THALESNano

Versatile Chemistry Examples Performed On The Phoenix High Temperature, High Pressure Flow Reactor

INTRODUCTION

The ability to explore wider chemistry space to discover new chemistry and compounds is becoming increasingly more critical as increased R&D costs go hand in hand with lower new registered molecules year on year. To achieve this, we, as chemists, must seek to expand the capabilities that we have in the lab in terms of temperature and pressure, but in a reliable and safe way. The Phoenix Flow Reactor™ is technology designed specifically for this process. With the ability to perform homogeneous and heterogeneous chemistry up to 450 °C and 200 bar, the Phoenix Flow Reactor™ is versatile enough to create new or improve on existing chemistry.

In this application note, we demonstrate the flexibility of the Phoenix Flow Reactor™ by presenting various applications such as *N*-substitution, thermal Boc removal, scalable Claisen rearrangement, and synthesis of soluble polyphosphide anions.

INSTRUMENTATION

The Phoenix Flow Reactor™ is a precise heating system which can be fed with different loops for homogeneous reactions and columns for heterogeneous reactions (Table 1). The system can be utilized either coupled to an H-Cube Pro™ or by itself in "standalone" mode.

In the following examples the Phoenix Flow Reactor™ will be utilized in "standalone" mode where an HPLC pump is responsible for delivering the starting material into the heated element (reaction zone) of the Phoenix Flow Reactor™ and a pressure regulator unit (Pressure Module) delivers the pressure using back pressure (up to 200 bar).

One important part of the Phoenix Flow Reactor™ is the Heat Exchanger, which heats up the starting material and cools down the product in one step, minimizing the dead volume of the system to ensure maximum efficiency for product collection at nearly room temperature.

Type	Volume (mL)	Max. T. (°C)
MidiCart, CatCarts		
MidiCart	7.6	150
30 mm CatCart®	0.38	250
70 mm CatCart®	0.76	250
Metal-metal sealed cartridge		
125 mm (1/4 SS id 3 mm)	0.9	450
125 mm (1/4 SS id 3.8 mm)	1.3	450
125 mm (1/2 SS id 9.4 mm)	9	450
250 mm (1/4 SS id 3 mm)	1.8	450
250 mm (1/4 SS id 3.8 mm)	2.6	450
250 mm (1/2 SS id 9.4 mm)	18	450
Loops		
Teflon (up to 15 bar)	4, 8, 16	150
Stainless Steel, Hastelloy	4, 8, 16	450

Table 1: Heated elements and their volume

Phoenix Flow Reactor™ Application Note

AbbVie, Inc. together with the University of Kansas have published two different applications in Tetrahedron Letters [1] and Organic Letters [2] detailing results in nucleophilic aromatic substitution and thermal Boc removal reactions respectively. In both cases, they used an 8 mL stainless steel loop placed into the Phoenix Flow Reactor™.

NUCLEOPHILIC AROMATIC SUBSTITUTION OF HETEROCYCLES

First, a model reaction between 2-chloroquinazoline and benzylamine was investigated involving a Stat-Ease Design Expert 7 to speed up the optimization process and evaluate the effect of temperature, pressure and flow rate. After successful execution and analysis of the predesigned reactions using DoE software, they concluded that lower temperature and higher pressure is needed to avoid decomposition and side product formation. Thus, they carried out the library synthesis applying the optimum conditions of 225 °C or lower, 0.5 mL/min (16 min residence time) and 12 MPa (120 bar). Figure 1 shows the model reaction, while selected examples are represented in Table 2. In summary, S_NAr reactions of either 2-chloroquinoxaline or benzimidazole with primary and secondary amines afforded the desired products in modest yields.

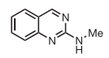
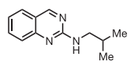
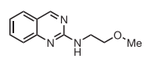
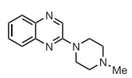
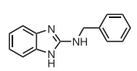
	Product	Isolated yield (%)
1		73
2		92
3		92
4		60
5		78

Table 1: Results of nucleophilic aromatic substitution of heterocycles. Reaction conditions: 0.25 mL of 2-chloroquinoxaline and 0.5 mL of amine were premixed and injected via a 1 mL loop into the Phoenix Flow Reactor™. Flow rate: 0.5 mL/min, residence time of 16 min, 225 °C, and 12 MPa.

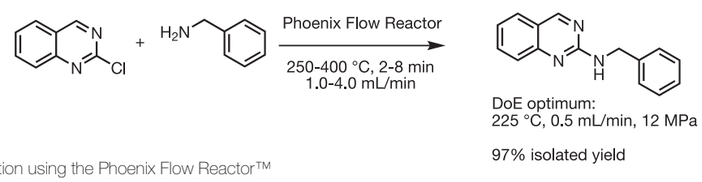
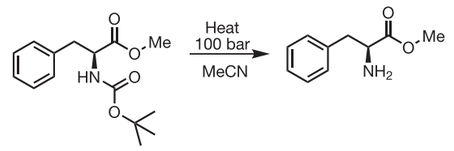


Figure 1: Nucleophilic substitution using the Phoenix Flow Reactor™

THERMAL BOC REMOVAL

The same group has published an article in Org. Lett. on thermal Boc deprotection stepping out of the conventional temperature range. Furthermore, they combined 2 synthetic steps in flow. This novel approach eliminates the use of acids associated with Boc removal reducing the work-up to solvent evaporation only.

The application provides a widely usable and scalable method, since Boc protection is presented in 50% of literature about amine protection so any medicinal chemistry lab can benefit significantly from this development. The reaction was carried out using the same set up as for the S_NAr reaction; an 8 mL loop was heated up under pressure. The initial reaction showed that Boc removal requires 300 °C reaction temperature and 2 min residence time (Table 3). Then, they applied the same protocol for various starting materials, including examples with other different protection groups, resulting in the Boc deprotected product in excellent yield (Figure 2).



entry	temp (°C)	flow rate (mL/min)	residence time (min)	% conv (UV)	% product (MS ion count)
1	200	1.0	1.0	0	
2	250	1.0	1.0	49	
3	300	1.0	1.0	>99	52
4	300	2.0	1.0	>99	68
5	300	3.0	1.0	>99	77
6	300	4.0	1.0	>99	820
7[a]	200		1.0	0	

[a]Sample run in Biotage microwave at 200 °C for 8 min.

Table 3: Optimization of thermal Boc removal

Finally, the deprotection step was included into multistep, flow syntheses as one of the examples shows in Figure 3.

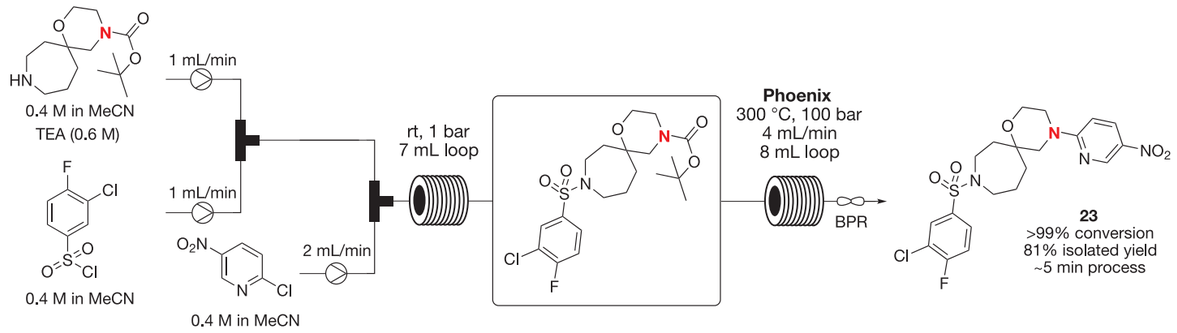
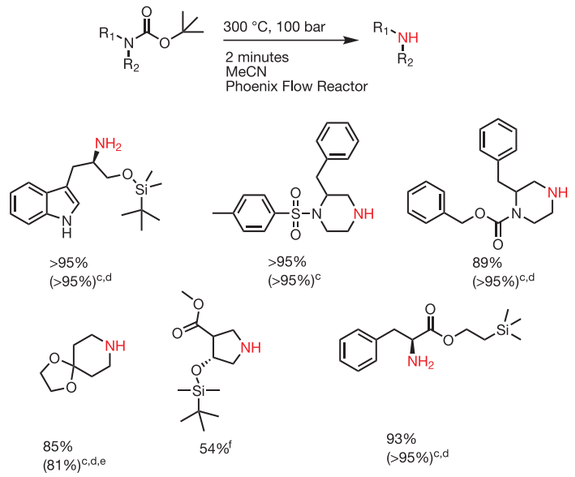


Figure 3: Multistep reaction including Boc removal step by the Phoenix Flow Reactor™



[a]Isolated yield after solvent removal [b]The bold red notrogen indicates the amine that has been deprotected. [c]Isolated yield after treatment with TFA. [d]A mixture of product was seen by ^{1}H NMR. [e]10 % piperdin-4-one was seen by ^{1}H NMR. [f]Isolated yield after purification using normal-phase chromatography.

Figure 2: Results of thermal Boc removal

PROCESS INTENSIFICATION – CLAISEN REARRANGEMENT

Steven Ley's group at the University of Cambridge has published a green, process intensification method under solvent free conditions [3]. The method involved a Claisen rearrangement reaction using a Phoenix Flow Reactor™. First, the Phoenix Flow Reactor™ was fitted with a 1 mL volume loop, and the neat starting material (allyl phenyl ether) was introduced at 1 mL/min flow rate and 100 bar reaction pressure. Optimization produced 2-allylphenol in a 94% yield and 60 g/h production. Then, the reaction zone volume was increased to 8 mL/min, and in parallel, the flow rate to 8 mL/min keeping the 1 min reaction time. This linear increase of reaction parameters afforded the same level of conversion, but with a higher 480 g/h production.

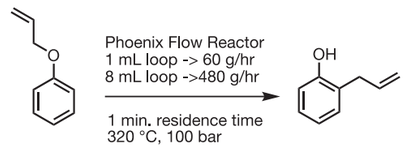


Figure 4: Claisen rearrangement

RED PHOSPORUS ACTIVATION

At the Florida State University, the Phoenix Flow Reactor™ was used to activate red phosphorus with KOEt to produce soluble polyphosphide anions [4]. Soluble polyphosphides can show fascinating reactivity and can be used as precursors of high performance materials, but their synthesis is either dangerous (from white phosphorus) or the isolation of the product is difficult. The Phoenix Flow Reactor™, fitted with a red phosphorus filled column, provided a safe and easy way towards the synthesis of soluble polyphosphides by applying an 80 °C temperature and 8 bar pressure. After 5 h of continuous operation, 150 mL of 0.03 M polyphosphide solution was obtained.

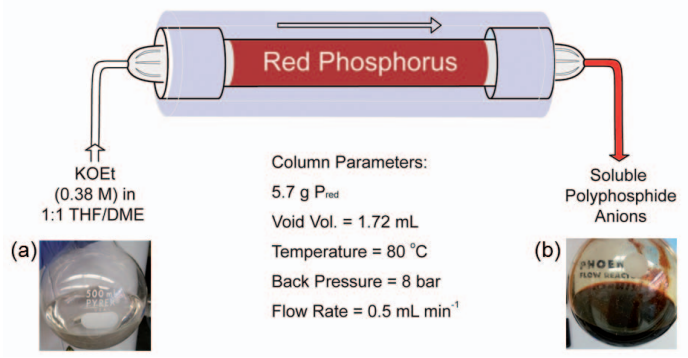
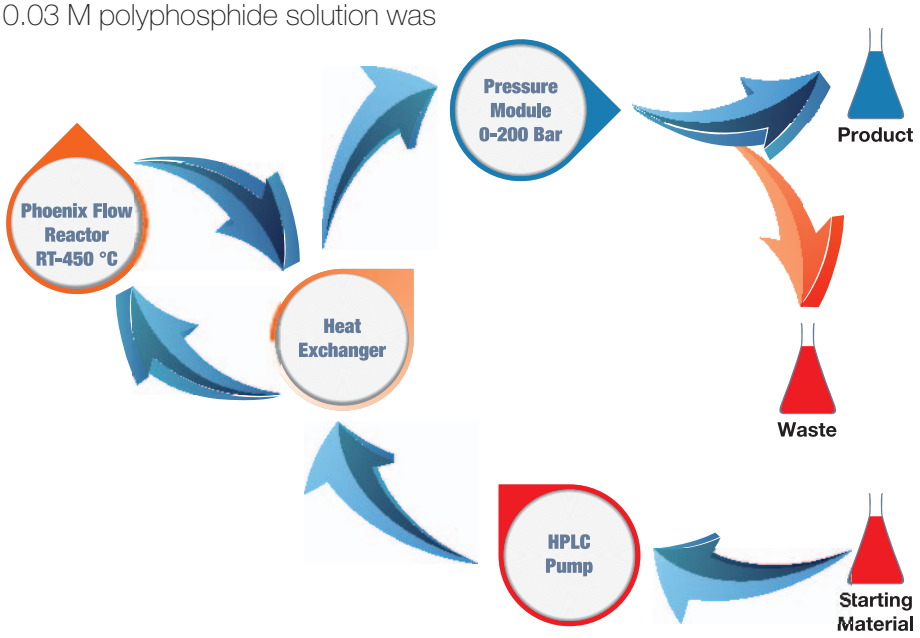


Figure 5: Red phosporus activation



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For more information on how flow chemistry can benefit you please visit www.thalesnano.com

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