AFRICA Application Note — Note Number : 2

Planning Successful Reactions

1 Summary

This application note gives hints & tips for planning successful AFRICA reactions.

2 Planning Chemistry

Performing reactions in flow is analogous to batch chemistry; there are however some differences. A number of flow-specific features are worth taking into consideration when planning AFRICA reactions and these are outlined below.

2.1 Solubility

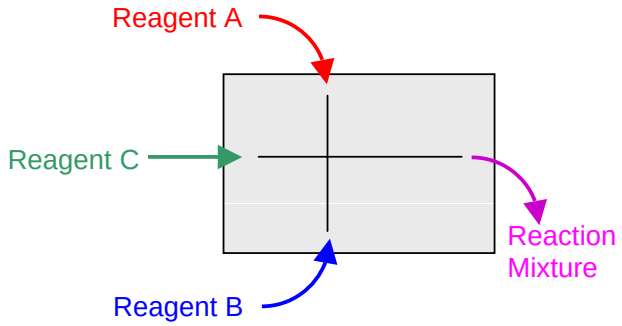
All substrates/reagents need to be in solution before they enter the reactor. The only exception to this is if solid phase reagents are used in a “column” and flowed through. It is recommended that all substrates/reagents for a given reaction are dissolved in the same solvent or mixture of solvents. This avoids the risk of the substrates/reagents precipitating in the reactor.

2.2 Reaction time

Reaction time in the AFRICA system is generally the same as the batch reaction. The reaction time can be accelerated by solvent superheating, as noted in section 2.7

2.3 How many inputs (solutions)?

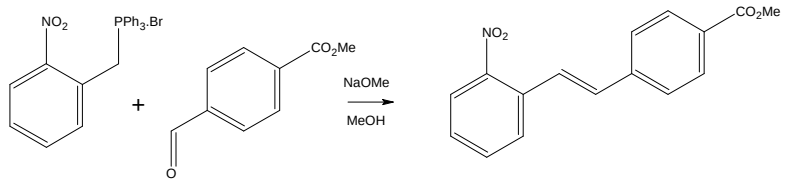
AFRICA reactors have either 2 or 3 inputs. This allows up to 3 solutions to be combined simultaneously in a controlled fashion, something that cannot be achieved in batch.



Note that it is possible to block off reactor inputs by inserting a “blocker” into the chip header, rather than an input pipe. This allows, for example, a 3 input reactor to be used for a 2 input reaction.

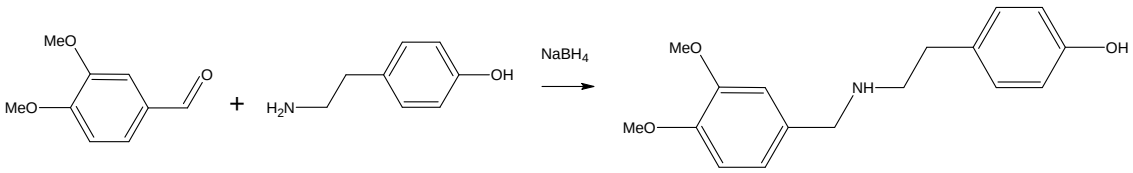
Typically when deciding how many solutions to make up for a reaction, the simplest approach is to have the smallest number of unreacting solutions. However to achieve the greatest flexibility, dividing the substrate/reagents into individual solutions allows the stoichiometry or order of addition of each to be varied.

E.g.
For the following Wittig reaction, the phosphonium salt, aldehyde and methoxide could all be added as individual components in a 3 input chip. Alternatively, because they will not react alone, the phosphonium salt and aldehyde could be combined as one solution and the methoxide be the other.

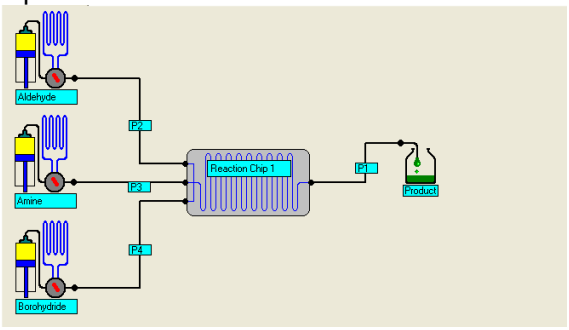


2.4 Order of addition & multiple reactors

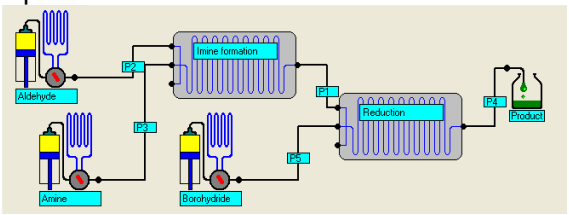
The AFRICA system allows excellent control over the timing of reagent addition. For example, in the reductive alkylation/amination below, the aldehyde, amine and borohydride could all be added simultaneously in one reactor. However, to avoid over alkylation, the imine could be formed in one reactor and flowed into a second reactor with the borohydride.



Option 1



Option 2 Preform imine



The AFRICA flow system allows up to 8 reactors and 8 heater/cooler plates to be combined in one continuous system. This allows extremely complex configurations of multi-step reactions to be controlled.

2.5 Substrate/Reagent Solution Concentrations

The software will calculate the relative flow rates required for each solution to generate the entered stoichiometry. The user simply enters the concentration of each solution and the required stoichoimetry. As a result, the exact concentration of each solution does not need to be a certain value, its value just needs to be known.

However, where possible, the solutions to be introduced to the chip should be made up such that a similar volume of each solution is required for the typical reaction stoichiometry. This avoids dramatically different flow rates for the different solutions and allows the greatest flexibility when varying stoichiometry.

2.6 Method of Reagent Addition

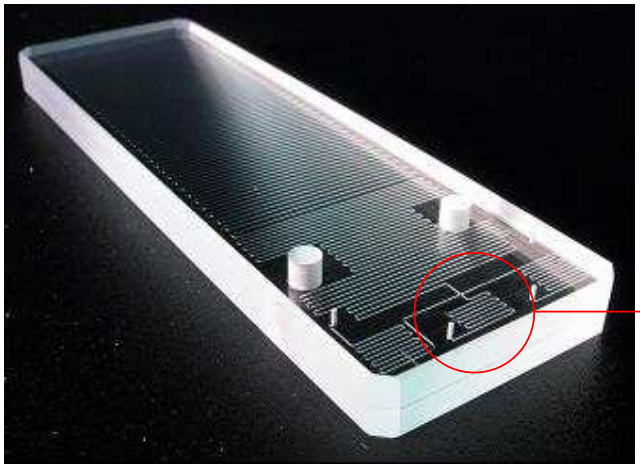
It is possible to pump “unlimited” quantities of reagents through the AFRICA pumps i.e. aspirate directly from a large vessel and pump the reagent through the syringes.
When using smaller quantities of reagents e.g. 1-10ml, the solutions can be loaded in to the sample loops in the Reagent Store.

2.7 Temperature

The temperature range of the standard AFRICA Heater/Cooler module is 0°C – 150°C. The output of the AFRICA system can be pressurised up to approx 8bar using the pressurisation module to superheat solvents. This allows solvents to be heated between approximately 40°C and 90°C above their atmospheric reflux temperature (depending on volatility) allowing more reaction space to be investigated. E.g. THF can be heated to 140°C.

2.8 Preheating/cooling

On each reactor chip there is a temperature equilibration section of a few cm length which preheats/cools the reagents before they mix.



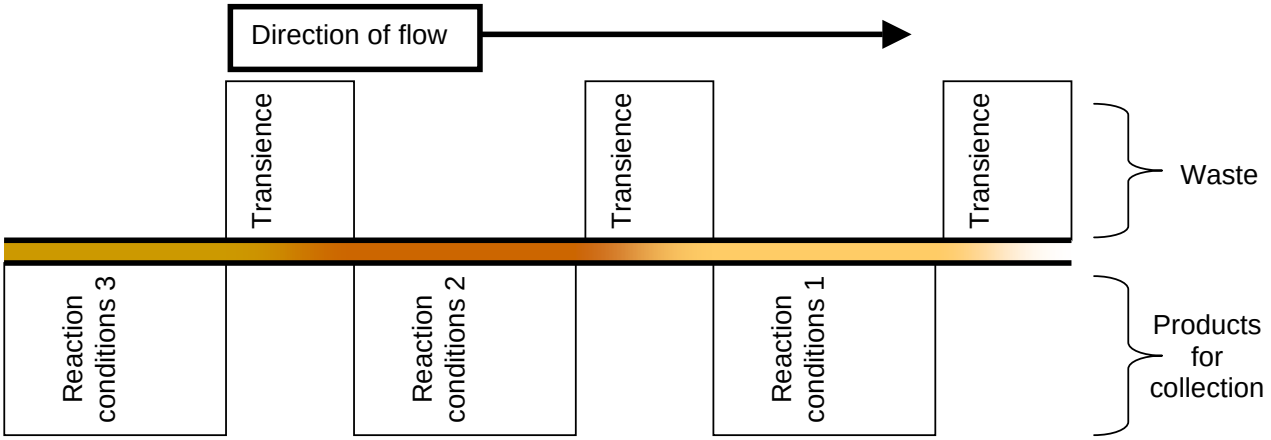
2.9 Gas evolution

If the reaction you intend to perform evolves a gas, it is recommended that the pressurisation module is used at its maximum setting of approximately 8 bar. This suppresses bubbles being formed which can propel the reactor contents out of the reactor.

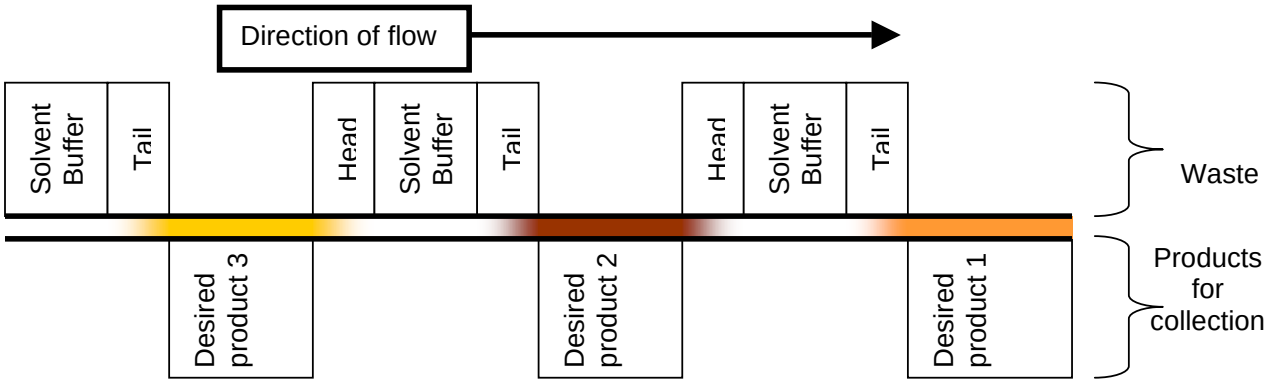
2.10 Running Sequential Reactions

The AFRICA software allows a number of reactions to be performed in a serial fashion. Typically one reaction directly follows another. Because of the "plug flow" environment the first reaction is simply pushed out and cleaned by the second and the software accounts for any dispersion/diffusion at the boundary of the two – see 2.11.1.
In the fully automated system reactions can be separated with pure solvent – see 2.11.2.

2.10.1 Fixed Reagents (varying temp & time)



2.10.2 Fixed temperature & flow rate (varying reagents)



2.11 Product Collection

Product collection can be carried out in the following 3 ways.

2.11.1 Manual

The output tube from the reactor is manually moved from a waste pot to a collection vessel at the time indicated by the software ("Sample Collection Starts") and returned when the software indicates "Stop Sample Collection"

2.11.2 Automated analysis

The output tube from the reactor is connected to the Sampler & Dilutor AFRICA module. This module will automatically take a 5µl sample, dilute it and inject it onto the HPLC.

2.11.3 Automated Sample Collection

Connect the output of the reactor to the PCM (Product Collection Module) and the fraction collector will automatically collect each sample in a new vial.