

Concentrated Butyllithium Solutions from Albemarle

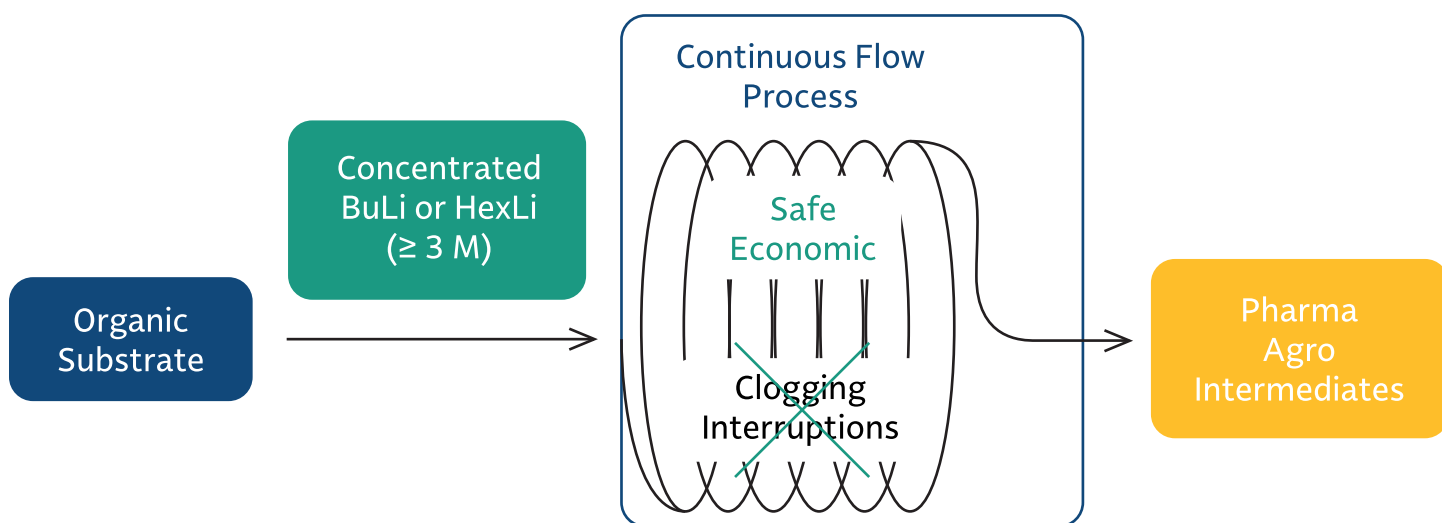
Enabling trouble-free continuous flow processes

BACKGROUND

Organometallic reactions involving highly reactive organolithium reagents are widely used in organic synthesis. However, the application of such organometallics in batch mode on a pilot and industrial scale is challenging for safety reasons and frequently requires expensive cryogenic process conditions. A change to continuous processing in flow mode can provide major advantages for process safety and economics.

Nevertheless, the much higher specific surfaces of microflow reactors compared with that of batch reactors and the small diameters of their channel structures also provide challenges in reactions with butyllithium. Many users observed decreasing flow rates and finally blockages, so-called “reactor fouling,” in the course of time. These clogging phenomena are attributed to various reasons, such as the precipitation of salt-like or polymeric solids. Clogging has been found to be the largest obstacle restricting a smooth and continuous operation.¹ As a result, flow reactions with organolithium compounds can frequently not be run stable for longer periods of time.

ALBEMARLE SOLUTION

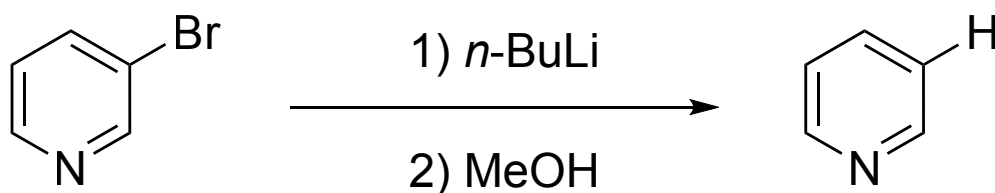


By applying a reduced hydrocarbon concentration in the reaction mixture, which can easily be realized by using higher concentrated (3–6 M) *n*-BuLi or the corresponding concentrated hexyllithium solutions, the yield and the robustness of organolithium-enabled reactions like Br/Li exchange and deprotonations, can be significantly improved. Furtheron, the space/time yield can be maximized by using less solvent if compared to corresponding batch experiments: thus, increased reactant concentrations of, for example, 2 M and higher, are enabled. This is the result of studies carried out by Albemarle in cooperation with a team from New Path Molecular, Cambridge UK and company Flowid, Eindhoven NL. For further information, please refer to the detailed results, recently published in OPRD journal.² The advantages of using higher concentrated BuLi solutions are exemplified by the Br/Li exchange of 3-bromopyridine. With the highest BuLi concentration tested (abt. 50 wt%), the yield was improved to 86 %, while no clogging was observed:

¹ Laue, S.; Haverkamp, V.; Mleczo, L. "Experience with Scale-Up of Low-Temperature Organometallic Reactions in Continuous Flow", Org. Process Res. Dev. 2016, 20, 480–486.

² Wietelmann, U.; Klösener J.; Rittmeyer P.; Schnippering S.; Bats, H.; Stam, W., „Continuous Processing of Concentrated Organolithiums in Flow Using Static and Dynamic Spinning Disc Reactor Technologies”, Org. Process Res. Dev. 2022, 26, 1422–1431.

BR/LI EXCHANGE OF 3-BROMOPYRIDINE WITH N-BULI PRODUCTS:



BuLi stock sln (mol/L)	conversion (%) using different 3-bromopyridine concentrations (mol/L)	
	0.5 M in THF	0.75 M in THF
1.6	38	blockage
3.2 ^a	66	blockage
5.8 ^a	86	97

^aDiluted with THF to 1.6 M before use.

Albemarle offers pure (free from oil) concentrated organolithium products with up to 75 wt% concentration:

ALBEMARLE CONCENTRATED ORGANOLITHIUM REAGENTS FOR FLOW APPLICATIONS:

Organolithium for flow application	solvent	concentration wt%	mol/L	availability
<i>n</i> -BuLi	hexanes	30	~3.2	pilot
<i>n</i> -BuLi	hexanes	50	~5.3	pilot
<i>n</i> -BuLi	hexanes	75	~8.0	pilot
HexLi	hexanes	on demand		lab

While lab samples are supplied in glass bottles, larger quantities are filled into returnable steel cylinders. Albemarle recommends the use of a Swagelok® emptying system which is available with 3.1 EN 10204 certificate. In view of the highly reactive nature of concentrated RLi solutions, also a specific drip-free unloading system can be supplied:

ALBEMARLE DRIP-FREE EMPTYING SYSTEM FOR PILOT QUANTITIES:



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