Deprotection Reactions Using the H-Cube® Advance Continuous Flow Reactor

INTRODUCTION

Protecting groups play a central role in modern organic synthesis. The benzyl groups and benzyl carbamate or Cbz groups are some of the most commonly used protecting groups and play a central role in the protection of alcohols, carboxylic acids, and amines. The benzyl and benzyl carbamate groups are removed using **catalytic hydrogenation** using elevated temperature. The **H-Cube® Advance** is able to remove benzyl groups from amines, acids, or alcohols very efficiently in one pass through a **10% Pd/C CatCart®**. This application note gives examples of deprotection reactions performed on the H-Cube® Advance reactor.

O-BENZYL DEPROTECTION

Parameter Optimization

To find the optimal parameters of catalytic hydrogenolysis, the *O*-debenzylation of *O*-benzyl protected *N*-Boctyrosine *(Figure 1.)* was investigated by Knudsen et al[1]. A series of experiments over **10% Pd/C** catalyst in **EtOH:EtOAc** (1:1) solvent were performed to probe the effects of flow rate, temperature, and concentration using an automated hydrogenation platform.

Results showed a faster catalyst deactivation rate with increasing concentration and flow rate, but at higher temperature, they found dramatically increased conversion rates. At room temperature, the conversion rate was half of that observed at 60 °C.

100% conversion was reached, when the concentration of reactant solution was **0.1 M**, the applied temperature was **60 °C**, and the flow rate was **1 mL/min**.

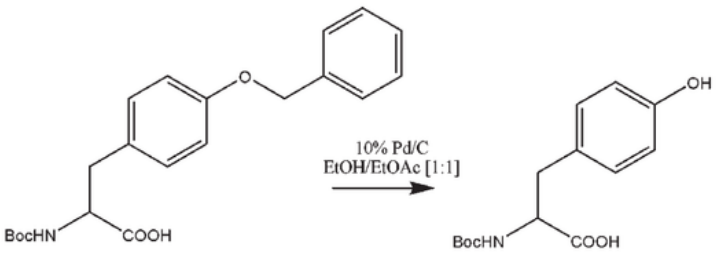

Figure 1: *Debenzylation of O-benzyl protected N-Boc-tyrosine*

Catalyst Reactivation

As the catalyst can be poisoned and deactivated over a long reaction time, **catalyst reactivation** is a key factor in heterogeneous catalysis. To increase the catalyst lifetime, the following reactions were performed. Equal amount of reactant was introduced to the system in two different ways: **continuously** and through **repeated injections** of **small amounts**. With the injection method, there was a short period of time between each injection where the solvent regenerated the catalyst by washing off any adsorbed material. This short washing period generated higher conversion rates compared to continuous pumping of the material through the catalyst.

N-CBZ DEPROTECTION

Reaction Optimization and Library Synthesis

An ***N*-deprotection** reaction was also optimized by Knudsen and co-workers[1] with the reaction shown in *Figure 2*. After finding the optimized reaction conditions, such as elevated temperature of **80 °C**, pressure of **1 bar**, and solvent concentration of **0.05 M** using **10% Pd/C** as catalyst, a small library of ***N*-protected compounds**, including **dipeptide** and **amino acid** derivates, was successfully hydrogenated. As seen in the previous reaction series, the temperature also had a significant effect on the conversion rate. The observed yield of isolated products were high in each case and are displayed in *Table 1*.

When **Cbz-(OBn)Tyr-OMe** (*Table 1, line 4.*) was introduced to the automated H-Cube® Advance system, **selective Cbz deprotection** was observed and the desired product was isolated in 83% yield.

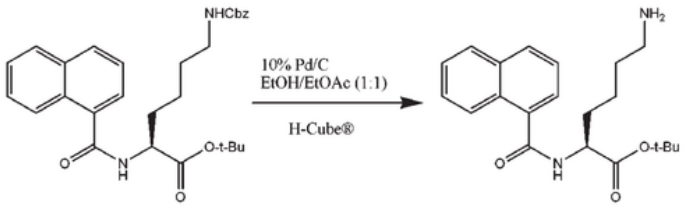

Figure 2: *Deprotection of ε-[N-Cbz] lysine tert-butyl ester*

Substrate	Conversion (%)	Yield (%)
Cbz-Pro-OMe	99	99
Cbz-Piperazine	99	80
Cbz-Asp(OMe)-OMe	99	77
Cbz-(OBn)Tyr-OMe	97	83
Cbz-Ser-OMe	98	82
Boc-(N-Cbz)-Lys-O(Naph)	95	86
Cbz-Thr-Tyr(O-t-Bu)-O-t-Bu	99	96
Cbz-Pro-tetrazole	99	99

Table 1: *Deprotection of eight N-Cbz protected compounds*

Part of New Synthesis Pathway

A practical and safe synthesis of **(S)-pyrrolidine-2-yl1H-tetrazole** was developed by Franckevicius and coworkers[2] to prepare a catalyst which can be used in Mannich and aldol reactions leading to high yields. The synthetic steps **eliminate** the generation of **hazardous materials** such as **ammonium azide** and the use of **nonvolatile solvent**.

In the first synthetic step a protected pyrrolidine derivate was synthesized, which was subsequently transformed to the **tetrazole derivate** of the **Cbz protected pyrrolidine** with **sodium azide**. Overall **yield** was **92%**.

In the last step, **Cbz deprotection** (*Figure 3.*) was achieved by the H-Cube® Advance using a volatile solution mixture of **EtOAc:EtOH:AcOH = 1:1:1**. The method dramatically reduces the reaction time. In **batch** when **9:1 acetic acid:water solvent** mixture was used, the reaction time and time-consuming work-up extended the total reaction time to **3 days**. While in continuous **flow**, 3 g of desired compound was synthesized in **3.5 hours**.

The reaction seen in *Figure 4.* was performed using full hydrogen mode at a flow rate of **1 mL/min**, temperature of **80 °C**, and a starting material concentration of **0.05 M**. **10% Pd/C** was used as catalyst. Working-up the reaction was carried out by simple evaporation of the solvent.

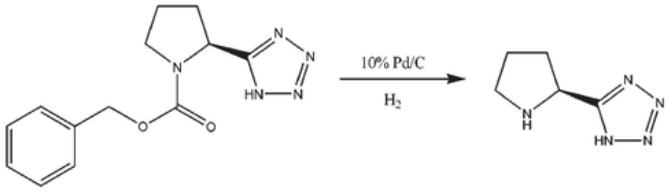

Figure 3: *Deprotection step of (S)-5-pyrrolidin-2-yl-1H-tetrazole synthesis*

Yield of the deprotection was **98%** and resulted in an **overall yield** of **90%** for the total synthesis.

O-DEBENZYLATION

Part of New Reaction Pathway

A debenzylation step was performed by Desai and Kappe to produce **dihydropyrimidine** (DHPM) **C5 carboxylic acids**[3]. The synthesis of the acids can be readily achieved by **hydrogenolysis** of the corresponding **benzyl esters**. The previously reported batch reaction resulted in high yields and used an external hydrogen gas source, while when the **H-Cube® Advance** was used with **10% Pd/C** catalyst, there was no need for a gas cylinder. The reaction scheme and the isolated yield values obtained are seen in *Figure 4.* and *Table 2.* Under these circumstances in continuous flow („CF") mode, **80 - 95% isolated yields** of the DHPM acids were obtained.

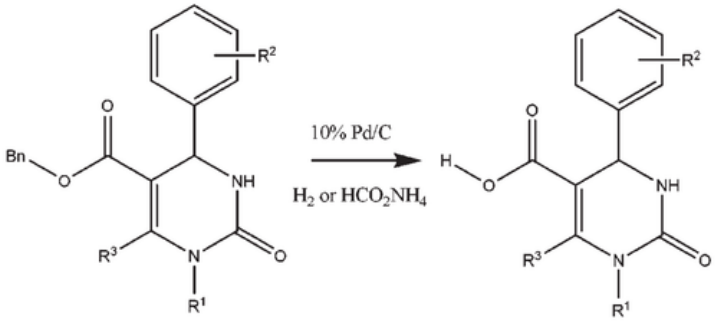

Figure 4: *Hydrogenation of DHPM C5 Benzyl Esters*

R1	R2	R3	Yield (rt, %)	Yield (MW, %)	Yield (CF, %)
H	H	Me	66	62	95
H	H	Ph	65	60	80
Me	H	Me	57	55	85
H	4-Me	Me	56	53	85

Table 2: *Isolated yield values of hydrogenation of DHPM C5 benzyl esters*

Yields were also obtained from the deprotection reaction of DHPM esters under other conditions. Namely, **room temperature catalytic transfer hydrogenation** („rt") in ammonium formate, and **microwave-assisted transfer hydrogenation** („MW") in ammonium formate[4].

When room temperature hydrogenation was applied, reactions took **8 - 10 h reaction time** and only **56 - 66% yields** were obtained. The **microwave-assisted method** did not result in significant enhancement of the yields. The obtained values were between **53 - 62%**, but the reaction times were reduced to **minutes**.

Compared to the batch and microwave techniques, **H-Cube® Advance** gave yields between **80 - 95%**. The major advantage as they emphasized that these excellent yields were obtained after a **simple evaporation**, thus, this easy work-up makes this method an attractive solution for automated library generation.

MULTIDEBENZYLATION AND DOUBLE BOND REDUCTION

A **debenzylation** in conjunction with a **double bond reduction** reaction plays an important role in the **synthesis** of **polyhydroxylated oxamacrolides**, as reported by Matos and Murphy[5] in a multi-step synthesis.

In the previous step, before the reduction, a mixture of **macrolactones** was produced, separated, and then introduced into the H-Cube® Advance. **Deprotection** of the **four benzyl groups** and the **saturation** of the **double bond** (*Figure 5.*) was carried out at **80 bar** pressure, **60 °C** reaction temperature and a flow rate of **1 mL/min** over **5% Pd/C** catalyst in **ethanol**. In the first experiment, lower yield was observed due to the low solubility of the product in ethanol. The structure of colorless oil was confirmed by **X-ray crystal structure**.

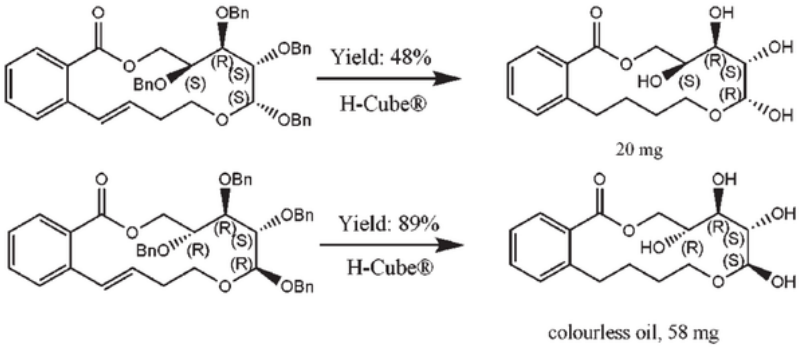

Figure 5: *Synthesis of polyhydroxylated oxamacrolides*

CONCLUSION

H-Cube® Advance continuous flow reactor is proven to be an ideal tool for performing **deprotection catalytic hydrogenation**. The **excellent yields** in all cases and the **easy handling** of **catalysts** suggest this method to be a **fast**, **efficient**, and **safe** way to perform **benzyl deprotection** compared to batch and microwave methods.

REFERENCES

[1] K.R. Knudsen, J. Holden, S.V. Ley, M. Ladlow; *Adv. Synth. Catal.*; **2007**; 349; 535-538
[2] F. Franckevicius, K.R. Knudsen, M. Ladlow, D.A Longbottom, S.V. Ley; *Synlett*; **2006**; 6; 889-892
[3] B. Desai, C.O. Kappe; *J. Comb. Chem.*; **2005**; 7; 641-643
[4] B. Desai, D. Dallinger, C.O. Kappe; *Tetrahedron.*; **2006**; 62; 4651-4664
[5] M-C. Mathos, P.V. Murphy; *J. Org. Chem.*; **2007**; 72; 1803-1806

For more information, please visit www.thalesnano.com

ThalesNano Inc.
Záhony utca 7.
H-1031 Budapest | Hungary
Email: sales@thalesnano.com
www.thalesnano.com

US Office
50 S. Penn St. Suite B-2
Hatboro PA. 19040 USA
Phone: 215-534-3365
E-mail: USAsales@thalesnano.com