times without loss of activity



References

- Seddon, K. R., *Journal of Chemical Technology & Biotechnology*, 68, 1997, p. 351.
- Wiles, C. & Watts, P., *European Journal of Organic Chemistry*, 2008, p. 1655.
- Mathews, C., *Chem. Commun.*, 2000, p. 1249.

