



Carbon-Carbon Coupling Reactions Using the X-Cube™ continuous-flow reactor.

The X-Cube™ is a continuous flow reactor, capable of performing chemical reaction under inert conditions, temperatures up to 200°C and pressures up to 150 bars. This paper shows that carbon-carbon forming reactions are far more efficient on the X-Cube™ in comparison to batch mode.

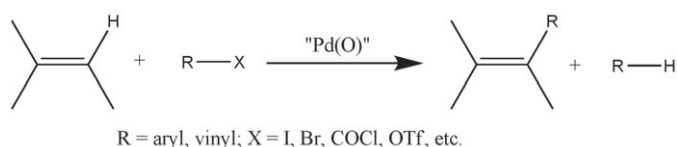


Figure 1. General Heck reaction

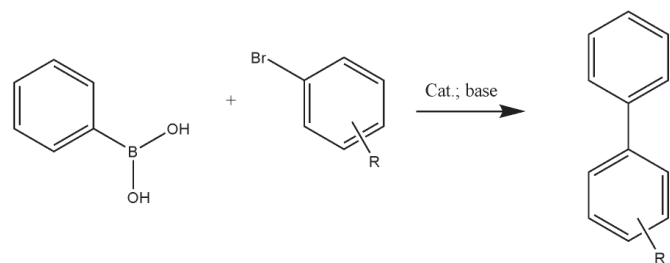


Figure 3. General Suzuki reaction

More than two decades ago, Mizoroki and Heck discovered the palladium-catalyzed arylation and vinylation of olefins independently (Figure 1.). These reactions were carried out in the presence of Pd(OAc)₂, TPP and a base. The reactions took hours or days, even at elevated temperatures. Another widely used C-C bond forming reaction is the palladium catalyzed Suzuki coupling between boronic acids and aryl halides in the presence of

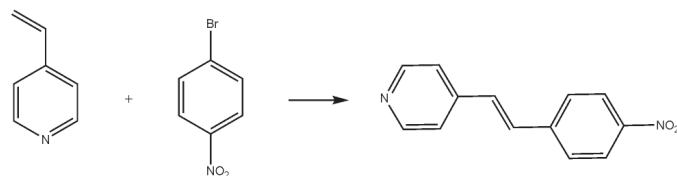


Figure 2. Specific Heck reaction

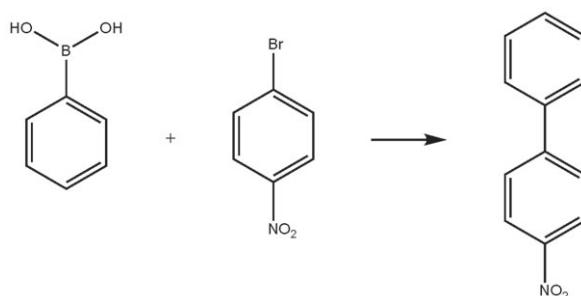


Figure 4. Specific Suzuki reaction

a base by to form biaryls. The Heck and Suzuki reactions are widely used in synthetic laboratories these days. However, high temperatures and long reaction times lead to the formation of undesired side products. The following page outlines the optimised experimental protocol used on the X-Cube™ to perform Suzuki and Heck C-C coupling reactions.



STANDARD EXPERIMENTAL PROTOCOL

The reaction conditions, pressure, temperature and flow rate were set using the touch screen of the X-Cube™. The reaction solvent was allowed to flow through the X-Cube™ system for 10 minutes to equilibrate the filled CatCart® with heterogeneous or immobilized-homogeneous reagent/catalyst. A sample of the starting materials in the reaction solvent was pumped through the X-Cube™, the total amount of product mixture was collected to sample vial and the column was washed with the eluent to remove any material still absorbed to the CatCart® the product mixture was analyzed by HPLC-MS and NMR.

1. EXPERIMENTAL - HECK REACTION

The starting solution containing 4-ethenylpyridine (1.0 mmol), 4-bromonitrobenzene (1.0 mmol) and tetrabutylammonium fluoride trihydrate in THF (3 mmol) was dissolved in isopropyl alcohol which was the eluent also under N₂ atmosphere. This mixture was passed through two CatCarts® prepacked with FibreCat™ 1001 at 0.3 mL/min, 1bar and 80°C. The reaction was carried out for 2.1 h and the product was analyzed by LCMS and NMR.

RESULT - HECK REACTION

The crude yield was 60% with conversion rate of 100%. After HPLC-MS purification the isolated yield was to 52% and the ¹H-NMR showed 95% purity of *E*-isomer.

BATCH REACTION

A mixture of 4-ethenylpyridine (18.8 mmol), 4-bromonitrobenzene (15 mmol), palladium(II)acetate (0.15 mmol), triethylamine (18.8 mmol) and PPh₃ (0.3 mmol) was sealed in a Schlenk tube under N₂, and heated to 100°C for 3 days. After aqueous work-up and recrystalliation the product was analyzed by NMR and LCMS spectrometry.

RESULT - BATCH REACTION

The yield of purified product was 70% and NMR and MS measurements confirmed the structure of the desired product.

2. EXPERIMENTAL - SUZUKI REACTION

A mixture of phenylboronic acid (1 mmol), 4-bromonitrobenzene (1 mmol) and 1M tetrabutylammonium in THF (3 mmol) was passed through two CatCarts® filled with FibreCat™ 1001 in one flow at 0.1 mL/min pressure of 1 bar and temperature of 80°C. After 2.1 h reaction time product was analyzed by LCMS and NMR spectroscopy.

RESULT - SUZUKI REACTION

Analysis of product gave 62% of purity with 100% conversion rate and isolated yield of 73%.

COMPARISON: FLOW AND BATCH MODE

Analysis of catalyst TOF (Turn Over Frequency) was also measured and found to be 0.95 h⁻¹ in batch and 1.98 h⁻¹ in flow technology. This further emphasises the observed accelerated reaction times in flow mode compared to the batch mode.

CONCLUSION

These reactions demonstrate that the X-Cube™ can be used to perform C-C coupling reactions with high conversion rates, purity and yields. Furthermore, the reaction times were dramatically reduced in comparison to the commercial batch mode.

REFERENCES

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