CONTINUOUS FLOW SYNTHESIS OF α-CHLOROKETONES FROM ESTERS

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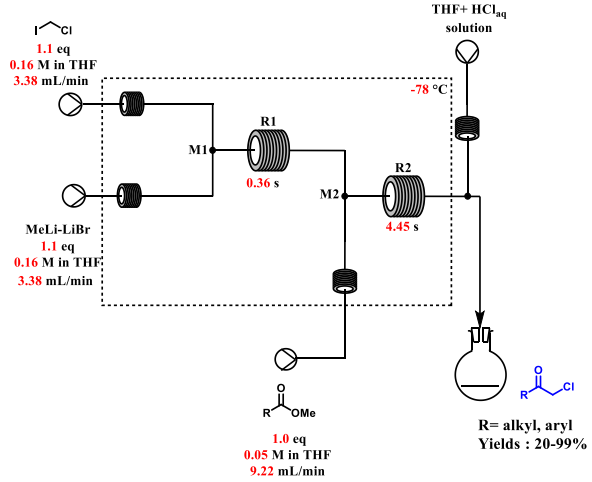
Continuous flow chemistry has offered since several decades a lot of benefits concerning reaction efficiency, safety, scalability, selectivity and temperature control. It is particularly appealing for processes implying highly reactive organometallic intermediates, as demonstrated by Yoshida and others.[1] Flash chemistry, which combines flow microreactor technology and very short residence time, allows efficient and selective carbon-carbon or carbon-heteroatom bonds formation.[2] Therefore, arduous processes or even impossible chemistry with conventional batch reactors, such as external trapping of reactive carbenoids with electrophiles, can be achieved.[3]

Flow chloromethylation has shown to be an attractive way to access chloromethylketones, which are valuable synthons that can be post-functionalized for bioactive compounds preparation.[4] In this work, we developed a new procedure by taking advantages of flow chemistry to trap thermally unstable chloromethyllithium intermediate with esters, challenging electrophiles, due to a limited relative reactivity. Thus, thanks to precise control of the residence time and of the stoichiometry, the chloromethylketone products can be chemoselectively obtained with high optimized yields. This novel method has been applied on a large range of functionalized esters with good to excellent yields.[5]



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