THALESNano

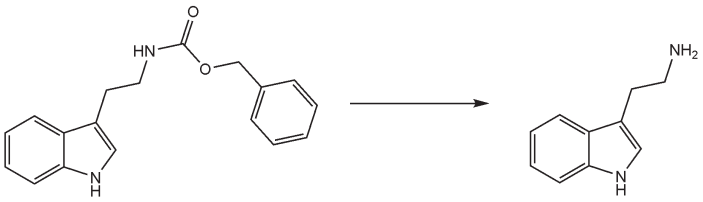
Fast Optimization Of Continuous Flow Hydrogenation Reactions Using CatCart Changer™

To demonstrate the benefits of the CatCart Changer™ system two different reactions are optimized in terms of catalyst screening and reaction temperature. The two select reactions were the deprotection of cbz-tryptamine and the nitro reduction of 3-chloro-7-nitroindole.

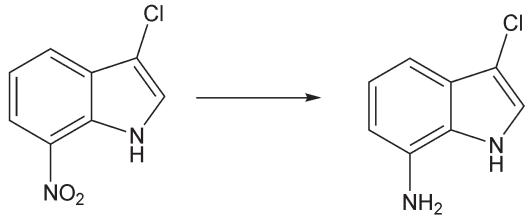
INTRODUCTION

The optimization of reactions is a timeconsuming process. Particularly when there are many different parameters to optimize. When hydrogenation is performed in batch reactors, if different temperatures, catalysts, or pressures need to be validated a separate reaction must be performed for each set of conditions. With the H-Cube® and CatCart Changer™ system, injections can be made at different temperatures and pressures on different catalysts without having to perform separate reactions. To demonstrate the ability of the CatCart Changer™ to validate reactions quickly, two reactions were performed. 6 catalysts were screened for the deprotection cbz-tryptamine and the reaction temperature was validated for the selective reduction of 3-chloro-7-nitroindole without removing the chlorine.

Catalyst screening:



Optimization of the temperature:



CatCart Changer™ DESCRIPTION

The CatCart Changer™ is made of 6 reactions zones where catalysts can be reacted at temperatures and pressures. A valve, controlled by software, changes the direction of the flow to any of the 6 zones. Compound may be injected at different temperatures and pressures on 6 different catalysts. A fraction is collected for each set of parameters.

CATALYST SCREENING EXPERIMENT

6 different CatCarts® were placed in the CatCart Changer™ holders: 5% Pd/C, 5% Rh/C, 5% Re/C, 5% Ru/C, 20% $Pd(OH)_2$/C and 10% Pt/C. The catalysts were selected with to represent a full range of catalysts with differing abilities. The cbz protecting group is widely used for protecting amines, and is essential in peptide synthesis. Cbz deprotection is usually carried out via hydrogenation at elevated temperature with the protecting group decomposing to CO_2 and toluene. The deprotection can performed using many different heterogeneous catalysts.

EXPERIMENTAL PROTOCOL

The 6 different CatCarts® were placed in the CatCart Changer™'s holders. Solvent was run through each of the CatCarts® to remove the air from the system. Previously validated set

conditions of 1 mL/min, 70°C, and 40 bars were used for all 6 catalysts. The valve was set to CatCart® 1. The conditions were equilibrated using pure ethanol. Once the hydrogen was produced under the desired conditions a solution of 0,05 M cbz-tryptamine solution in EtOH was passed through the first CatCart®. An analytical sample was taken after 5 minutes. While this reaction was progressing CatCart® 2 was being heated to the set temperature independently. The valve then changed to position 2 without stopping the flow of starting material or hydrogen generation. After switching between the 2 positions an amount of 3 mL was collected as waste, which is the equivalent to the dead volume of the system. This was to make sure the catalyst systems did not mix. After an interval period of five minutes a sample was taken from CatCart® 2. This process continued until samples were taken from all 6 CatCarts®.

RESULTS

The results are shown below in Table 1. The three recommended catalysts for deprotection gave conversion rates of 93-100%. The other three catalysts gave poor results with conversions of 4-9%. The full time for optimzation of 6 different catalysts took approximately 2 hours.

Catalyst	Recommended	Conv. / %	Sel. / %
5% Pd/C	Yes	100	85
5% Rh/C	Yes	64	93
5% Re/C	No	4	0
5% Ru/C	No	9	0
20% $Pd(OH)_2$/C	Yes	98	96
10% Pt/C	No	4	0

Table 1.:
Result of catalyst screening using CatCart Changer™

OPTIMIZATION OF THE TEMPERATURE

The CatCart® holders in the CatCart Changer™ can heat independently, therefore the reactor can switch between systems without pausing for heating or cooling.

EXPERIMENTAL PROTOCOL

0,01 M 3-chloro-7-nitroindole was dissolved in ethyl acetate and passed through four 5% Ru/C filled CatCarts® at 70 bars and 1 mL/min. Each of the catalysts were set to a different temperature, 25°C, 50°C, 75°C, and 100°C respectively, to determine the best temperature for the nitro reduction without dehalogenation. After each reaction zone change, a 5 mL sample was discarded. After a futher 5 minutes an analytical sample was taken and the conversion recorded.

RESULTS

Analytical samples were measured by HPLC-MS and ^{1}H-NMR and displayed in Table 2. The temperature of 75 °C afforded complete conversion to the desired product with ^{1}H-NMR purity of 97%. The time of the total experiment was 1 hour.

T / °C	SM Conv. / %	Desired Prod. / %
25	18	100
50	26	100
75	100	76
100	100	0

Table 2.:
Effect of temperature to the conversion and the selectivity

CONCLUSION

The CatCart Changer™ can be utilized for fast optimization. In 2 hours, 6 different catalysts or different temperatures can be validated. In a standard batch reactor, a separate reaction would have to be performed for each set of conditions increasing the research time considerably to days. The system may be combined with an autosampler for fully automated optimzation.

Reference:

Jones, R. V., Godorhazy, L., Varga, N., Szalay, D., Urge, L., Darvas, F: Continuous-flow High Pressure Hydrogenation Reactor for Optimization and High-Throughput Synthesis. *J. Combi. Chem.* **2006,** 8(1), 110-116.

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