H-CUBE MINI

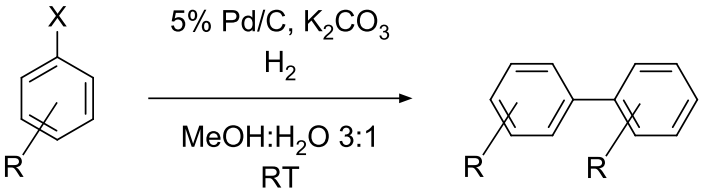
Ullmann-type reductive homo-coupling reactions at room temperature

Introduction

The implementation of sustainable and environmentally friendly protocols is an emerging field of the chemical industry. The need for safe and reliable processes as the alternative of demanding, wasteful, toxic or hazardous methods is pointing towards a new paradigm in organic synthesis. Enabling technologies, like flow chemistry, especially continuous flow heterogeneous catalysis makes green and sustainable chemical procedures available.[1,2]

In this application note we summarize the preparation of biaryls in a safe, fast and environmentally friendly continuous flow protocol (**Scheme 1**) of Luque, Feiz and their coworkers, where our H-Cube Mini™ reactor[3] has been applied in a non-traditional way.[4]

Basically, this type of reactions needs heterogeneous catalysis or harsh conditions and, in many cases, long reaction times.[5] In the presented research, the aqueous homo-coupling of aryl halides was carried out at room temperature with short residence time and quantitative yields. The longevity and reusability of the prefilled catalyst cartridges (CatCarts™) were also investigated.[4]



Scheme 1. The reductive homo-coupling of aryl halides

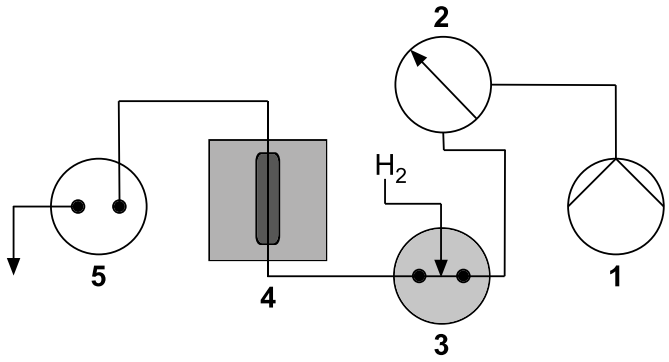


Figure 1. Schematic view of the applied instrument: 1. HPLC pump; 2. Pressure sensor; 3. Gas-liquid mixer; 4. Heater block (with CatCart™); 5. Pressure regulator

Instrumentation

The reductive homo-coupling of various aryl halides was implemented utilizing ThalesNano's H-Cube Mini™ system[3], which consists of the following parts (**Figure 1**): (1) HPLC pump (to ensure the continuous flow of the solutions), (2) inlet pressure sensor, (3) gas-liquid mixer (for the mixing of the *in situ* generated hydrogen gas with the liquid flow), (4) heater block (with the prefilled CatCart™), (5) pressure regulator.

Risk assessment and hazards: Always use the system in a well ventilated fume hood to prevent the inhalation of solvent vapors. Avoid contact with the heated parts.

Experimental

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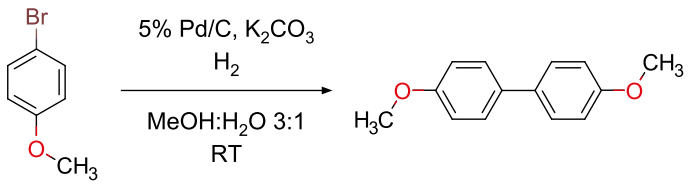

1 **2**

4,4′-Dimethoxybiphenyl (2): 4-bromoanisole (**1**, 0.1 M) and potassium carbonate (0.25 M) were dissolved in a 3:1 mixture of methanol and water. The following parameters were set on the H-Cube Mini™: 0.3 mLmin^{-1} liquid flow rate, 25°C and 2 bar (H_2). After the system reached the stable state, the solution was pumped through a fresh Pd-containing 30 mm CatCart™. The crude reaction mixture was collected and concentrated. The identity of the product was confirmed by GC-MS.

Results and discussion

The homo-coupling of phenyl iodide in the presence of potassium carbonate was selected as a model reaction. To ensure the optimal solubility of all reagents and products, a 3:1 mixture of methanol and water was used as solvent. First, 10% Pd/C and 10% Pd/PBSAC CatCarts™ were tested at 90°C temperature, 8 bar hydrogen pressure, and 0.3 $mLmin^{-1}$ flow rate. Quantitative conversion to the desired biphenyl was achievable within approximately 40 seconds residence time (calculated with 208 µl dead volume for a filled CatCart™). For comparison, catalyst-free blank reactions were performed with inert CatCart™ filled with quartz sand: no conversion of the starting material was observed. Reactions without hydrogen were also unsuccessful. The decrease of the catalyst amount (5% Pd/C) did not have any significant impact on the conversion. The temperature could be reduced to 25°C and the pressure to 2 bar while the conversion remained above 90%.

For the investigation of catalyst leaching, a number of samples from the collected reaction mixtures were analysed by ICP-MS. Negligible leaching (less than 5 ppm Pd) was detected in almost every case. A notable amount of palladium was found only in the final mixture after 20 hours of continuous run (above 100 ppm) at room temperature. The examination of the Pd content in the CatCarts™ confirmed these results: only after the long experiment was any significant decrease observed (from 4.93 wt.% to 4.49 wt.%). The reusability of the CatCarts™ was also investigated: after ten consecutive reactions (5% Pd/C CatCart™, 20 hours of discontinuous run), almost no palladium leaching was observed, while the activity and selectivity of the catalyst remained unaffected.

The optimized reaction conditions were applicable to the homo-coupling of bromobenzene, 4-bromoanisole and 4-chlorobenzaldehyde. High selectivity was observed in all cases, no hydrodehalogenation compounds or major byproducts were formed.

The proposed mechanism of the reactions assumes the coordination of two aryl halides to the palladium which results in the formation of Ar-Pd-Ar and PdX_2 compounds. The biaryl unit is generated from the Ar-Pd-Ar species in the reaction with hydrogen, while Pd(0) is formed simultaneously. PdX_2 may also react with hydrogen to yield Pd(0) (**Figure 2.**).[4-6]

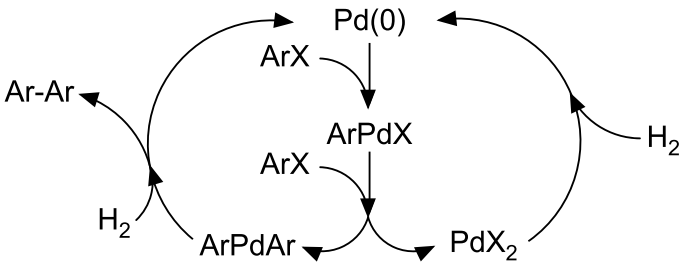

Figure 2. The proposed mechanism for the Ullmann-type reductive homo-coupling reaction[4-6]

Conclusion

Various biaryls were synthesized in the Ullmann-type reductive homo-coupling of aryl halides in a simple and efficient continuous flow method under mild conditions. The longevity and stability of the tested commercially available catalysts were investigated: all CatCarts™ proved to be stable under the investigated reaction conditions, without any significant loss of activity or Pd leaching, and throughout a series of experiments. In summary, the reported reductive homo-coupling process may find extensive use in the fine and medicinal chemistry area, showing the H-Cube Mini™ as a simple, and practical device to carry out such reactions.

Acknowledgement

ThalesNano would like to thank the authors for their contribution.

Keywords

Reductive homo-coupling, Ullmann-type reaction, Pd-catalysis, H-Cube Mini, University of Cordoba, ThalesNano

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