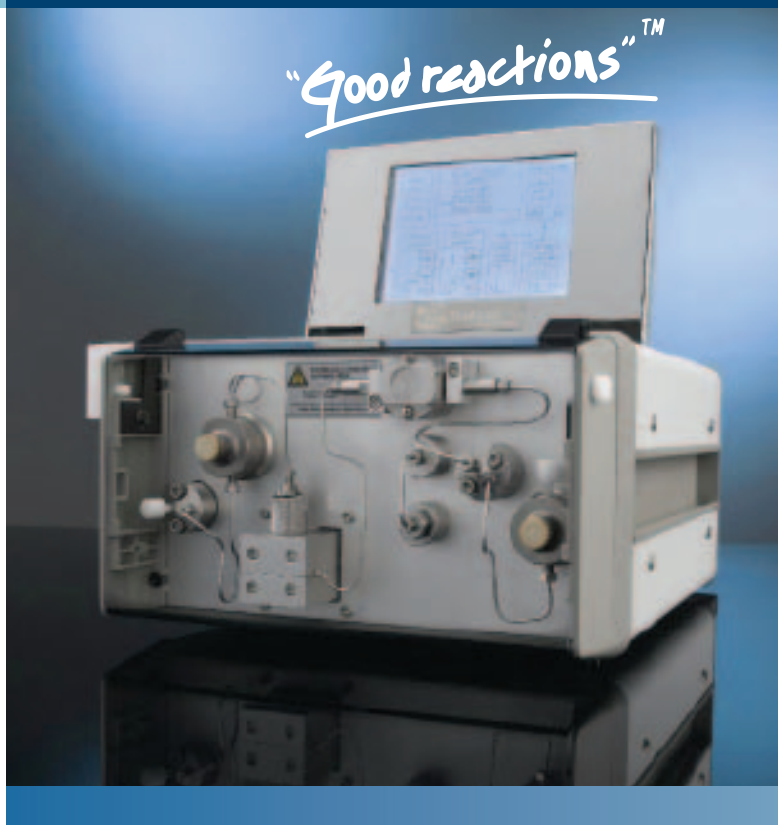
THALESNano



Sonogashira and Suzuki Reactions Using H-Cube® Continuous Flow Reactor

ThalesNano's H-Cube® is mainly used to perform hydrogenation reactions, however it can also perform reactions in the absence of hydrogen. When utilizing the "No H2" mode, the H-Cube® acts like a general flow reactor capable of performing other heterogeneous reactions at temperatures and pressures up to 100°C and 100 bar respectively.

INTRODUCTION

The Sonogashira reaction (Figure 1.) is a powerful tool for the synthesis of various aryl alkynes, although the used copper salts, toxic phosphine ligands, amines and homogenous Pd catalysts are generally difficult to remove or recycle. The use of polymer supported palladium catalysts combined with recent synthetic methods, which do not require the addition of copper, offer up the potential to solve these difficulties.

Another method of performing a C-C coupling is the Suzuki reaction (Figure 3.). It is the reaction between an organoboron compound and an electrophile (aryl halide), typically catalyzed using palladium. For the coupling, the presence of a base is necessary to activate the boronic acid. These C-C coupling reaction types generally produce some side-products in conjunction with longer reaction times.

At ThalesNano we have performed the above reactions on the H-Cube® using solid-supported Pd catalysts in the presence of sodium hydroxide as base.

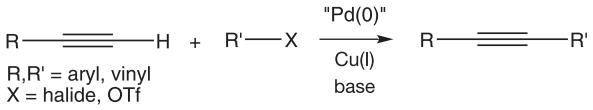


Figure 1. General Sonogashira reaction

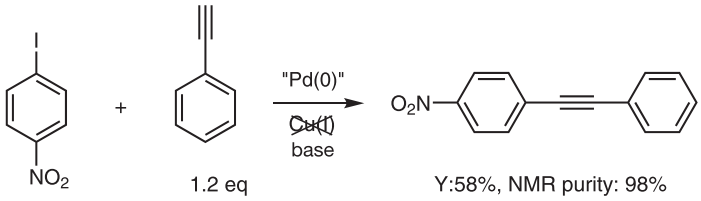


Figure 2. Specific Sonogashira reaction

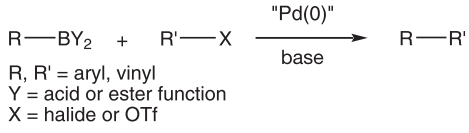


Figure 3. General Suzuki reaction

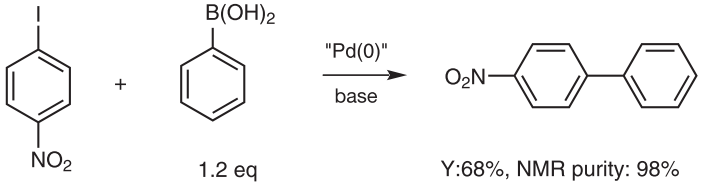


Figure 4. Specific Suzuki reaction

STANDARD EXPERIMENTAL PROTOCOL

Both reactions (Figure 2. and 4.) were carried out using a stock 0.02 M solution of 1-iodo-4-nitrobenzene using methanol as solvent in the presence of 3 eq. NaOH, previously dissolved in a small amount of water. The mixture of reactants also contained 1.2 equ. phenylacetyl and phenlyboronic acid for the Sonogashira and Suzuki reactions respectively. First, solvent was pumped continuously through the H-Cube® for 10 minutes to prepare the CatCarts®, then, after setting the desired reaction parameters, the solution of reactants was passed through the H-Cube® in "No H2" mode followed by a washing step with pure solvent. Finally, the collected product solution was evaporated and purified on silica gel. The pure products were analysed by ^{1}H-NMR and HPLC-MS.

EXPERIMENTAL – SONOGASHIRA REACTION

The mixture of 1-iodo-4-nitrobenzene, 1.2 equ phenylacetyl in methanol and base, previously dissolved in a small amount of water, were pumped into the H-Cube® at a temperature of 100°C, flow rate of 0.2 mL/min and pressure of 20 bar. The catalyst used was FibreCat® 1007 packed into a CatCart®. The product was isolated from 25 mL product solution and analyzed by HPLC-MS and NMR.

RESULT - SONOGASHIRA REACTION

After evaporation of solvent and chromatography on silica gel, the product was obtained with a yield of 68% and NMR purity of 98%.

EXPERIMENTAL – SUZUKI REACTION

The mixture of 1-iodo-4-nitrobenzene, 1.2 equ. phenylboronic acid in methanol and base, previously dissolved in a small amount of water, was pumped into the H-Cube® using a temperature of 50°C, flow rate of 0.2 mL/min and pressure of 20 bar.

The catalyst used was FibreCat® 1001 packed into a CatCart®. The product was isolated from 25 mL product solution and analyzed by HPLC-MS and NMR.

RESULT – SUZUKI REACTION

After evaporation of solvent and chromatography on silica gel, the product was obtained with a yield of 58% and NMR purity of 98%.

CONCLUSION

Utilizing the H-Cube® reactor, a Sonogashira and Suzuki reaction were performed in flow to give quantitative conversion with acceptable yields for both reactions. Both yields were achieved after column chromatography using a mixture of hexane and ethyl acetate as eluent. The polymer supported catalyst remained in the CatCart® during the whole reaction and could be used for other experiments. The results demonstrate how the H-Cube® may be utilized for non-hydrogenation reactions further expanding its capabilities.

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