Rapid Oxidation and Carbonylation in the H-Cube® Advance Continuous Flow Reactor

INTRODUCTION

Continuous flow tri-phasic, gas-liquid-solid reactions employing immobilized metal catalysts have increased significantly over the past few years. For heterogeneous catalytic gas-liquid reactions, the primary advantages of continuous flow technologies result from the **high specific interfacial area**. The power of this technique is particularly obvious in **gas-liquid-solid triphasic reactions** involving **various gases**, a substrate dissolved in a solvent, and an immobilized solid precious metal catalyst. Owing to the **large interfacial areas** and the **short path** required for **molecular diffusion** in the very **narrow microchannel space**, very efficient gas-liquid-solid interaction occurs.

In microreactors, reactions could take place **in minutes** instead of hours, which is not attainable in normal batch systems. An additional advantage of flow reactors is that the small volume reduces the damage potential of explosions and therefore conforms to the **12th principle of green chemistry**. Another green advantage: using gaseous reagents over chemicals **reduces work-up** and **purification** [1].

GAS-LIQUID REACTIONS IN CONTINUOUS FLOW

Aside from in-situ generated hydrogen, the **H-Cube® Advance** flow reactor allows the use of **13 additional gases** (or any other gases with well-known thermokinetic properties) at up to **100 bar pressure** via the touchscreen interface. Reactions such as **carbonylation** or **oxidation** can be performed on the H-Cube® Advance at high pressures and in a user-friendly manner, offering a safe and efficient solution for a wide range of **heterogeneous syntheses**.

H_2 O_2 N_2 CO CO_2 Air Ar C_2H_4 C_2H_6 CH_4 He N_2O NO Syn

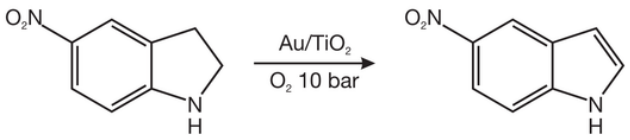
FEATURES OF THE H-CUBE® ADVANCE:

- Connect **13 gases** (or any other gases with well-known properties) directly via the external gas inlet
- Powerful: **0-150 °C temperature range**, up to **100 bar pressure**
- Fast: Reactions with gases can complete in **less than 10 minutes**
- Simple: easy control via the intuitive **touchscreen interface**
- Robust: Choose between **manual** or **automated operation mode**
- Modular: Compatible with ThalesNano's **FlowChemFleet™ platform**, and **third-party devices** (pumps, switch valves, analytical tools etc.)

OXIDATION OF INDOLINE TO INDOLE

The **H-Cube® Advance** was connected to an **oxygen cylinder**. The following reaction parameters were set before starting the experiment using **pure acetone**; temperature: **150 °C**; liquid flow rate: **0.5 mL/min**; gas flow rate: **50 mL/min**; catalyst applied: 70 x 4 mm **Au/TiO_2**; system pressure: **10 bar**. Reactant solution was prepared by dissolving **82 mg 5-nitroindoline** (0.5 mmol) in **10 mL acetone**.

After all parameters stabilized in the H-Cube® Advance, the inlet valve was switched from “Solvent” to “Reagent”, and the solution of 5-nitroindoline passed through the catalyst cartridge. Collection of the product started after switching the outlet valve to “Product”. When all the 10 mL reactant solution was used up, the inlet valve was switched back to Solvent. **Product collection** continued for an additional **10 min**, to recover the total amount of product from the catalyst cartridge. The product solution was analyzed by **GC-MS** without any further dilution.



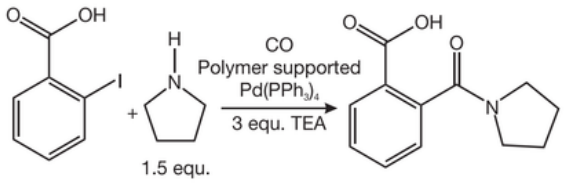
Sample (mL)	Liq. flow (mL/min)	O_2 flow (mL/min)	Temp. (°C)	Conversion (%)
1	1	10	75	8
1	1	10	150	95
8	1	10	150	50
1	**0.5**	**50**	**150**	**>98**
5	**0.5**	**50**	**150**	**>98**
5	**0.5**	**50**	**150**	**>98**

Table 1. *Conditions and results of oxidation reaction*

Batch reference: **Oxidative aromatization** using activated carbon molecular oxygen system [2]. Yield: 63 %, 120 °C, 9 h

AMINOCARBONYLATION OF IODO BENZOIC ACID WITH PYRROLIDINE

The H-Cube® Advance was coupled with a **carbon monoxide cylinder**. The following reaction parameters were set before starting the experiment using **pure acetone**; temperature: **100 °C**; liquid flow rate: **0.5 mL/min**; gas flow rate: **10, 30, 60 mL/min**; catalyst applied: 70 x 4 mm **$Pd(PPh_3)_4$ polymer-bound**; system pressure: **30 bar**. Reactant solution was prepared by dissolving **496 mg 2-iodo benzoic acid** (2 mmol), **213 mg pyrrolidine** (3 mmol) and **607 mg triethylamine** (6 mmol) in **200 mL tetrahydrofuran**.



CO flow rate (mL/min)	10	30	30	30	60	60	60	60
Conversion (%)	60	65	66	62	79	79	79	82

Table 2. *Results at various CO flow rates*

After all parameters stabilized in the H-Cube® Advance, the inlet valve was switched from “Solvent” to “Reagent”, and the reaction mixture passed through the catalyst cartridge. Collection of the product started after switching the outlet valve to “Product”. When the 10 mL reactant solution was used up, the inlet valve was switched back to “Solvent”. **Product collection** was continued for an additional **10 min**, to recover the total amount of product from the catalyst cartridge. The product solution was analyzed by **LC-MS** without any further dilution.

CONCLUSION

The H-Cube® Advance shows several advantages: the **gas insertion** is very **well-regulated** for **high reproducibility**; it can generate **high-capacity gas flow** of **various gases** with **excellent gas mixing**, which allows the user to perform many **gas-liquid-solid reactions** in **flow** that are normally difficult to carry out in batch. The H-Cube® Advance readily increases the chemistry and parameter space, making it more accessible to organic chemistry laboratories.

REFERENCES

[1] Irfan, M; Glasnov, T; Kappe, C O; *ChemSusChem*, 4, 3, 300–316, **(2011)**
[2] Nomura, Y; Kawashita, Y; Hayashi, M; *Heterocycles*, 74, 629 - 635, **(2007)**

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