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A direct and sustainable synthesis of tertiary butyl esters enabled by flow microreactors

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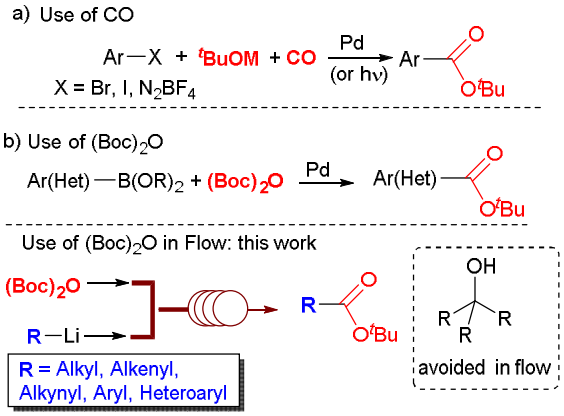
Tertiary butyl esters find large applications in syntetic organic chemistry. A straightforward method for the direct introduction of the tert-butoxycarbonyl group into a variety of organic compounds has been developed using flow microreactor systems. The flow process resulted more efficient, versatile and sustainable compared to batch.

The prominence of ester functionality is widely recognized in organic chemistry. Esters are predominant among organic compounds such as fine chemicals, materials, natural and pharmaceutical products, and synthetic chemists have developed several strategies for their preparation.[1] Among the ester groups, tertiary butyl esters hold great importance because the *tert*-butyl group acts as protecting group for acids, alcohols, phenols and in peptide synthesis,[2] it is stable toward strong organometallic bases, such as organolithiums and organomagnesiums, and it is readily removed by acids.
However, the preparation of tertiary butyl esters is not as straightforward as thought, and for this reason the development of mild methodologies for their synthesis remain a current challenge.[3] In fact, several methodologies have recently appeared into the literature for the preparation of tertiary butyl esters. In Scheme 1, some of these strategies currently used for the introduction of the *tert*-butoxycarbonyl (Boc) functionality into organic molecules are reported. An old strategy relies on the use of gaseous isobutylene which poses safety concerns for large scale applications because of the high flammability of the gas and the explosion danger.[4] Alternative strategies use *tert*-butyl methyl ether and carboxylic acids under harsh conditions.[5] Metal-catalyzed and metal-free carbonylation strategies, developed for the introduction of the Boc group on the aromatic ring, have the drawback of using toxic CO, transition metals, and seldom are conducted in not so green solvents (Scheme 1, a).[6],[7] The use of *tert*-butyl peroxide has been proposed by Wei for the conversion of aldehydes into the corresponding *tert*-butyl esters.[8] However, this strategy uses a peroxide and a transition metal. An interesting strategy, using the safer and inexpensive di-*tert*-butyldicarbonate $(Boc)_2O$ and aryl- and heteroarylboronates, has been recently reported by Islam and co-workers.[9] This greener approach relies on the use of mesoporous silica grafted Pd(II) complex and works well for the preparation of aromatic and heteroaromatic derivatives (Scheme 1, b).



Scheme 1. Strategies for accessing tertiary butyl esters.

Although $(Boc)_2O$ is a well recognized electrophilic partner for O- and N-nuclophiles, this could not be verified in the case of strong C-nucleophiles such as organolithiums or organomagnesiums, and we were able to find only few isolated examples into the literature.[10] One reasonable reason for the missing use of $(Boc)_2O$ with carbanions could be the predictable side reaction of multiple addiction. Thus, we reasoned that coupling of $(Boc)_2O$ with nucleophilic organometallics could be a direct and straightforward strategy, for preparing a plethora of *tert*-butyl esters, complementing those reported in Scheme 1. With the aim to develop a direct and more sustainable approach to *tert*-butyl esters we investigated this strategy using flow microreactor systems and the results of this study are reported herein. The use of flow microreactors as sustainable technology for performing chemical synthesis is now growing in importance and is being appreciated in both academia and industry. [11]
The precise thermal profile realized in a microreactor, allows to avoid or limit side products especially for rapid and very

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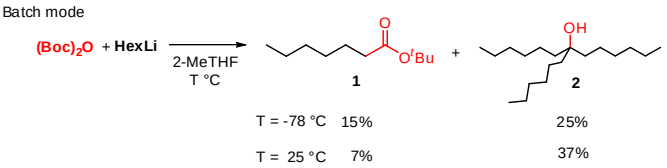
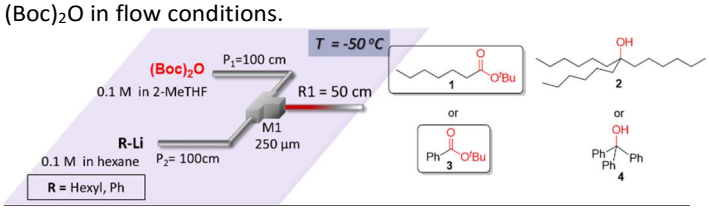
exothermic reactions.[12] This is especially true in the case of organolithiums which react rapidly with electrophiles giving often highly exothermic reactions, under traditional batch conditions, thus requiring cryogenic conditions. However, Yoshida widely demonstrated that flow microreactor systems could be used to handle organolithiums bearing sensitive functional groups, by controlling the residence time and the temperature. In fact, this technology enabled the direct introduction of substituents on the aromatic ring, without protecting the nitro-, cyano-, keto- and alkoxycarbonyl-groups, definitively susceptible to attack by the organolithium itself.[13] In continuation of a research programme focused on the use of microreactor technology in the development of sustainable synthetic processes[14], we became involved in the preparation of tertiary butyl esters by addition of organolithiums to $(Boc)_2O$. The investigation started using hexyllithium as suitable nucleophile, $(Boc)_2O$ as electrophile and 2-MeTHF as a greener solvent.[15], [14b] The reaction was first conducted in batch conditions (Scheme 2); to a solution of Boc_2O in 2-MeTHF, an equimolar amount of HexLi was added at two different temperatures, -78 °C and 25 °C obtaining in each case a different mixture of adducts **1** and **2**. As expected, even at low temperature (i.e. -78 °C) considerable amounts of tertiary alcohol **2** formed, and it becomes the main product running the reaction at 25 °C. However, such side reaction is likely responsible for the low conversions (up to 44%) observed.



Scheme 2. Addition of organolithiums to $(Boc)_2O$.

Thus, we transferred the reaction in a flow microreactor system consisting in a T-shaped stainless steel micromixer (M1), two pre-cooling units (P1, P2) and a microtube reactors (R1) (Table 1). Optimization experiments were carried out feeding the flow system with a solution of $(Boc)_2O$ (0.1 M in 2-MeTHF), and a solution of hexyllithium (0.1 M in hexane) at -50 °C, and quenching the reaction at the output with an aqueous solution of NH_4Cl (Table 1). The reactants were introduced into the flow system by using syringe pumps. The residence times in R1 (t^{R1}) were determined by choosing properly the flow rates while maintaining an almost equimolar stoichiometry for HexLi and $(Boc)_2O$ (Table 1). The optimization study demonstrated that the residence time is a critical parameter. In fact, longer residence times (Table 1, entries 1-3) favor the multiple addition of the organolithium. Reducing the residence to 5.6 seconds, gave the best results in terms of selectivity furnishing 96% of the desired ester **1** (Table 1, entry 4). We considered that, higher flow rates could guarantee a better mixing efficiency in a multilamination-type micromixer, by virtue of the short diffusion path, along with a shorter residence time thus avoiding multiple addition products. Under such optimized conditions, the use of PhLi resulted in 95% yield of *tert*-butyl benzoate **3** (Table 1, entry 5).
It is worth pointing out that this reaction performed in batch at -78 °C, under the same conditions reported in Scheme 2, furnished almost exclusively alcohol **4**.

Table 1. Optimization of the reaction of organolithiums with $(Boc)_2O$ in flow conditions.



Entry	Flow [a]	t^{R1} (s)	R-Li (eq)	$(Boc)_2O$	Ester[b]	Alcohol[b]
1	A	23.56	HexLi (1)	1	44	56
2	B	11.78	HexLi (1)	1	50	50
3	C	6.04	HexLi (1)	0.95	75	25
4	**D**	**5.61**	**HexLi**	**1**	**96**	**4**
5	**D**	**5.61**	**PhLi (1.1)**	**1**	**95**	**5**

[a] Flow rate: A: RLi = 0.5 mL/min, Boc_2O = 0.5 mL/min; B: RLi = 1 mL/min, Boc_2O = 1 mL/min; C: RLi = 2 mL/min, Boc_2O = 1.9 mL/min; D: RLi = 2.2 mL/min, Boc_2O = 2 mL/min. [b] Calculated by gas chromatoghraphy.

Next, the temperature effect on the progress of the reaction was evaluated using HexLi and $(Boc)_2O$ (Table 2). Three different conditions were considered, increasing the temperature of about 25 °C for each run. With our delight, we found that the process can be conducted efficiently even at 25 °C maintaining the amount of the alcohol **2** at acceptable level.

Table 2. Effect of the temperature.[a]

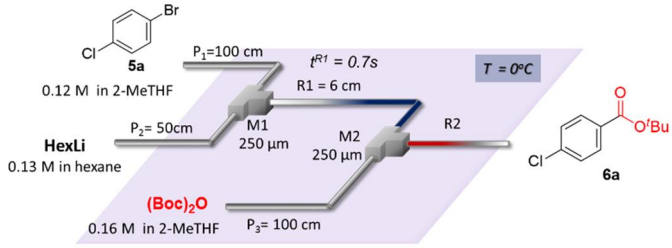
HexLi (eq)	t^{R1} (s) [b]	Boc_2O (eq)	T (°C)	**1** %[c]	**2** %[c]
1.1	5.61	1	-30	93	7
1.1	**5.61**	**1**	**0**	**95**	**5**
1.1	5.61	1	25	93	7

[a] The microflow system reported in Table 1 was employed. [b] Flow rate: HexLi = 2.2 mL/min, Boc_2O = 2 mL/min. [c] Calculated by gas chromatoghraphy.

Further, we decided to explore the scope of this process using other organolithiums, easily generated by halogen/lithium exchange reaction or by deprotonation. With the aim to develop a more sustainable process, hexyllithium, which is more stable and less pyrophoric compared to MeLi, *t*-BuLi, *i*-PrLi and *n*-BuLi, was chosen as the lithiating agent for the halogen exchange reactions on readily available aryl- and heteroaryl bromides.[15] The greener 2-MeTHF was employed as the solvent. First, the Br/Li exchange reaction was optimized using 1-bromo-4-chlorobenzene **5a** as reference substrate, and using a flow microreactor system consisting of three precooling units (P1, P2 and P3), two residence units (R1 and R2), and two T-shaped micromixer (M1 and M2) (Table 3). In order to set up the microflow system, conditions reported by Yoshida and co-workers were used as reference for the halogen/lithium exchange reaction and for setting R1 and t^{R1}.[16] In our system (Table 3) a residence time t^{R1} of 0.7 s was found as optimum for a complete Br/Li exchange. However, the reaction of the aryllithium with $(Boc)_2O$ needed further optimization as reported in Table 3. In order to get high conversion, the residence time in R2 (t^{R2}) was optimized using conditions reported in Table 3. Tert-butyl ester **6a** was obtained in 90% yield with 17.1 s as t^{R2} (Table 3, entry 4). It is worth mentioning

that the lithiation/esterification sequence was performed at 0 °C and not under cryogenic conditions (i.e. -78 °C).

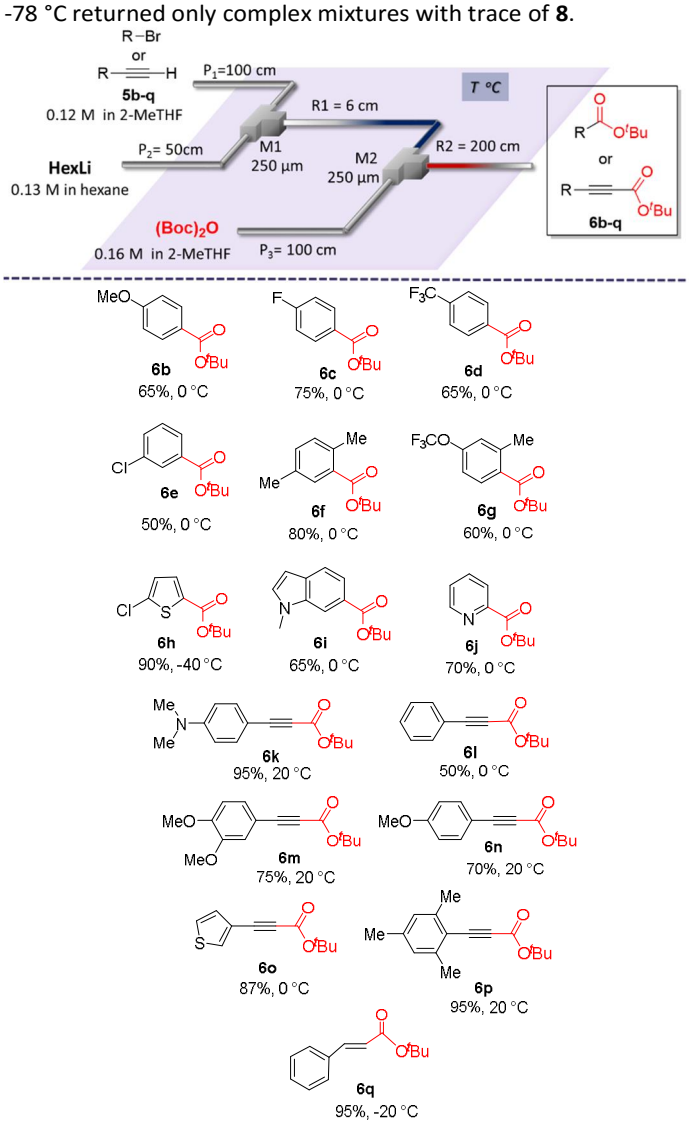
Table 3. Optimization study of the lithiation/trapping sequence.



Entry	Flow [a]	R_2 (cm)	t^{R2} (s)	$(Boc_2)O$ [b]	**6a** yield[c]
1	A	145	7.35	58%	42%
2	B	145	9.11	55%	45%
3	C	145	11.38	40%	60%
4	**D**	**200**	**17.1**	**10%**	**90%**

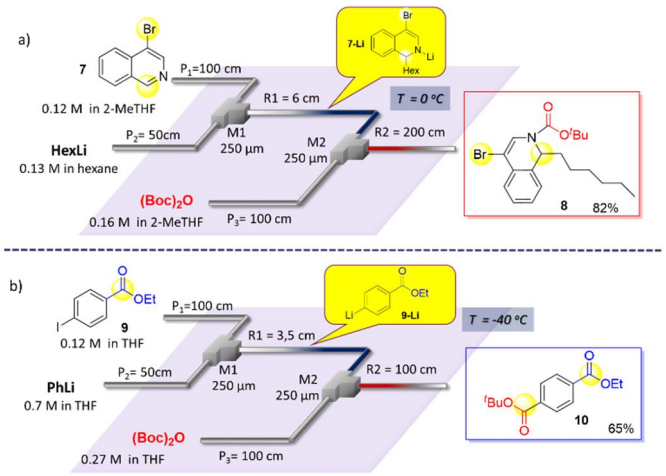
[a] Flow rate: A: ArBr 2 ml/min, HexLi 2 ml/min, Boc_2O 5,3 ml/min; B: ArBr 2 ml/min, HexLi 2 ml/min, Boc_2O 3,5 ml/min; C: ArBr 2 ml/min, HexLi 2 ml/min, Boc_2O 2 ml/min; D: ArBr 2 ml/min, HexLi 2 ml/min, Boc_2O 1,5 ml/min. [b] Remaining $(Boc)_2O$. [c] Calculated by ^1H NMR of the crude reaction mixture.

Under optimized conditions, tert-butyl ester **6a** could be obtained with a productivity of 1.3 g/h just feeding the microreactor system for 30 minutes with the reactants' solutions. Once optimized the reaction under flow conditions for 1-bromo-4-chlorobenzene, we explored the scope of this direct lithiation/*tert*-butoxycarbonylation (Scheme 3 and supplementary material). We were pleased to find that this protocol worked well for several aryl and heteroaryl bromides **5b-j**, and could be conducted at higher temperature with respect to batch mode. In the case of fluorinated derivative **5c**, the use of tmeda was mandatory in order to prevent precipitation of the lithiated intermediate, and clogging of the flow system. Heteroaryl bromides **5h-j** were effectively functionalized without observing any side reaction. In the case of **5h**, the reaction needed a lower temperature (-40 °C) to succeed. Under optimized conditions, the lithiation/ter-butoxycarbonylation of different acetylene derivatives was pursued. This reaction is particularly useful because *tert*-butyl propiolates are difficult to obtain, and are useful starting material in [4 +2] cycloaddition reactions.[17] The microfluidic system reported in Scheme 3 allowed to prepare aryl and heteroaryl *tert*-butyl propiolates **6k-p** with good to excellent yields at temperatures in the range between 20 and 0 °C (Scheme 3). The direct introduction of the tertiary ester was extended to β-bromo styrene **5q** obtaining the corresponding ester **6q** in almost quantitative yield. However, in this case sec-BuLi was used as lithiating agent at a temperature of -20 °C.[18] As further application of this strategy for the direct preparation of tertiary butyl esters, we investigated two challenging substrates where regioselectivity problems can be envisaged. As reported in Scheme 4, 4-bromoisoquinoline **7** if reacted with an alkyllithium could undergo either bromine/lithium exchange reaction or nucleophilic attack at the C1. Under optimized conditions (t^{R1} 0.7 s, t^{R2} 17.1 s, T = 0 °C) using 1 equiv of **7** and 1.1 equiv of HexLi (see supplementary material) a regioselective nucleophilic addition at the C1 occurred leading to **7-Li** that reacted at the nitrogen with $(Boc)_2O$ in M2 giving 82% yield of adduct **8**. It is worth pointing out that this kind of bromo derivatives could serve as synthons for other transformations, and are difficult to obtain straightforwardly under batch conditions. In fact, running this reaction in batch mode even at -78 °C returned only complex mixtures with trace of **8**.



Scheme 3. Scope for the direct *ter*-butoxycarbonylation in flow.

Aware of the importance of tert-butyl esters, we attempted the direct tert-butylcarbonylation on the aromatic ring of **9** where another ethyl ester was already installed (Scheme 4, b). Starting from Yoshida conditions,[13c] using the microfluidic system reported in Scheme 4 working at -40 °C with t^{R1} 0.3 s, we were able to generate the organolithium **9-Li** in R1, after mixing **9** with PhLi. Transferring **9-Li** in M2 allowed its reaction with **(**Boc_2)O that was completed in R2 in 5.4 s leading to the bis-ester **10** in 65% yield. This result is, in our opinion, remarkable because it shows how microreactor systems can make practicable reactions that are difficult to perform in batch conditions.



Scheme 4. Application of the direct *tert*-butoxycarbonylation to challenging systems.

In conclusion, in this work we have demonstrated that precise control of residence time and temperature, realized in a flow microreactor system, allow to perform a direct and straightforward C-tert-butoxycarbonylation of highly reactive organolithiums in 2-MeTHF as the solvent. It is worth mentioning that this reaction is difficult to perform in batch conditions unless heavy cryogenic conditions are used. In addition, this strategy complement well with the recently introduced direct carboxylation, leading to carboxylic acids, reported by Kappe, Jamison, Hessel, Ley and Yoshida.[19]

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