Rapid Catalyst Screening for Sonogashira Coupling Using H-Cube® Continuous Flow Reactor

ThalesNano's H-Cube® can be used to perform reactions other than hydrogenation by utilizing "No H2" mode. In "No H2" mode, the H-Cube® reactor can perform reactions at temperatures and pressures up to 100 °C and 100 bar, respectively in the absence of a reagent gas. In this application note we will be focusing on Sonogashira chemistry.

INTRODUCTION

Pd-catalyzed Sonogashira coupling is currently the most practical method for synthesizing aryl-(vinyl) acetylenes from the corresponding terminal alkynes and arylhalides. Copper-free modification suppresses the dimerization of the alkynes (Figure 1). Several homogeneous as well as immobilized catalysts were developed over the years. To select the most appropriate catalyst for a particular coupling reaction often requires time and resources. With their ability to change reaction conditions "on the fly", continuous flow devices provide a convenient tool for rapid catalyst and parameter screening.

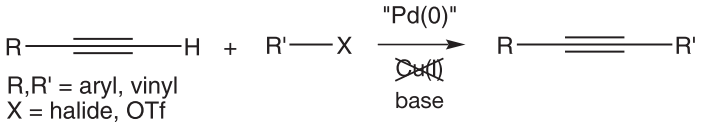


Figure 1. Copper-free Sonogashira reaction

To facilitate the reaction, we applied immobilized catalysts in a fixed-bed flow reactor, the H-Cube®. The H-Cube® system can be utilized for many heterogeneous catalytic reactions including cross coupling using immobilized transition metal catalysts in prepacked-columns „catalyst cartridges" (CatCart®s). For mg to g scale operation, 70 mm standard catalyst cartridges are typically applied and we have chosen this size for our current study. The void volume for the 70 mm cartridges is between 0.5-0.8 mL (for 10% Pd/C: 0.669 mL), therefore the estimated residence time at a 0.1 mL/min flow rate is between 5-8 min. We tested 3 polymer-bound catalysts and in addition 10% Pd/C (Table 1.).

Catalyst	Source	Composition	Weight in 70 mm column [g]	Pd content [mmol/g]	Catalyst load in CatCart® [mmol/CatCart®]
$PdCl_2(PPh_3)_2$, DVB	Sigma Aldrich	Dichlorobis(triphenylphosphine)palladium(II) 2% cross-linked with divinylbenzene	0.551	1.0	0.551
FibreCat® 1001	Johnson Matthey	Palladium(II)Acetate-Triphenylphosphine polyethylene fibres	0.242	0.47	0.114
FibreCat® 1007	Johnson Matthey	Palladium(II)Acetate-Dicyclohexyl-phenyl-phosphine polyethylene fibres	0.351	0.47	0.165
10% Pd/C	Szilor llc	10% Palladium on carbon	0.275	0.94	0.258

Table 1. Description and properties of tested catalysts

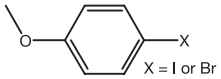
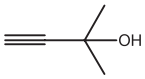
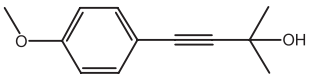
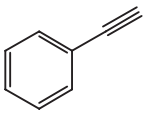
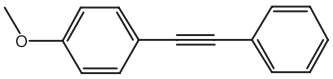
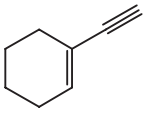
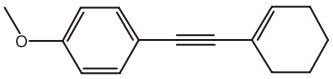
Reactants/Product	 X = I or Br
	
	
	

Table 2: List of reacted aromatic halides and alkynes

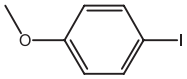
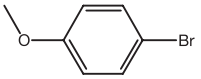
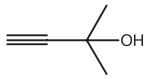
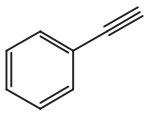
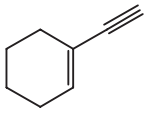
Reactants/Results		
	FibreCat® 1007 Conv.: 92%, Sel.: 66% $PdCl_2(PPh_3)_2$ DVB Conv.: 95%, Sel.: 51%	$PdCl_2(PPh_3)_2$ DVB Conv.: 89%, Sel.: 99%
	FibreCat® 1007 Conv.: ~99%, Sel.: 99% $PdCl_2(PPh_3)_2$ DVB Conv.: 99%, Sel.: 85%	$PdCl_2(PPh_3)_2$ DVB Conv.: 42%, Sel.: 52%
	FibreCat® 1001 Conv.: ~97%, Sel.: 97% $PdCl_2(PPh_3)_2$ DVB Conv.: 99%, Sel.: 85%	FibreCat® 1001 Conv.: 44%, Sel.: 84% $PdCl_2(PPh_3)_2$ DVB Conv.: 50%, Sel.: 47%

Table 3: Best results obtained

GENERAL EXPERIMENTAL PROTOCOL

A methanolic solution was prepared containing 0.05 M (1 eq.) of aromatic halide, 1.2 eq. of alkyne (Table 2) and 3 eq. of sodium hydroxide. The H-Cube® system was flushed with methanol for 10 min in order to wet the catalyst. After such conditioning the reaction parameters (100 ºC, 100 bar) were set and the previously prepared solution was pumped through the H-Cube® system in „No H2" mode at 0.1 mL/min flow rate. The solution containing the product was then collected.

Isolation of the product:

The methanolic solution was diluted with dichloromethane and washed with water, then brine, and finally dried over $MgSO_4$. The product purity was analyzed by LC-MS. The crude product was then purified with column chromatography (Eluent: hexane:EtOAc = 20:1). For 4-iodo-anisole, $PdCl_2(PPh_3)_2$ DVB showed higher conversion, but LC-MS showed a significant amount of unknown impurities. The selectivity was therefore lower (51 %). However, when 4-bromo-anisole was applied as the aromatic halide coupling reagent, $PdCl_2(PPh_3)_2$ DVB gave superior results in both conversion and selectivity. For phenyl-acetylene and ethynyl-cyclohexene, the coupling of the bromo species resulted in low conversion as well as selectivity for most of the polymer-bound catalysts, but FibreCat® 1001 showed relatively good selectivity for ethynyl-cyclohexene. This study confirms that the performance of the catalysts is strongly dependent on the nature of the reactants. 10% Pd/C was also screened, but a reaction was only achieved with the rather reactive 4-iodo-anisole (highest conversion: 53%).

RESULTS

The study's main aim is demonstrating the potential of flow technology for rapid catalyst screening. Table 3. shows the best performing catalysts and their results for each reaction. For coupling the alkynes with 4-iodo-anisole the FibreCat® type catalysts showed the highest performance if both the conversion and the selectivity were taken into consideration.

CONCLUSION

Each catalyst evaluating reaction lasted approx. 10 min (plus another 10 min for washing the system). To complete a reaction matrix of 24 reactions (6 reactions x 4 catalysts) it requires only 8 hours. Performing the HPLC evaluation can be done in parallel and the whole process can be automated using the CatCart Changer™ and H-Cube Autosampler™ available from ThalesNano.

LEGAL INFORMATION

ThalesNano Nanotechnology Inc.
Zahony u. 7.
H-1031 Budapest
Hungary
Tel.: +36 1 880 8500
Fax.: +36 1 880 8501
E-mail: sales@thalesnano.com

US Office
50 S. Penn St. Suite B-2
Hatboro
PA. 19040
USA
Phone: +1 732 274 3388
E-mail: USAsales@thalesnano.com

www.thalesnano.com