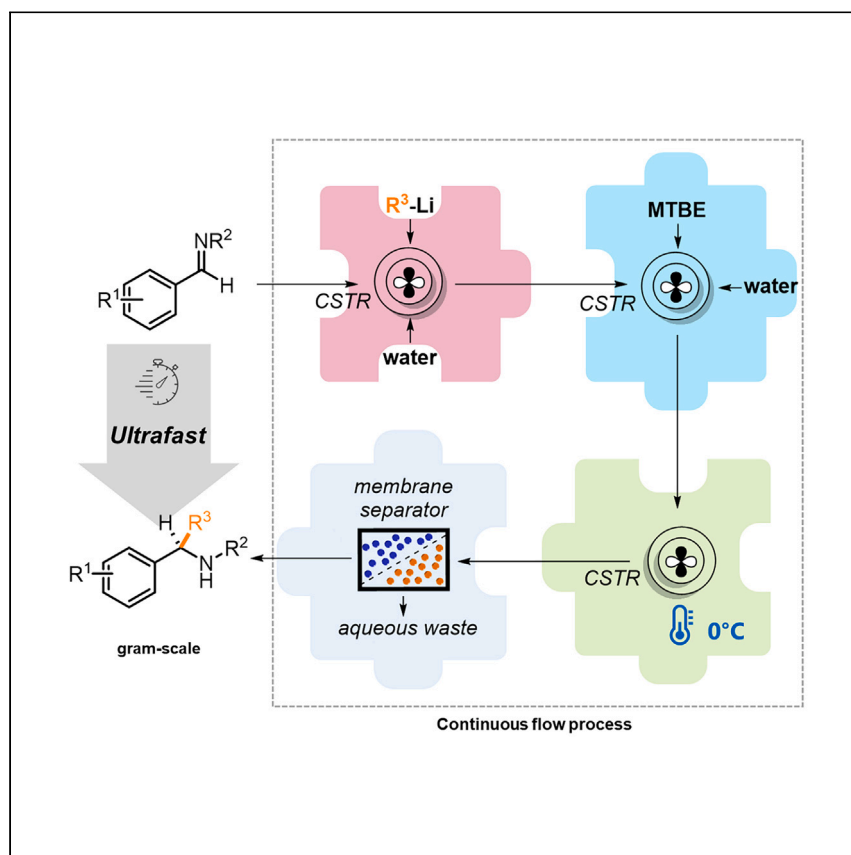


Article

# A three-minute gram-scale synthesis of amines via ultrafast "on-water" *in continuo* organolithium addition to imines



Organometallic compounds are useful reactants in organic synthesis; however, their use on a large scale is hampered by their high reactivity. Here, Bruccoli et al. present an ultrafast continuous-flow "on-water" addition of organolithium reagents to imines, preparing up to 5 g amine in only 3 min.

Jacopo Bruccoli, Alessandra Puglisi, Sergio Rossi, Davide Gariboldi, Davide Brenna, Ivano Maule, Maurizio Benaglia

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### Highlights

"On-water" addition of organolithium reagents to imines in a continuous stirred tank reactor

Large-scale reaction to prepare 5 g amine in 3 min

Continuous process comprising synthesis, in-line extraction, and separation

Calorimetric study is used to understand the thermal behavior of the reaction

## Article

A three-minute gram-scale synthesis of amines via ultrafast “on-water” *in continuo* organolithium addition to iminesJacopo Brucoli,<sup>1</sup> Alessandra Puglisi,<sup>1</sup> Sergio Rossi,<sup>1</sup> Davide Gariboldi,<sup>1</sup> Davide Brenna,<sup>2</sup> Ivano Maule,<sup>2</sup> and Maurizio Benaglia<sup>1,3,\*</sup>

## SUMMARY

Although “on-water” organic reactions, including organometallics, are a sustainable alternative to traditional strategies, serious concerns related to the safety and feasibility of large-scale application exist. Here, the on-water continuous-flow addition of organolithium reagents to imines is studied in a continuous stirred tank reactor. Fast reaction times (10–20 s) lead to a more productive (gram scale in a 2.5 mL continuous stirred tank reactor) and safer methodology compared to the in-batch reaction. A calorimetric study is performed to understand the thermal behavior and the critical parameters that affect the safety of the process. The methodology is applied to the synthesis of an enantiopure amine. A telescoped process, comprising 3 units of operation (synthesis-inline extraction-separation) that resembles an industrial operation line, is developed, demonstrating the feasibility of the scaleup. Functionalized secondary amines can be synthesized on water, *in continuo*, with high yields and very short reaction times.

## INTRODUCTION

The registration, evaluation, authorization, and restriction of chemicals regulation has been recently adopted in Europe, aiming to protect both human health and the environment from the risks posed by chemicals.<sup>1</sup> In this context, organic solvents, largely used in organic synthesis, present serious issues for the environment and the operators due to exposure, explosiveness, and flammability.<sup>2</sup> Water behaves as an atypical but ideal reaction medium for many organic transformations, and it could represent a safe, non-toxic, cheap, and environmentally friendly alternative.<sup>3</sup> Since the seminal work of Breslow in 1980,<sup>4</sup> a large variety of organic reactions have been shown to take place in aqueous media, sometimes with impressive results compared to classic organic solvent-based systems.<sup>5–8</sup>

Water can be regarded as a medium where no solvation of the reaction components takes place (i.e., processes “on water”) or where it does take place (i.e., “in water”). On-water applications represent ideal candidates to be investigated for the development of green and sustainable processes.<sup>9</sup> Recently, Capriati et al. have highlighted the benefits of using water as the reaction medium with organometallic compounds<sup>10,11</sup> such as the nucleophilic addition of organolithium reagents to imines (Scheme 1A)<sup>12</sup> or Pd-mediated cross-coupling reactions (Scheme 1B).<sup>13,14</sup>

Imines are poorly electrophilic in conventional hydrocarbons or ethereal solvents, while the use of protic solvents such as methanol leads mainly to protonolysis.

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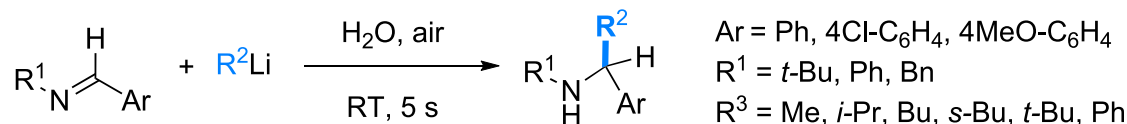
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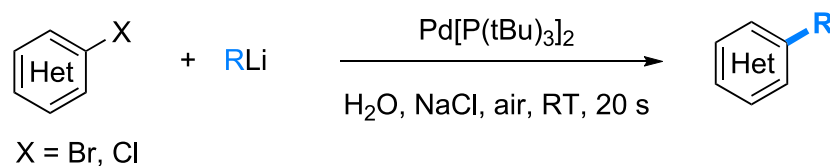
\*Correspondence: [maurizio.benaglia@unimi.it](mailto:maurizio.benaglia@unimi.it)  
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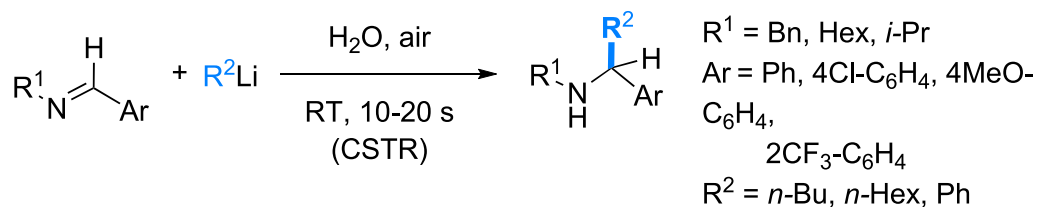
**A Nucleophilic addition of organolithium reagents to imines**



**B Pd-mediated cross coupling reactions**



**C This work: fast in continuo on water organolithium addition to imines**



**Scheme 1. Organolithium reagent reactions**

- (A) On-water organolithium addition to imines.  
 (B) On-water Pd-mediated cross-coupling reaction.  
 (C) This work: ultrafast, on-water, *in continuo* organolithium addition to imines.

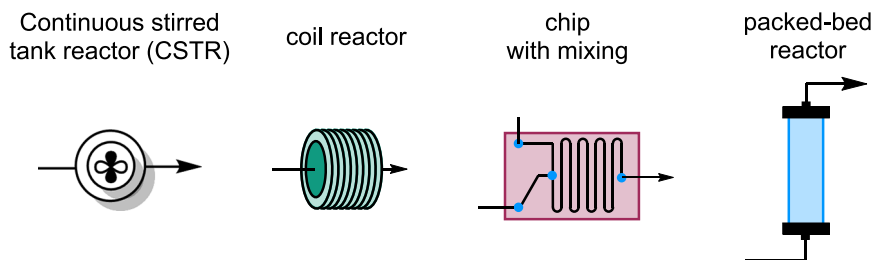
However, in the on-water organolithium addition to imines, the reaction is significantly accelerated. The reaction “on D2O” showed a significant isotope effect, consistent with proton transfer or substrate activation by interfacial water molecules. The authors highlighted the importance of controlling two parameters to achieve high conversion: highly efficient stirring and fast organolithium addition to the reaction mixture.<sup>15,16</sup>

Despite these brilliant results, some concerns related to the safety of the process and the feasibility of the on-water reactions of organometallic species in large-scale applications exist.<sup>17</sup> The requirement of very efficient stirring and fast addition of the organolithium solution into water, and the dangerous gas evolution, are intrinsic limitations for the large-scale batch applicability. Moreover, the use of significant amounts of organolithium reagents has proven to be an onerous task because of troublesome stock, difficult heat dissipation, and formation of precipitates.

## RESULTS AND DISCUSSION

### Preliminary studies

We reasoned that switching from batch to *in continuo* processes<sup>18–22</sup> could solve some of the major issues that hamper a possible industrialization of this methodology.<sup>23–25</sup> Flow chemistry has enabled a safer regime for the employment of organometallics.<sup>26–29</sup> A continuous-flow chemistry platform provides a viable alternative for the control and handle of the risk associated with these reactions, and examples of



**Figure 1. Reactor types**

Representation of continuous stirred tank reactors (CSTRs; fReactor), coil reactors, microchips, and catalytic reactors for flow applications.

organolithium reactions performed in flow have been recently reviewed.<sup>30</sup> Recently, the in-flow addition of organolithium reagents to ketones and imines in deep eutectic solvents, by using a microfluidic biphasic segmented flow, has been reported.<sup>31</sup>

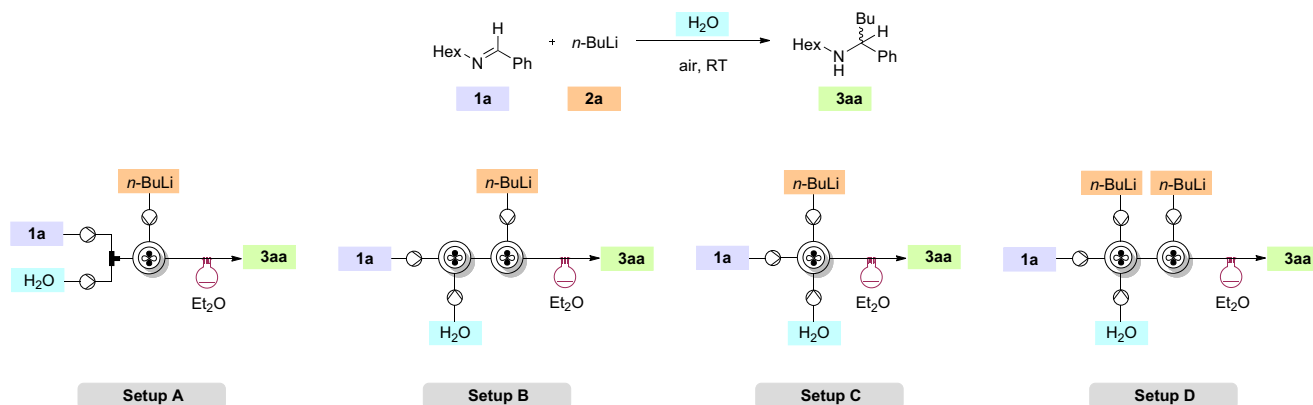
However, as far as we know, *in continuo*, on-water organolithium chemistry has never been reported. Our study aims to develop the organolithium addition to imines *in continuo*, minimize the risk and improve the safety of this reaction, and, possibly, to increase the selectivity, thanks to a better control on the reaction parameters. If successful, the methodology would allow us to carry out, for a long time, highly risky but also very fast reactions with minimum hazard.<sup>32,33</sup>

Different devices and equipment are commercially available to run *in continuo* transformations (Figure 1), including coil, micro-/mesochip, and catalytic reactors, but additional opportunities are offered by continuous stirred tank reactors (CSTRs), which are nowadays available even on laboratory scale.<sup>34</sup>

To overcome existing limitations related to the on-water organolithium chemistry, we decided to investigate the *in continuo* addition of alkyllithium reagents to N-alkyl and N-benzyl liquid imines on water using a CSTR (fReactor).<sup>35</sup> The addition of n-BuLi 2a to N-hexyl benzaldimine 1a to afford amine 3aa was chosen as a model reaction and studied using different experimental setups (Scheme 2).

In the attempt to reproduce the original in-batch conditions,<sup>12</sup> the configurations A and B of Scheme 2 were employed, featuring a premixing zone where the imine-water emulsion is created by a T-junction (setup A) or a CSTR (setup B) and a second zone where the organolithium addition occurs into a CSTR; the outlet is collected into a flask filled with diethyl ether. However, because moderate yields were obtained under those conditions, alternative setups C and D were tested. In C, a simultaneous addition of the three components into one CSTR was performed, while in D, a further addition of the organolithium solution in a second CSTR was designed. The most promising results were observed with setup C, which was selected for further optimization studies.

Preliminary investigations on the role of water, the stoichiometry of organolithium, and some experimental parameters such as stirring, reaction time, and temperature were undertaken in order to improve chemical conversion and address possible technical issues, like clogging or uncontrolled heating. After an extensive study, some important characteristics were identified as crucial to perform a safe, productive, and reproducible reaction: (1) high stirring rate, (2) operation at room temperature, and (3) comparable flow rates for imine and water. Different conditions were



### Scheme 2. Continuous-flow setups

Continuous-flow, on-water addition of *n*-butyllithium to imines in CSTRs: different experimental setups.

tested in the *in continuo* model reaction of *n*-BuLi with *N*-hexyl benzaldimine, and some selected results are reported in Table 1.

Imine solution is fed into the reactor at 1.5 mL/min, as well as water (if 1 mL solution is used), while 2.3 M *n*-BuLi hexane solution was added at 6 mL/min. Preliminary investigations of the *in continuo*, on-water addition of butyllithium to imines in coil reactors evidenced reproducibility problems, mainly due to uncontrolled overheating, irregular flow, and clogging issues. Therefore, we focused on the use of a CSTR. Considering that the 2.5 mL CSTR has a reactor volume of about 1.6 mL, the residence time may be evaluated as 9–12 s. Control experiments showed that similar results could be obtained using 1.6, 2.3, or 2.5 M hexane solution of *n*-BuLi. A residence time of about 10 s was found to be a good compromise to guarantee efficiency and reproducibility. The effect of the amounts of organolithium and water were evaluated. By increasing the moles of organolithium, higher conversion was obtained; however, by using 3 mol equiv BuLi, clogging and overheating of the reaction mixture, difficult to control, were observed; therefore, 2 mol equiv was selected as the best option.

In a typical procedure, according to setup C, 1 mL imine, 1–10 mL water (55–550 mmol), and the organolithium solution are placed in SGE syringes and connected to the CSTR with a maximum rate stirring (1,500 rpm for an RCT basic IKA plate); the output tube is connected to a receiving flask filled with Et<sub>2</sub>O or MTBE that can be refrigerated if needed. In entries 1–5 of Table 1, for 1 mL imine, 10 mL water was used, analogously to the reported conditions for the *in-batch* reaction<sup>12</sup>; however, by operating *in continuo*, the amounts of both water and organolithium could be reduced. Under the best reaction conditions (10-s residence time, room temperature, 11 mol/equiv water, and 2 mol/equiv *n*-BuLi), product 3aa was isolated in 80% yield after chromatographic purification. Under those conditions, the productivity value is 375 (mmol/h), while the space time yield, considering a reactor volume of 1.5 mL, is 250 (mmol/h\*mL).

The effect of temperature and additives was also investigated: when the reaction was carried at 0°C and –40°C, moderate conversions were obtained. Using NaCl saturated (sat.) solution did not show any significant effect.<sup>12</sup> Of note, when reaction was performed without water (entry 11), a very high conversion in product 3aa was observed, but the method was affected by serious issues of reproducibility due to frequent clogging phenomena.

**Table 1. Continuous-flow, on-water addition of n-BuLi to imine 1a in a CSTR: Reaction parameter investigation**

Entry	RLi (mol/equiv)	Water (mol/equiv)	Residence time (s)	Yield (%) <sup>a</sup>
1	1,4	110	10	23
2	1,4	110	20	31
3	1,4	110	60	58
4	2,0	110	10	71
5	3,0	110	10	77
6	1,4	11	10	71
7	2,0	11	10	80
8 <sup>b</sup>	2,0	11	10	66
9 <sup>c</sup>	2,0	11	10	<5
10 <sup>d</sup>	2,0	11	10	79
11 <sup>e</sup>	2,0	–	10	91

<sup>a</sup>Isolated yield after column chromatography.

<sup>b</sup>Experiment conducted at 0°C.

<sup>c</sup>Experiment conducted at –40°C.

<sup>d</sup>Reaction run in the presence of NaCl sat. sol.

<sup>e</sup>Neat reaction; no water was added.

### Optimization studies and reaction scope

Based on the results reported in Table 1, further studies were carried out to test the robustness and reproducibility of the experimental procedure. Therefore, the n-BuLi and n-HexLi additions to N-hexyl and N-benzyl imines 1a–1b were performed in a CSTR (Table 2). As shown in the table (entries 1, 3, 5, and 7), a residence time of 10 s, 11 mol/equiv water, and 2 mol/equiv alkyl lithium guaranteed the best yields, affording amines 3aa, 3ab, 3ba, and 3bb in 75%–97% yields (see also the supplemental information; Table S1).

The scope of the ultrafast, on-water, *in continuo* organolithium addition to imines was then further extended (Figure 2). Under the optimized conditions of entry 8 in Table 1,

**Table 2. Continuous-flow, on-water, ultrafast addition of n-alkyllithium to N-hexyl imine 1a and N-benzyl imine 1b in a CSTR**

R = Hex **1a**

R = Bn **1b**

R<sup>1</sup> = n-Bu **2a**

R<sup>1</sup> = n-Hex **2b**

R=Hex, R<sup>1</sup> = n-Bu **3aa**

R=Hex, R<sup>1</sup> = n-Hex **3ab**

R=Bn, R<sup>1</sup> = n-Bu **3ba**

R=Bn, R<sup>1</sup> = n-Hex **3bb**

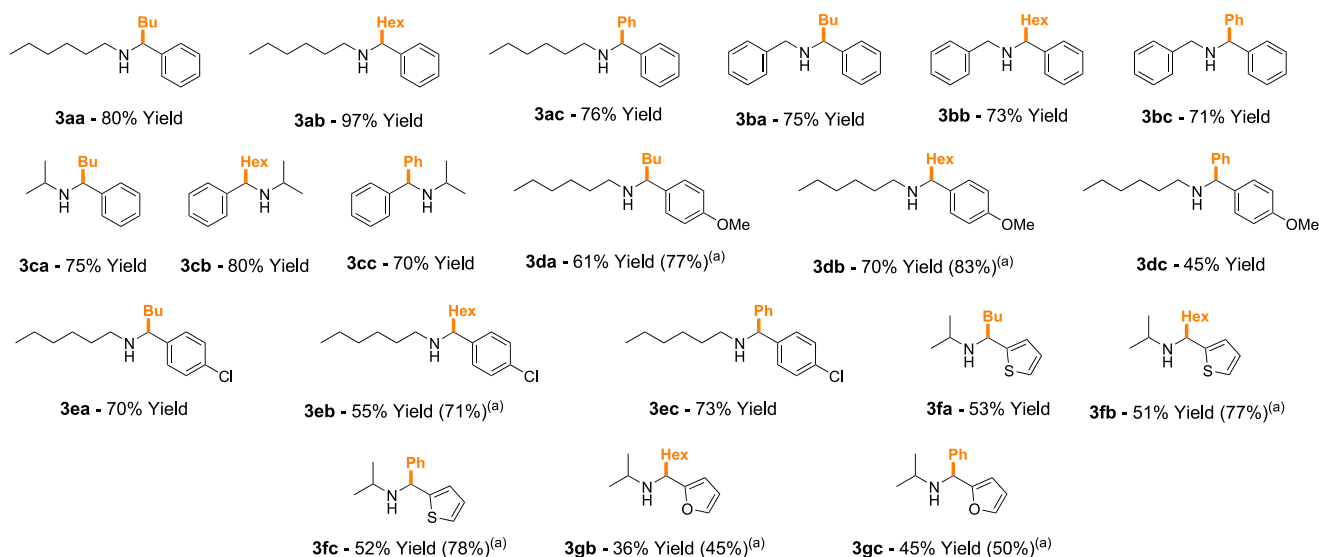
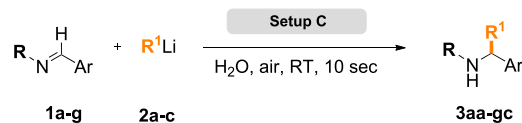
Entry <sup>a</sup>	R <sup>1</sup> Li (mol/equiv)	Product	Yield (%) <sup>b</sup>
1	2	3aa	80
2	1,4	3ab	73
3	2	3ab	97
4	1,4	3ba	60
5	2	3ba	75
6	1,4	3bb	61
7	2,0	3bb	77

<sup>a</sup>Reaction conditions: imine (1 mol/equiv), room temperature, residence time 10 s, H<sub>2</sub>O (11 mol/equiv).

<sup>b</sup>Isolated yield after column chromatography.



R = Hex; Ar = Ph	<b>1a</b>	
R = Bn; Ar = Ph	<b>1b</b>	R <sup>1</sup> = <i>n</i> -Bu <b>2a</b>
R = <i>i</i> -Pr; Ar = Ph	<b>1c</b>	R <sup>1</sup> = <i>n</i> -Hex <b>2b</b>
R = Hex; Ar = 4-OMePh	<b>1d</b>	R <sup>1</sup> = Ph <b>2c</b>
R = Hex; Ar = 4-ClPh	<b>1e</b>	
R = <i>i</i> -Pr; Ar = Thiophene	<b>1f</b>	
R = <i>i</i> -Pr; Ar = Furan	<b>1g</b>	



**Figure 2. Reaction scope**

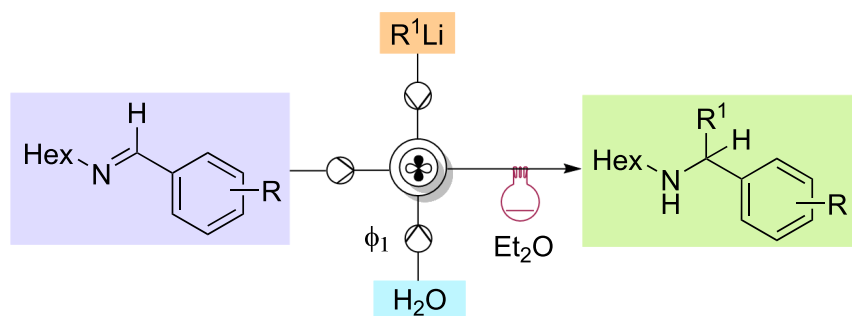
Continuous-flow, ultrafast, on-water addition of organolithiums to imines in CSTRs (picture of the typical experimental setup is shown). Isolated yields after chromatographic purification are reported.

<sup>a</sup>NMR conversion determined on the crude.

a small library of secondary amines was synthesized by reacting different imines **1a–1g** with three different commercially available organolithium reagents (*n*-BuLi **2a**, *n*-HexLi **2b**, and PhLi **2c**). The picture of the typical experimental setup is shown in the [Figure 2](#). The reaction worked well with *N*-alkyl and with *N*-benzyl imines, affording the products in 70%–97% yield. Good results were achieved both with electron-rich and electron-poor imines, while with imines of 2-thiophene and furfural, **1f** and **1g**, under those non-optimized conditions, lower yields were generally observed.

However, it should be noted that in some cases, high conversion was observed by nuclear magnetic resonance (NMR) analysis on the crude, probably indicating a not-optimized isolation procedure. Therefore, in a few cases, when low yields were observed, some additional experiments were performed in order to improve the yields ([Scheme 3](#)).

For example, the reactions to afford products **3da** and **3eb** were reinvestigated, and it was found that yields may be improved simply by changing the flow rate of water and adjusting the amount of water. By using a 2:1 imine/water flow rate ratio, amine



entry	R	R <sup>1</sup>	$\phi_1$ (ml/min)	product	yield
1	4-Cl	Hex	0.75	<b>3da</b>	93
2	4-Cl	Hex	1.5	<b>3da</b>	51
3	4-MeO	<i>n</i> -Bu	0.75	<b>3eb</b>	80
4	4-MeO	<i>n</i> -Bu	1.5	<b>3eb</b>	51

### Scheme 3. Optimization of selected examples

Optimization studies: selected examples.

**3da** and product **3eb** were obtained in 93% and 80% isolated yields, respectively, by using about 6 mol/equiv water (see the [supplemental experimental procedures](#)).

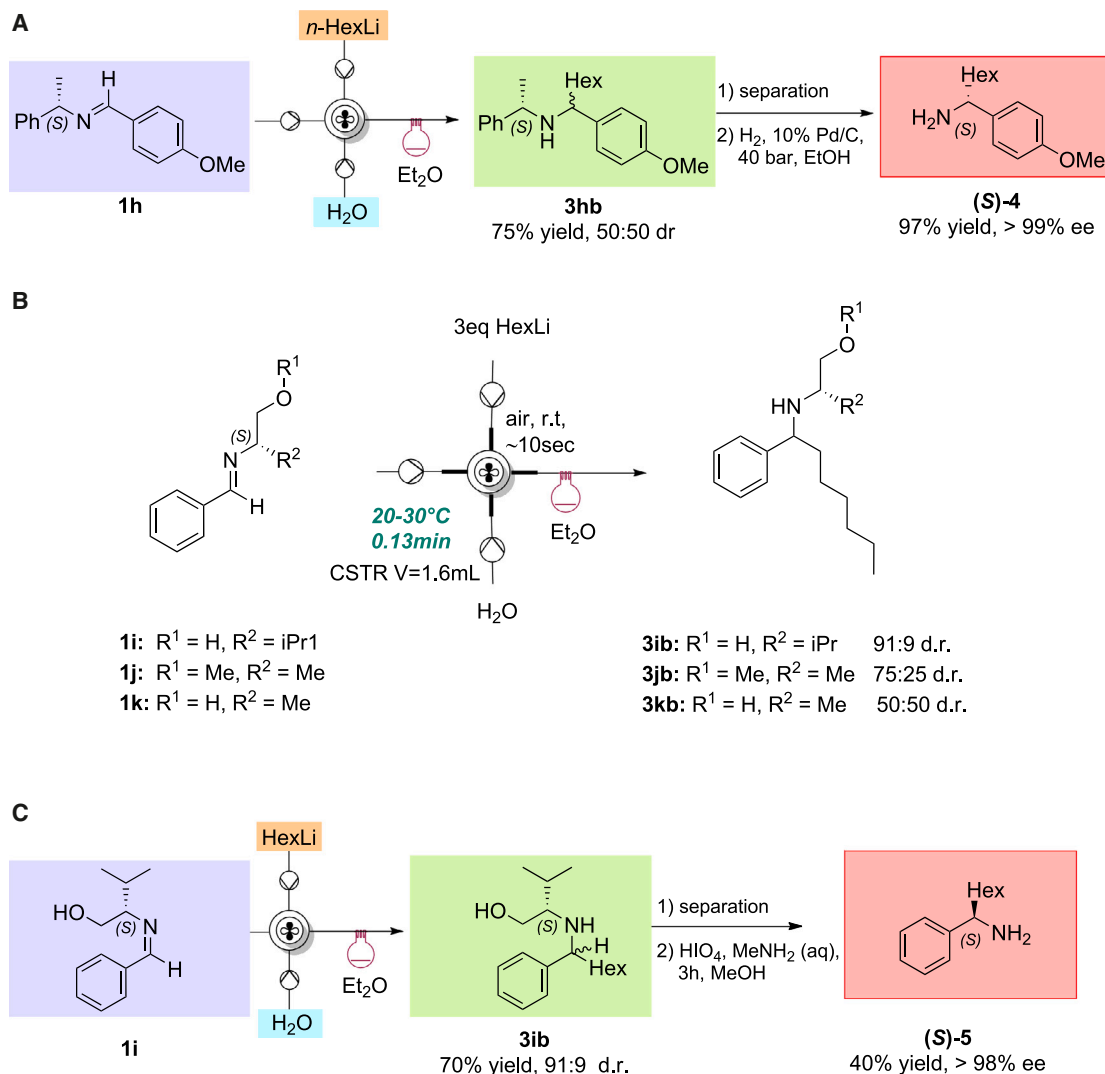
### Synthetic applications

The methodology was successfully employed also in the organolithium addition to chiral imines ([Scheme 4](#)). The reaction of *n*-HexLi with imine **1h** of 4-methoxybenzaldehyde with 1-(*S*)-phenylethylamine affords in 75% yield two diastereoisomers of amine **3hb**, in a 50:50 ratio, which can be separated. One diastereoisomer is then converted to the corresponding enantiopure 1-(4-methoxyphenyl)-eptanamine **4** by Pd/C-catalyzed hydrogenolysis, as reported in [Scheme 4A](#).

With the goal to further expand the scope of the in-flow, on-water addition of organolithium derivatives to imines and to improve the stereoselectivity of the process, the addition of *n*-HexLi to chiral imines prepared from enantiopure 1,2-aminoalcohols was investigated ([Scheme 4B](#)). Imines **1i**, **1j**, and **1k** were prepared from benzaldehyde and (*S*)-valinol, (*S*) alaninol-OMe, and (*S*)-alaninol, respectively, and reacted with *n*-HexLi with the CSTR technology. The in-flow, on-water reaction worked with all imines, affording the products in yields ranging from 50% to 75%. In particular, we were pleased to find that the organolithium addition to imine **1i** afforded the chiral amine **3ib** in 70% isolated yield and 91/9 diastereoselectivity ([Scheme 4C](#)). The major isomer was isolated as a pure compound, and upon removal of the chiral auxiliary, chiral amine (*S*)-**5** was obtained as a pure compound (98% e.e., determined by high-performance liquid chromatography; for further details on the determination of the e.e. and of the absolute configuration, please see the [supplemental experimental procedures](#)).

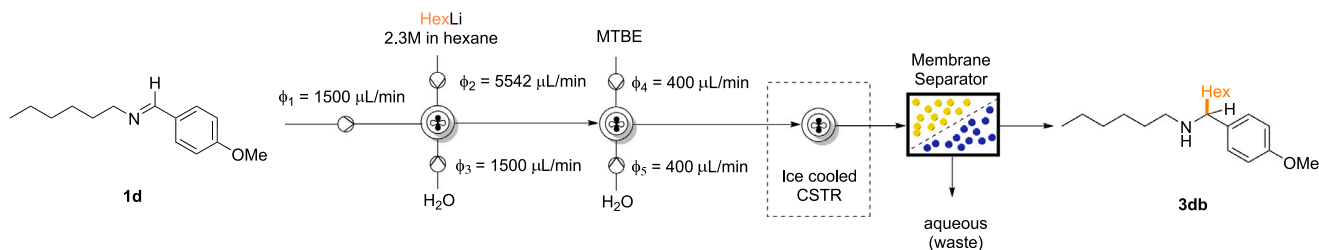
Furthermore, we have studied a scaleup of the reaction and developed a telescoped process made by three different operation units: synthesis, workup, and separation ([Scheme 5](#)). First studies showed that with a single CSTR, the reaction of *n*-hexyllithium with imine **1d** produced about 5 g of product in 3 min. However, mainly due to issues related to temperature raising and gas-release phenomena, in the attempt to develop a process *in continuo*, some optimization was necessary for the phase separation and isolation of the product.



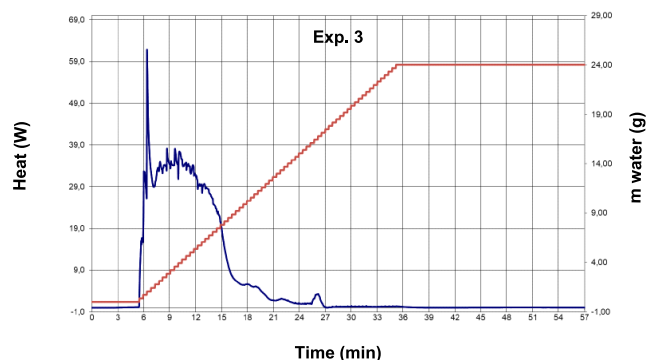
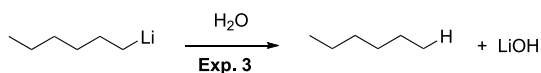
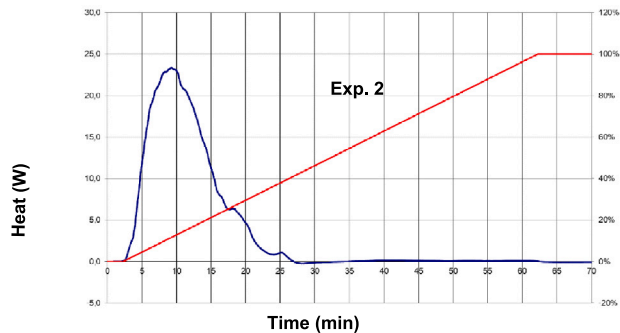
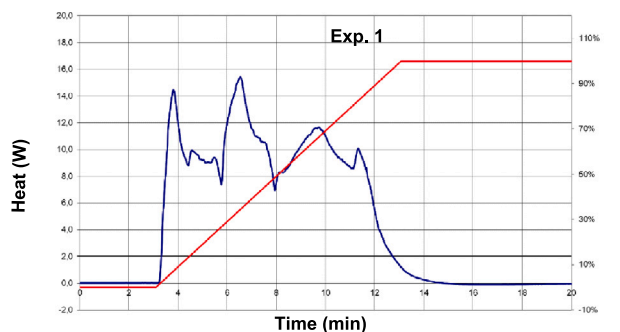
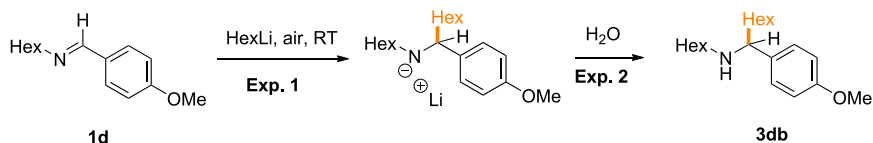


**Scheme 4.** Diastereoselective addition of *n*-HexLi to chiral imines **1h** and **1i**

In the final setup, the reaction occurred in a first CSTR, followed by the addition of water and MTBE in a second CSTR; after being cooled in an ice bath in a third CSTR, the reaction mixture enters into an in-flow membrane separator. Amine **3db** could be then isolated by simple solvent evaporation of the organic solvent (see [Video S1](#) for a video of the experimental procedure).



**Scheme 5.** Gram-scale, *in continuo* synthesis of amine **3db**



**Figure 3. Calorimetric analysis**

Exp. 1: n-HexLi addition to imine, Exp. 2: water addition to amine Li salt, and Exp. 3: water addition to n-HexLi 2.3 M in hexanes.

In order to evaluate the risk associated with this type of transformation under classical procedures, calorimetric studies were performed. Differential scanning calorimetry (DSC) analysis of the starting imine 1d and of the reaction mixtures did not show particular thermal behavior that can compromise the safety of the process. A calorimetric analysis allowed us to evaluate separately two steps of the reaction and to calculate the heat associated with these transformations. As shown in [Figure 3](#), both the organolithium

addition to imine **1d** and the quench of the reaction product, the amine Li salt, to afford the final amine **1da** are exothermic phenomena (Figure 3, Exp. 1 and Exp. 2).

The first step is very fast, and, in adiabatic conditions, the heat generated is able to evaporate about 40% of the solvent volume (hexanes of HexLi solution). As expected, the second step, the quench of the reaction product with water, is even more exothermic, and in adiabatic conditions, the heat generated would evaporate all the solvent (hexanes); the addition of water to n-HexLi solution is highly exothermic too (Figure 3, Exp. 3). This picture would lead to sudden heat peaks and a continuous variation of pressure inside the reactor. Although the problems could be at least partially overcome by controlling the exothermicity by a very slow addition of water and the reagents into the reactor, a large-scale application by traditional batch chemistry would have significant risks and significant long operation times that can be avoided by adopting the CSTR technology here described.

In conclusion, we have developed a highly productive, ultrafast, *in continuo*, on-water organolithium addition to imines, overcoming existing batch limitations and positively addressing the safety issues of the process. Remarkably, in a single 2.5 mL CSTR, 5 g amine can be synthesized in only 3 min. The methodology was applied to a variety of different substrates, thus highlighting the wide scope of the strategy. The addition of n-HexLi to chiral imines prepared from enantiopure 1,2-aminoalcohols was also investigated and led to the formation of the product in 70% yield and up to 91/9 diastereoselectivity. The major isomer was isolated as a pure compound, and upon removal of the auxiliary, the chiral amine was obtained as a pure compound (98% e.e.). Further studies are ongoing to further expand the scope of the reaction and to realize the telescoped synthesis of active pharmaceutical ingredients.

## EXPERIMENTAL PROCEDURES

### Resource availability

#### Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Maurizio Benaglia ([maurizio.benaglia@unimi.it](mailto:maurizio.benaglia@unimi.it)).

#### Materials availability

All materials generated in this study are available from the lead contact upon reasonable request.

#### Data and code availability

All data supporting the findings of this study are included within the article and its [supplemental information](#). This paper does not report on original code or datasets.

### Flow reactor setup and analysis

A typical experimental procedure was as follows: 1 equiv imine (1 mL) and 10–11 equiv water (1 mL) were fluxed at the same flow rate (1.5 mL/min) simultaneously with 2 equiv commercial organolithium solution, with the flow rate adjusted considering the concentration of the organolithium solution and with respect to the mmol of imine. The resulting residence time is  $t_{res} = 9\text{--}14$  s, depending on the specific imine, with a  $CSTRV = 1.6$  mL.

Syringes are placed on the syringe pumps and the CSTR on the plate, stirring is set at the maximum speed, and the output tube is connected to a receiving flask filled with ether (Et<sub>2</sub>O or MTBE) and water that can be refrigerated as needed. Syringes are started simultaneously, and the end of the pumping is continued until all volumes are delivered

(0.67 min for reagent flux). At the end of the reaction, the reactor and the tubes are washed with ether in order to recover remaining material and to avoid clogging of tubes.

The reaction mixture is then separated, and the organic fraction is collected into a flask, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The organic solution is concentrated under vacuum, and <sup>1</sup>H NMR analysis is made in order to evaluate the conversion. The reaction crude is purified on column chromatography, starting from 99:1 to 70:30 hexanes:ethyl acetate and increasing the polarity 5 units at time, and, if needed, an additional 10% of methanol is added to the 70:30 eluent mixture. For additional details, see the [supplemental experimental procedures](#).

Calorimetric analysis was performed on a Mettler-Toledo Easy Max 102 equipped with HF Cal and ECB (see [supplemental experimental procedures](#)).

### SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.xcrp.2024.101838>.

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### AUTHOR CONTRIBUTIONS

Investigation, J.B. and D.G.; writing – original draft, J.B. and M.B.; writing – review & editing, A.P., S.R., and M.B.; resources, D.B. and I.M.; methodology, A.P. and S.R.; supervision, A.P., S.R., and M.B.; conceptualization, M.B.

### DECLARATION OF INTERESTS

The authors declare no competing interests.

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