

Organolithium Chemistry

How to cite: *Angew. Chem. Int. Ed.* **2023**, *62*, e202214377

International Edition: doi.org/10.1002/anie.202214377

German Edition: doi.org/10.1002/ange.202214377

In Situ Quench Reactions of Enantioenriched Secondary Alkylolithium Reagents in Batch and Continuous Flow Using an I/Li-Exchange

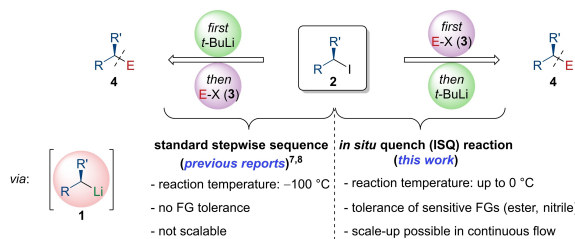
Alexander Kremismair, Henrik R. Wilke, Johannes H. Harenberg, Benjamin R. G. Bissinger, Matthias M. Simon, Nurtalya Alandini, and Paul Knochel*

Dedicated to Dieter Seebach on the occasion of his 85th birthday.

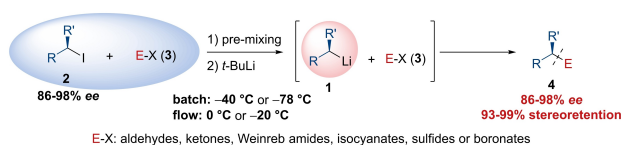
Abstract: We report a practical in situ quench (ISQ) procedure involving the generation of chiral secondary alkylolithiums from secondary alkyl iodides (including functionalized iodides bearing an ester or a nitrile) in the presence of various electrophiles such as aldehydes, ketones, Weinreb amides, isocyanates, sulfides, or boronates. This ISQ-reaction allowed the preparation of a broad range of optically enriched ketones, alcohols, amides, sulfides and boronic acid esters in typically 90–98% *ee*. Remarkably, these reactions were performed at -78°C or -40°C in batch. A continuous flow set-up permitted reaction temperatures between -20°C and 0°C and allowed a scale-up up to a 40-fold without further optimization.

The enantioselective synthesis of small molecules has attracted increasing interest in pharmaceutical and agrochemical research.^[1] Especially, the preparation of enantioenriched organometallics is an important goal as it gives straightforward access to numerous enantiopure compounds after quenching with electrophiles.^[2] Nevertheless, many reported chiral maingroup organometallics bear a heteroatom in α -position for stabilization, preventing fast epimerization.^[3] Therefore, we investigated a general preparation of optically enriched non-heteroatom stabilized organometallics.^[4] Recently, we have reported the preparation of chiral non-heteroatom stabilized^[5] secondary alkylolithiums (**1**) from the corresponding iodides (**2**) via an I/Li-exchange with *t*-BuLi. The resulting organolithium species^[6] were either directly quenched with electrophiles (**3**) or trapped after stereoretentive transmetalations^[7] leading to various products of type **4** (Scheme 1a, left).^[8] However, the drawback of such approaches was the very low temperatures

a) Reported stepwise procedure (left) and *in situ* quench (ISQ) method (right) via chiral alkylolithiums:



b) This work: *In situ* quench (ISQ) of chiral secondary alkylolithiums in batch or flow



Scheme 1. Previous standard sequence and highly stereoretentive ISQ-reactions involving secondary alkylolithium intermediates.

required for the generation of the organolithium species (-100°C). Furthermore, the functional group tolerance was limited and the scale-up of these reaction sequences proved to be difficult affording poor yields and low optical purities. Thus, we have found that an *in situ* quench (ISQ, also known as Barbier conditions)^[9] of chiral alkyl iodides in the presence of a suitable magnesium reagent with *t*-BuLi allowed the performance of the I/Li-exchange at up to -50°C with high stereoretention (up to 99%) providing, upon transmetalation, several chiral secondary Grignard reagents.^[10] Yet, the resulting chiral alkylmagnesiums proved to be unreactive towards some important classes of electrophiles (**3**) including enolizable or sterically hindered ketones.

Hence, we envisioned an ISQ-reaction involving the treatment of enantioenriched secondary alkyl iodides (**2**) in the presence of electrophiles (**3**) using *t*-BuLi at -78°C or higher temperatures (Scheme 1a, right). These conditions combined with the use of a continuous flow set-up might allow even higher temperatures and previously impossible reaction scales. These perspectives would greatly improve the practicability of our method. Herein, we report such an *in situ* quench (ISQ) reaction of chiral alkylolithiums (**1**), including for the first time highly functionalized substrates, in the presence of a broad range of electrophiles such as aldehydes, ketones, Weinreb amides, isocyanates, sulfides, or boronates (**3**) after the addition of *t*-BuLi at -78°C or

[*] A. Kremismair, H. R. Wilke, J. H. Harenberg, B. R. G. Bissinger, M. M. Simon, Dr. N. Alandini, Prof. Dr. P. Knochel
 Department Chemie, Ludwig-Maximilians-Universität München
 Butenandtstrasse 5-13, Haus F, 81377 München (Germany)
 E-mail: paul.knochel@cup.uni-muenchen.de

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even -40°C . This allowed the facile preparation of diversely functionalized products of type **4** with high enantiomeric purity (up to 98% *ee*) via intermediate alkylolithiums of type (**1**, Scheme 1b). Furthermore, we were able to transfer the reaction into continuous flow conditions, in which it was scaled up to a 40-fold.

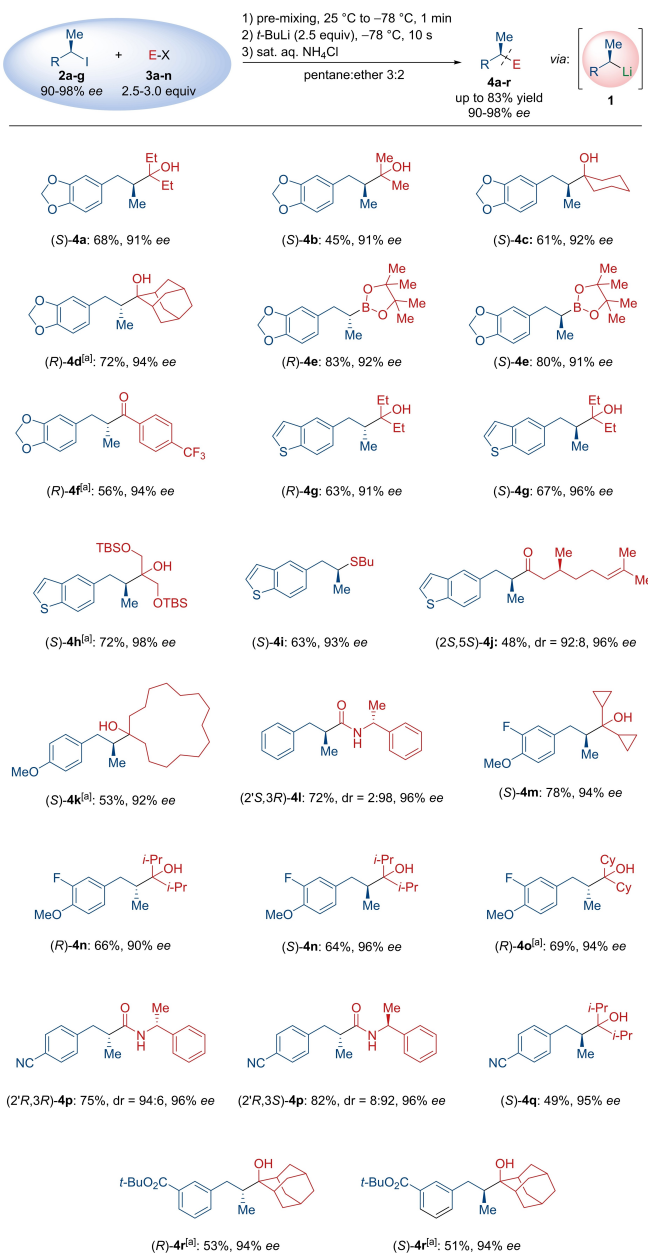
In preliminary experiments, we have converted the chiral secondary alkyl iodide (*R*)-**2a** (95% *ee*) into the corresponding organolithium (*R*)-**1a** at -100°C (addition of (*R*)-**2a** to *t*-BuLi within 60 s) resulting, after immediate quench with diethyl ketone (**3a**, 2.5 equiv), in the formation of the alcohol (*R*)-**4a** in 67% GC-yield and 92% *ee* (Table 1A, entry 1). Increasing the reaction temperature to -78°C or -40°C led to significant racemization of (*R*)-**4a** showing the limitations of the former two-step procedure (entries 2 and 3 of table 1A). In contrast, using the ISQ-procedure and mixing the iodide (*R*)-**2a** (95% *ee*, 1.0 equiv) with Et_2CO (**3a**, 2.5 equiv) in 3:2 pentane:ether and adding *t*-BuLi (2.1 M in pentane) within 10 s at -78°C provided (*R*)-**4a** in 60% isolated yield and 93% *ee* (entry 4). A temperature increase to -60°C led to (*R*)-**4a** in 52% GC-yield and still 92% *ee* (entry 5). A slight erosion of enantioselectivity was observed at -40°C , providing (*R*)-**4a** in 54% GC-yield and 90% *ee* (entry 6). A significant decrease in optical purity of (*R*)-**4a** was observed when the reaction was done at -20°C (44% GC-yield, 86% *ee*, entry 7) or at 0°C (41% GC-yield, 69% *ee*, entry 8). Changing the amount of electrophile used in the ISQ-procedure led to lower yields of (*R*)-**4a**.^[11]

Table 1: Preparation of the enantioenriched alcohol (*R*)-**4a** using a two-step sequence via alkylolithium (*R*)-**1a** followed by the addition of diethyl ketone (**3a**, method A) or via the in situ generation of (*R*)-**1a** in the presence of **3a** (method B).

A) two-step reaction procedure			
Entry	Temperature [$^{\circ}\text{C}$]	GC-Yield of (<i>R</i>)- 4a ^[a]	<i>ee</i> of (<i>R</i>)- 4a ^[b]
1	-100	67%	92%
2	-78	61%	53%
3	-40	54%	0%
B) in situ quench (ISQ) procedure			
Entry	Temperature [$^{\circ}\text{C}$]	GC-Yield of (<i>R</i>)- 4a ^[c]	<i>ee</i> of (<i>R</i>)- 4a ^[b]
4	-78	60% ^[c]	93%
5	-60	52%	92%
6	-40	54%	90%
7	-20	44%	86%
8	0	41%	69%

[a] The yield was determined by GC-analysis; [b] The enantiomeric excess (% *ee*) was determined by chiral HPLC-analysis; [c] Yield of isolated analytically pure product.

Based on these preliminary experiments, we have designed a general procedure for the in situ quench of various functionalized chiral secondary alkyl iodides of type **2** in the presence of electrophiles (E-X) of type **3** such as ketones, boronates, Weinreb amides, disulfides, aldehydes and isocyanates leading to functionalized chiral products of type **4** (Scheme 2). Thus, mixing (*S*)-**2a** and diethyl ketone (**3a**) in pentane:ether and adding *t*-BuLi within 10 s at -78°C followed by an immediate quench with sat. aq.

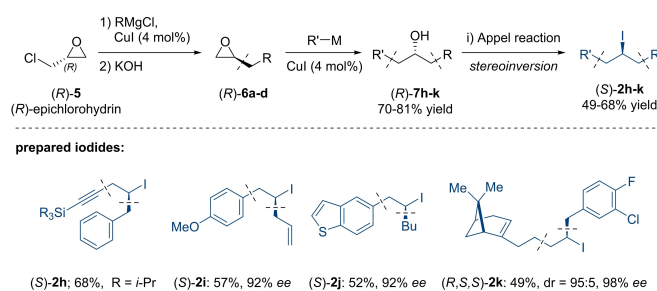


Scheme 2. Prepared chiral products **4a-r** by in situ quench (ISQ) of optically enriched secondary alkyl iodides **2a-g** in the presence of electrophiles **3a-n** using *t*-BuLi. Yields refer to isolated analytically pure products. The enantiomeric excess (% *ee*) was determined by chiral HPLC-analysis. The diastereomeric ratio (dr = *syn/anti*) was determined via GC- or NMR-analysis. [a] The reaction was performed at -40°C using 3.0 equiv of electrophile.

NH_4Cl solution, gave the expected alcohol (*S*)-**4a** in 68 % yield and 91 % *ee*. Using (*S*)-**2a** in the presence of other enolizable ketones such as acetone (**3b**) or cyclohexanone (**3c**) led to the chiral alcohols (*S*)-**4b** and (*S*)-**4c** in 45–61 % yield and 91–92 % *ee*. In the case of solid electrophiles such as adamantanone (**3d**), the reaction was performed at -40°C due to the limited solubility of the reaction mixture at lower temperatures. Nevertheless, the desired alcohol (*R*)-**4d** was isolated in 72 % yield and 94 % *ee*. Also, transmetalations to boronic acid esters like (*R*)- or (*S*)-**4e** were achieved with high stereoretention in up to 83 % yield and up to 92 % *ee* starting from (*R*)- or (*S*)-**2a** and methoxyboronic acid pinacol ester (**3e**).

Although, the Weinreb amide *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (**3f**) showed only limited solubility under our standard conditions (-78°C), the ISQ-reaction could be performed at -40°C providing the α -chiral ketone (*R*)-**4f** in 56 % yield and 94 % *ee*. Employing the benzothiophene derived alkyl iodides (*R*)- or (*S*)-**2b** in the presence of diethyl ketone (**3a**) and adding *t*-BuLi at -78°C gave the corresponding alcohols (*R*)- and (*S*)-**4g** in 63–67 % yield and 91–96 % *ee*. Also, a mixture of the chiral alkyl iodide (*S*)-**2b** and the silyl protected dihydroxyacetone derivative **3g** was only soluble at -40°C and therefore *t*-BuLi was added at this temperature affording (*S*)-**4h** in 72 % yield with high stereoretention (98 % *ee*). Electrophiles like Bu_2S_2 (**3h**) or citronellal (**3i**) reacted with (*S*)-**2b** providing the sulfide (*S*)-**4i** (63 % yield, 93 % *ee*) or (2*S*,5*S*)-**4j** (after oxidation with Dess–Martin periodinane,^[12] 48 % yield, *dr*=92:8, 96 % *ee*). Furthermore, the chiral alcohol (*S*)-**4k** was isolated after mixing (*S*)-**2c** with cyclopentadecanone (**3j**) and adding *t*-BuLi at -40°C in 53 % yield and 92 % *ee*. Isocyanates like (*R*)-**3k** also proved to be suitable electrophiles when mixed with the secondary alkyl iodide (*S*)-**2d** yielding, under standard conditions, the desired amide (2'*S*,3*R*)-**4l** in 72 % yield with *dr*=2:98 and 96 % *ee*. Moreover, the optically enriched iodides (*R*)- and (*S*)-**2e** underwent the ISQ-reaction with dicyclopropyl ketone (**3l**), di-*iso*-propyl ketone (**3m**) or dicyclohexyl ketone (**3n**, at -40°C) providing the alcohols **4m–o** in up to 78 % yield and up to 96 % *ee*. To our delight, chiral secondary alkyl iodides bearing sensitive functional groups like a nitrile (*R*- and *S*)-**2f** or an ester (*R*- and *S*)-**2g** were compatible with this method. Thus, the amides (2'*R*,3*R*)-**4p** (75 %, *dr*=94:6, 96 % *ee*) and (2'*R*,3*S*)-**4p** (82 %, *dr*=8:92, 96 % *ee*) as well as the alcohol (*S*)-**4q** (49 %, 95 % *ee*) were isolated after ISQ-reaction using (*R*)- or (*S*)-**2f** and either (*R*)- or (*S*)-**3k** or (**3m**). Likewise, (*R*)- and (*S*)-**4r** were obtained after reaction of the ester-containing alkyl iodide (*R*)- or (*S*)-**2g** with adamantanone (**3d**), after addition of *t*-BuLi, in up to 53 % yield and 94 % *ee* at -40°C .

While the reaction proceeded smoothly with chiral iodides of type $\text{AlkCH}(\text{Me})\text{I}$, we have also demonstrated that more substituted alkyl iodides may be used. The required alkyl iodides were prepared from commercially available (*R*)-epichlorohydrin (*R*)-**5** in a three step sequence (Scheme 3).^[13] Thus, (*R*)-**5** was treated with various Grignard reagents (RMgCl) in the presence of 4 mol% $\text{CuI}^{[14]}$ affording, after treatment with KOH , chiral epoxides

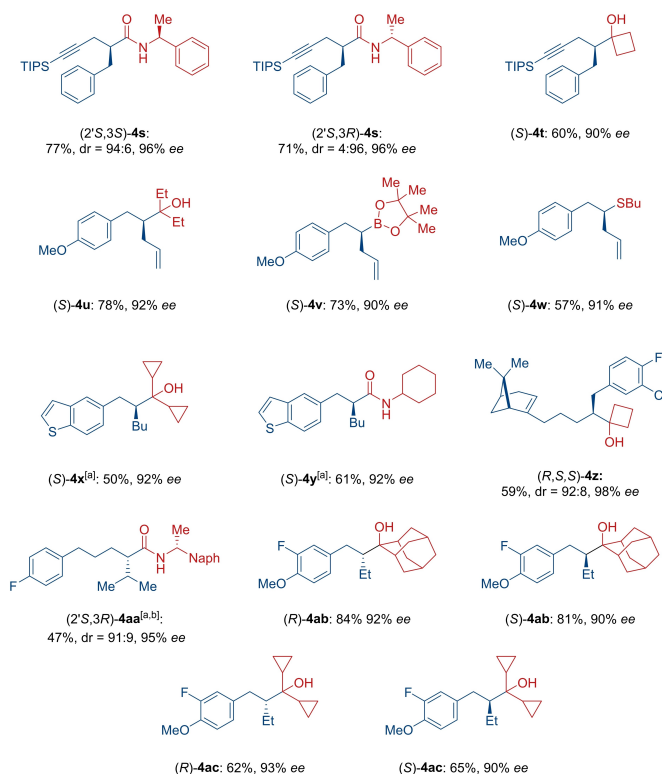
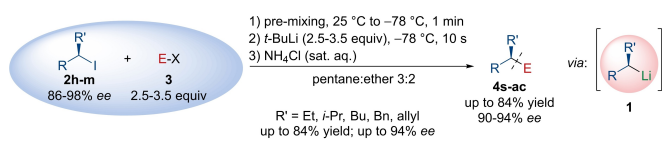


Scheme 3. Modular preparation of optically enriched secondary alkyl iodides (*S*)-**2h–k** from (*R*)-epichlorohydrin (*R*)-**5** via epoxide opening and closure sequences followed by stereoinvertive Appel reaction; i) (1.2 equiv PPh_3 , 1.2 equiv I_2 , 1.2 equiv *N*-methylimidazole, -10°C , 30 min).

of type **6**. Another ring opening of **6** with Grignard reagents ($\text{R}'\text{MgCl}$) or alkynyllithiums in the presence of 4 mol% CuI provided chiral alcohols of type **7** in 70–81 % yield (over 3 steps). A stereoinvertive Appel reaction furnished the desired secondary alkyl iodides (*S*)-**2h–k** in 49–68 % yield and 92–98 % *ee*.

With these chiral secondary alkyl iodides in hand, we performed several ISQ-reactions (Scheme 4). Thus, the chiral homobenzylic secondary alkyl iodide (*S*)-**2h** smoothly underwent the ISQ-reaction in the presence of the isocyanates (*R*)-**3k** or (*S*)-**3k** providing the diastereomerically and enantiomerically enriched amides (2'*S*,3*S*)-**4s** in 77 % with *dr*=94:6 and 96 % *ee* as well as (2'*S*,3*R*)-**4s** in 71 %, *dr*=4:96, 96 % *ee*. Furthermore, ISQ of (*S*)-**2h** with cyclobutanone (**3o**) at -78°C gave the chiral alcohol (*S*)-**4t** in 60 % yield and 90 % *ee*. Also, treating the allyl substituted iodide (*S*)-**2i** with diethyl ketone (**3a**), methoxyboronic acid pinacol ester (**3e**) or Bu_2S_2 (**3h**) led to the expected optically enriched alcohol (*S*)-**4u** (78 %, 92 % *ee*), to the boronic acid ester (*S*)-**4v** (73 %, 90 % *ee*), or to the sulfide (*S*)-**4w** (57 %, 91 % *ee*). In the case of the chiral secondary alkyl iodide (*S*)-**2j** bearing a butyl substituent, we observed that dropwise addition of 2.5 equiv of *t*-BuLi led to low conversion of this iodide to the corresponding alkyl lithium reagent. However, raising the amounts of *t*-BuLi and electrophile to 3.5 equiv led to the expected alcohol (*S*)-**4x** and amide (*S*)-**4y** in up to 61 % yield with full stereoretention (92 % *ee*) when using dicyclopropyl ketone (**3l**) or cyclohexyl isocyanate (**3p**) as electrophiles.

Also the terpene derived optically enriched iodide (*R,S,S*)-**2k** underwent the ISQ-reaction providing, after mixing with cyclobutanone (**3o**) and addition of *t*-BuLi, the desired alcohol (*R,S,S*)-**4z** in 59 % yield with *dr*=92:8 and 98 % *ee*. Even the sterically demanding secondary alkyl iodide (*S*)-**2l**, bearing an *iso*-propyl substituent,^[15] reacted with (*R*)-(-)-1-(1-naphthyl)ethyl isocyanate (*R*)-**3q** under high stereoretention providing (2'*S*,3*R*)-**4aa** in 47 % yield and *dr*=91:9 (95 % *ee*). Moreover, the optically enriched alcohols (*R*)- and (*S*)-**4ab** as well as (*R*)- and (*S*)-**4ac** were isolated after this ISQ-reaction from (*R*)- and (*S*)-**2m** in the presence of either adamantanone (**3d**) or dicyclopropyl ketone (**3l**) in up to 84 % yield and up to 93 % *ee*.



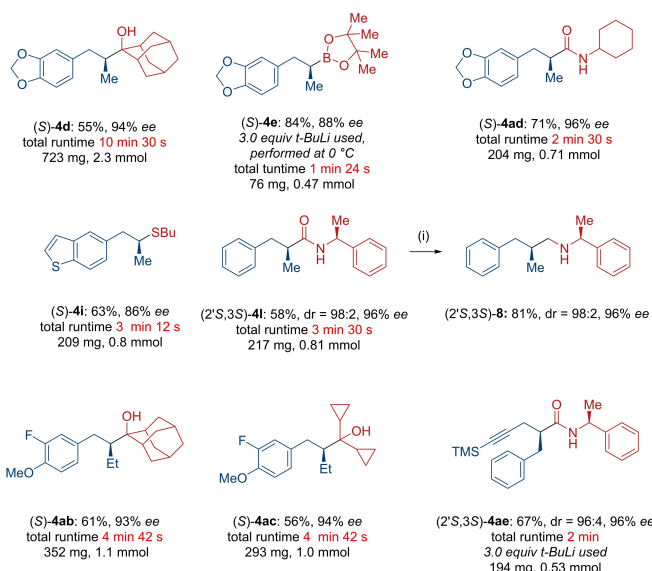
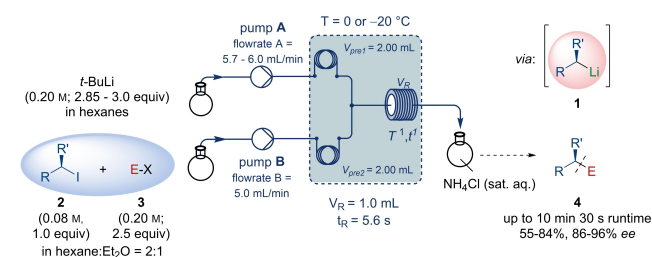
Scheme 4. Chiral products **4s-ac** prepared by in situ quench (ISQ) of functionalized optically enriched secondary alkyl iodides (**2h-m**) in the presence of electrophiles (**3**) using *t*-BuLi at -78 °C. Yields refer to isolated analytically pure products. The enantiomeric excess (% ee) was determined by chiral HPLC-analysis. The diastereomeric ratio (dr = *syn/anti*) was determined via GC- or NMR-analysis. [a] The reaction was performed using 3.5 equiv of *t*-BuLi and 3.5 equiv of electrophile; [b] Naph = naphthyl.

Although these ISQ-procedures provided various highly enantioenriched products, a scale-up above 0.3 mmol was complicated and gave erratic results. Recently, the use of continuous-flow setups and microreactors gained increasing interest in sustainable synthesis^[16] especially in terms of safer handling of thermally labile organometallics. Pioneering works by Ley,^[17] Yoshida,^[18] Organ,^[19] and others^[20] have popularized the performance of reactions involving highly reactive organometallics in continuous flow.

Therefore, we envisioned that this ISQ-reaction might benefit from the fast mixing properties and the efficient heat transfer of micro reactor technology. We utilized a commercial two pump system^[11] in which the beforehand prepared solution of *t*-BuLi (0.20 M in hexane)^[21] and the premixed solution of alkyl iodides of type **2** (0.08 M) and electrophiles of type **3** (0.20 M in hexane:Et₂O = 2:1) were passed through precooling loops (2.0 mL) using two peristaltic pumps. The streams were combined in a T-shaped mixer and pumped

through a coil reactor (1.0 mL). Upon reaching steady state, the reaction mixture was collected in a flask charged with *sat. aq.* NH₄Cl (Scheme 5).

After a short optimization,^[11] based on the previously found conditions, we observed that the continuous flow set-up allowed to raise the reaction temperature at which the ISQ was performed to -20 °C. Best results were obtained when pumping the premixed alkyl iodide and electrophile solution at a flowrate of 5.0 mL min⁻¹. Whereas the *t*-BuLi solution was pumped at a flowrate of 5.7 to 6.0 mL min⁻¹ depending on the substrate. Therefore, the residence time in the coil reactor varied between 5.5 to 5.6 s. Thus, also moderately soluble electrophiles like adamantanone (**3d**) in the presence of the secondary alkyl iodide (**S**)-**2a** were employed and, after mixing with *t*-BuLi, the corresponding alcohol (**S**)-**4d** was isolated in 55% with 94% ee. No clogging of the reactor was observed and the reaction mixture was collected for a total of 10 min 30 s, resulting in a 40-fold scale-up in comparison to batch conditions. The high optical purity of (**S**)-**4d** indicated that the elevated temperatures do not lead to any significant epimerization of the intermediate alkyl lithium (**1a**). Furthermore, X-ray diffraction analysis of (**S**)-**4d** using Flack parameter method^[22]



Scheme 5. Preparation of optically enriched products of type **4** via in situ quench (ISQ) of optically enriched secondary alkyl iodides in the presence of electrophiles (**3**) using *t*-BuLi in continuous flow. Yields refer to isolated analytically pure products. The enantiomeric excess (% ee) was determined by chiral HPLC-analysis. The diastereomeric ratio (dr = *syn/anti*) was determined via GC- or NMR-analysis. (i) LiAlH₄ (3.0 equiv), 0 °C to 50 °C, 14 h.

confirmed the (*S*)-configuration and an overall stereoretention.^[23] If (*S*)-**2a** was mixed with other electrophiles like boronic acid ester **3e**, the temperature could be increased even further to 0 °C, preventing precipitation in the precooling loop. Under these conditions, the optical purity decreased only slightly and (*S*)-**4e** was obtained in 84 % isolated yield and 88 % *ee*. Also, (*S*)-**2a** was treated with cyclohexyl isocyanate (**3p**) upon addition of *t*-BuLi and after collecting for 2 min 30 s the desired amide (*S*)-**4ad** was isolated in 71 % yield and 96 % *ee*. The reactions of (*S*)-**2b**, in the presence of Bu₂S₂ (**3h**), or (*S*)-**2d**, which was mixed with the isocyanate (*S*)-**3k**, and *t*-BuLi provided the sulfide (*S*)-**4i** (63 %, 86 % *ee*) or the amide (2'*S*,3*S*)-**4l** (58 %, *dr* = 98:2, 96 % *ee*). Furthermore, the optically enriched iodides (*S*)-**2m** and (*S*)-**2n** were also compatible with this continuous flow set-up and the scale-up of their reactions with either adamantanone (**3d**) or dicyclopropyl ketone (**3l**) as well as (*S*)-(-)-1-phenylethyl isocyanate (*S*)-**3k** gave (*S*)-**4ab**, (*S*)-**4ac** and (2'*S*,3*S*)-**4ae** in up to 67 % yield with up to *dr* = 96:4 and up to 96 % *ee*.

Further post-functionalizations have been achieved by reducing the chiral amide (2'*S*,3*S*)-**4l**^[24] to the corresponding amine (2'*S*,3*S*)-**8**^[25] with complete retention of the configuration (Scheme 5).^[26]

In summary, we have reported a practical and convenient ISQ-procedure for converting various secondary alkyl iodides, including ester or nitrile-functionalized iodides, to highly reactive secondary alkyllithiums in the presence of electrophiles such as ketones, aldehydes, Weinreb amides, isocyanates, boronates and disulfides. A wide range of chiral molecules such as alcohols, ketones, amides, boronic esters and thioethers were obtained with high retention of configuration. Remarkably, these ISQ-reactions were conducted between -78 °C and -40 °C in batch and between -20 °C and 0 °C in continuous flow. This continuous flow set-up also allowed to scale-up this reaction up to 40-fold without further optimization.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (DFG) and the Ludwig-Maximilians-Universität München for financial support. We also thank Albemarle for the generous gift of chemicals. We also thank Prof. Dr. K. Karaghiosoff for X-Ray crystal measurement. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric Synthesis · Barbier Reaction · Chiral Organometallics · Continuous Flow · Organolithium

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Manuscript received: September 29, 2022

Accepted manuscript online: October 21, 2022

Version of record online: November 29, 2022