Butyllithium-Mediated Coupling of Aryl Bromides with Ketones under In-Situ-Quench (ISQ) Conditions: An Efficient One-Step Protocol Applicable to Microreactor Technology

Sachio Goto, Janna Velder, Sherif El Sheikh, Yuki Sakamoto, Masatoshi Mitani, Said Elmas, Andreas Adler, Anne Becker, Jörg-Martin Neudörfl, Johann Lex, Hans-Günther Schmalz*

Institut für Organische Chemie, Universität zu Köln, Greinstr. 4, 50939 Köln, Germany
Fax +49(221)4703064; E-mail: schmalz@uni-koeln.de

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Abstract: Exploiting the high rate of bromine–lithium exchange reactions, aryl carbinols such as fenpy-type ligands are readily obtained by simply combining a mixture of a ketone and an aryl bromide with butyllithium.

Key words: organometallic reagents, lithiation, amino alcohols, microreactors, nucleophilic addition

The reaction of organolithium compounds with carbon electrophiles belongs to the most powerful and general C–C-bond-forming processes.[1] Besides deprotonation (e.g. *ortho*-directed metallation),[2] halogen–lithium exchange is certainly the most common technique for the (regioselective) generation of organolithium intermediates.[1,3] Typically, a THF solution of an aryl bromide or iodide (**1**) is treated at low temperature with butyllithium, and the resulting aryllithium species (**2**) is subsequently quenched with an electrophile, e.g. a ketone to give an alcohol of type **3** after aqueous workup (Scheme 1).

While routinely used in many laboratory syntheses, this two-step protocol is not particularly attractive especially for industrial applications because handling of highly reactive (air-sensitive) reagents on a larger scale in multistep batch processes requires extensive (and expensive) safety precautions. Also, low reaction temperatures are usually necessary to allow for an effective control of the exothermic reactions.

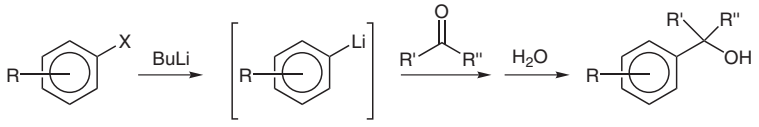
A new technology offering promising solutions for the above-mentioned problems is based on microstructured flow reactors.[4] The main advantages of such 'microreactors' are: (1) excellent heat-exchange properties (temperature control), (2) very efficient and rapid mixing of the reactive components, and (3) small reaction volumes. Therefore, microreactors are in principle ideally suited for the performance of fast and highly exothermic reactions in a very safe manner, and even multikilogram quantities of products can be produced, once appropriate parameters have been elaborated for a given transformation under the flow conditions.

Intending to use a commercially available (single-step) microreactor system[5] for transformations of the above-mentioned type (Scheme 1), we envisioned that such reactions could possibly be executed in a one-step fashion under in situ quench (ISQ) conditions.[6] As halogen–lithium exchange is known to be very fast even at low temperatures,[7] it seemed not impossible to (chemoselectively) generate the intermediates of type **2** in the presence of a ketone as a trapping agent.

We herein report the first results of a study, which proves the general feasibility of the concept and the usefulness of the operationally extremely simple ISQ protocol, both in the flask (batch) and in the microreactor (continuous).

As a first relevant reaction system we studied the synthesis of the chiral pyridinoalcohol **6** ('fenpy')[8] under ISQ conditions (Scheme 2). Indeed, when *n*-butyllithium (1.2 equiv) was simply injected into a stirred 1:1 mixture of fenchone (**4**) and 2-bromopyridine (**5**) in THF at –78 °C, the desired product **6** was formed in high yield (Table 1, entry 1).

As Table 1 demonstrates, the preparation of **6** under ISQ conditions proceeded smoothly and with virtually complete diastereoselectivity, even at comparably high temperatures (–30 °C or 0 °C). This is particularly remarkable, as the classical stepwise procedure gives acceptable yields and selectivities only at low reaction temperatures (–78 °C).[8b]



1 (X = Br, I) **2** **3**

Scheme 1 Common two-step protocol for the generation of an aryllithium species (**2**) and its subsequent reaction with a ketone

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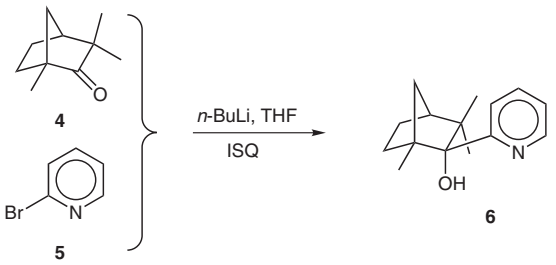


Scheme 2 Operationally simple one-step protocol for the coupling of fenchone (**4**) and 2-bromopyridine (**5**) under ISQ conditions

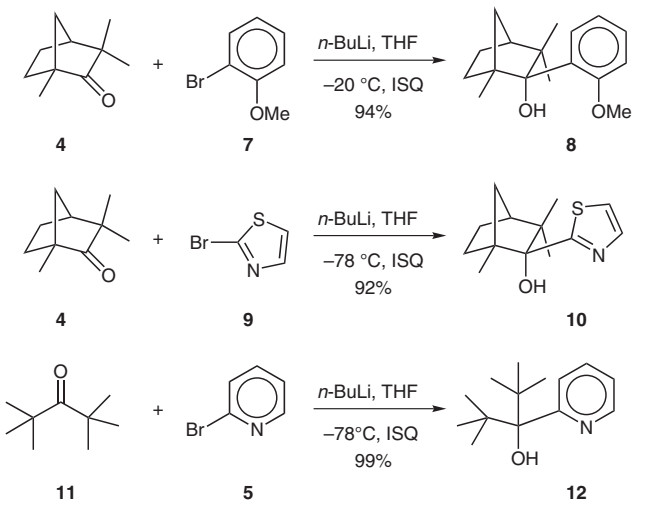
While the ISQ protocol also worked well with other aryl bromides (e.g. **7** and **9**), only nonenolizable dialkyl ketones, such as **4** and **11**, could be employed as long as *n*-BuLi was used as the reagent (Scheme 3). The stereochemical assignments of the fenchone-derived products were confirmed by means of an X-ray crystal structure analysis of **10**.[9]

Table 1 Synthesis of **6** According to Scheme 2

Entry	Method[a]	**4**/**5**/BuLi	Temp (°C)	Yield[b]	d.r.[c]
1	ISQ	1:1:1.2	–78	99%	≤99:1
2	stepwise[d]	1.1:1:1.1	–78	56%	≤99:1
3	ISQ	1:1:1.2	–30	84%	≤99:1
4	ISQ	1:1:1.2	0	87%	≤99:1
5	ISQ	2:1:1.5	–78	99%	≤99:1
6	stepwise	2:1:1.5	–78	88%	≤99:1
7	ISQ	2:1:1.5	–30	96%	≤99:1
8	stepwise	2:1:1.5	–30	63%	75:25
9	ISQ	2:1:1.5	0	88%	≤99:1
10	stepwise	2:1:1.5	0	≤7%	45:55

[a] ISQ: *n*-BuLi was added to a THF solution of **4** and **5**; stepwise: *n*-BuLi was added to a THF solution of **5** before **4** was added in a separate step.
[b] Isolated yield.
[c] Diastereomeric ratio (**6**/*epi*-**6**) as determined by GC–MS analysis of the crude reaction mixture.
[d] See ref. 8b (reaction was carried out in Et_2O).

Other ketones such as menthone (**13**), camphor (**15**), norcamphor (*rac*-**17**), and benzophenone (**19**) did not yield significant amounts of the desired coupling products under the *n*-BuLi-mediated ISQ conditions (Table 2, entries 4, 6, 8, and 10).[12] However, by using *tert*-butyllithium (2 equiv) instead of *n*-BuLi, in order to guarantee an irreversible and even faster bromine–lithium exchange,[13] a broader variety of ketones (including **13**, **17** and **19**) could be employed (Table 2). Only camphor, as a hindered and α-acidic ketone, did not afford any of the addition product (**16**), which can only be prepared through a stepwise procedure, preferentially in the presence of stoichiometric amounts of $CeCl_3$[8a] or $LaCl_3 \cdot 2LiCl$.[14]



Scheme 3 Synthesis of alcohols **8**,[10] **10**, and **12**[11] under ISQ conditions, i.e. by simply adding *n*-BuLi (1.2 equiv) to a 1:1 mixture of the ketone and the aryl bromide in THF

We also investigated the reaction of 2,6-dibromopyridine (**25**) under ISQ conditions employing fenchone (**4**) as a reliable electrophile (Table 2, entry 15). Using only a slight excess of *n*-BuLi, the mono-alkylated product **26** was obtained in high yield.

Having demonstrated the efficiency of the one-step ISQ protocol in the flask (batch mode) we next turned our attention to the performance of such reactions in a flow microreactor (Figure 1).[5] As a model reaction system we again used the *n*-BuLi-mediated coupling of 2-bromopyridine (**5**) with fenchone (**4**) to give **6** (Scheme 2).

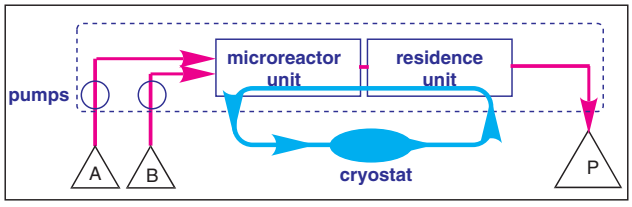
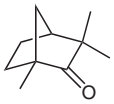
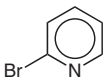
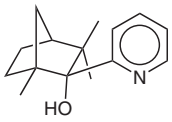
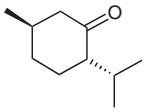
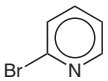
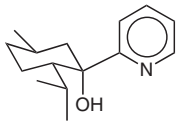
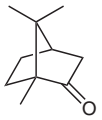
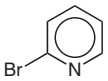
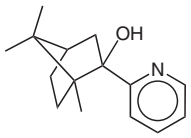
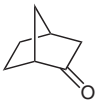
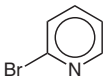
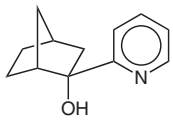
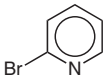
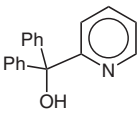
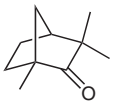
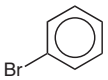
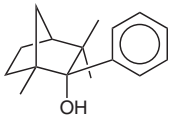
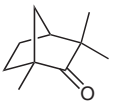
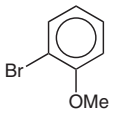
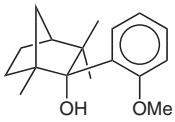
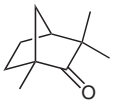
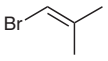
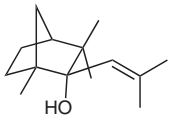
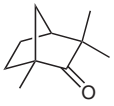
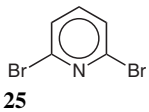
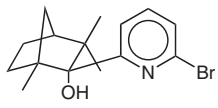


Figure 1 Schematic design of a CPC microstructured flow-through reactor (Cytos): two stock solutions (A and B) are pumped through a microstructured mixing and reaction unit cooled by a cryostat

The results (Table 3) testify that, after adjustment of reaction parameters, good yields of **6** can be achieved also under the flow conditions in the microreactor. As a second, even more convincing proof of principle, the synthesis of **26** (cf. Table 2) was achieved in 82% isolated yield on a 50-gram scale (see experimental section) by reacting a 1:1.2 mixture of dibromopyridine (**25**) and fenchone (**4**) in THF with a solution of *n*-BuLi (1.4 equiv) in hexane in the microreactor.

In conclusion, we have elaborated an operationally simple, high-yielding synthesis of aryl carbinols through BuLi-mediated coupling of aryl bromides with ketones exploiting the concept of ISQ.[15] While our original objective to develop a protocol transferable to single-stage flow

Table 2 BuLi-Mediated Synthesis of Various Alcohols under ISQ Conditions

Entry	Ketone[a]	Bromide	Product	Reagent[a]	Yield[b]
1	 **4**	 **5**	 **6**	*t*-BuLi	92%
2				*n*-BuLi	99%
3	 **13**	 **5**	 **14**	*t*-BuLi	58%
4				*n*-BuLi	<1%
5	 **15**	 **5**	 **16**	*t*-BuLi	<1%
6				*n*-BuLi	<1%
7	 **17**	 **5**	 **18**	*t*-BuLi	51%
8				*n*-BuLi	<1%
9	 **19**	 **5**	 **20**	*t*-BuLi	77%
10				*n*-BuLi	6%
11	 **4**	 **21**	 **22**	*t*-BuLi	97%
12	 **4**	 **7**	 **8**	*t*-BuLi	94%
13				*n*-BuLi	95%
14	 **4**	 **23**	 **24**	*t*-BuLi	90%
15	 **4**	 **25**	 **26**	*n*-BuLi	98%

[a] *n*-BuLi (1.2 equiv) or *t*-BuLi (2.0 equiv) was added at –78 °C to a THF solution of the ketone (1.0 equiv) and the bromide (1.0 equiv).
[b] Isolated yield; in all cases only a single diastereomer was formed according to ^{1}H NMR and GC–MS analysis of the crude reaction mixture.

microreactor systems was accomplished,[16] we could show the ISQ methodology to also open new options for the synthesis of compounds which cannot be obtained by other means in a comparably efficient manner. It should also be mentioned that compound **26** has recently been identified as a particularly useful fenpy-type ligand in the zinc-mediated enantioselective alkynylation of aldehydes.[17]

Further research in our laboratory is directed towards the exploration of the scope of the ISQ methodology using, for instance, other electrophiles instead of ketones. We are confident that the protocol disclosed here will find many applications in the future.

Table 3 *n*-BuLi-Mediated Coupling of Fenchone (**4**) with 2-Bromopyridine (**5**) under ISQ Conditions Performed in a Microreactor[a]

Entry	**4**/**5**/*n*-BuLi	Temp.	Yield[b]
1	1:1:1	–25 °C	56%
2	2:1:1.5	–25 °C	71%
3	2:1:1.5	0 °C	68%
4	2:1:2	–25 °C	91%

[a] Reactions were run in a flow-microreactor (see Figure 1) with a flow rate 5 mL/min; residence time: 3 min.
[b] Isolated yield of **6**.

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(9) The crystallographic data (excluding structure factors) for compounds **10**, **14** and **26** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 645156 (for **10**), CCDC 679624 (for **14**) and CCDC 645157 (for **26**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

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(11) Compound **12** was recently prepared in only 15% yield from the same starting materials following a stepwise procedure. See: Lomas, J. S.; Adenier, A.; Cordier, C. *J. Phys. Org. Chem.* **2006**, *19*, 295.

(12) In these cases, products arising from direct attack of *n*-BuLi at the ketone (**13**, **17**) or from ketone reduction (**19**) were isolated as main products, besides starting material(s)and the debrominated arene.

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(15) **General Procedure A for the Coupling of Aryl Bromides with Ketones (in a flask using *n*-BuLi)**: A stirred solution of an aryl bromide (5 mmol) and a ketone (5 mmol) in THF (10 mL) was cooled to –78 °C and *n*-BuLi (3.75 mL, 6 mmol, 1.6 M in hexane) was added dropwise via syringe. After 1 h at –78 °C, the stirred reaction mixture was allowed to warm to 0 °C. The reaction was quenched by addition of sat. aq NH_4Cl (5 mL) and H_2O (15 mL), extracted with MTBE or Et_2O (20 mL), and the organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo the crude product was purified by flash chromatography (typically cyclohexane–EtOAc, 30:1).
General Procedure B for the Coupling of Aryl Bromides with Ketones (in a flask using *t*-BuLi): A stirred solution of an aryl bromide (5 mmol) and a ketone (5 mmol) in THF (10 mL) was cooled to –78 °C and *t*-BuLi (6.5 mL, 10 mmol, 1.54 M in pentane) was added dropwise via syringe. After 4 h at –78 °C, the cooling bath was removed and the reaction mixture was stirred at r.t. for 2 h. The reaction was quenched by addition of sat. aq NH_4Cl (5 mL) and H_2O (15 mL), extracted with MTBE or EtOAc (3 × 30 mL), and the organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo the crude product was purified by flash chromatography (typically cyclohexane–EtOAc, 30:1).
(1*R*,2*R*,4*S*)-2-(2′-Pyridinyl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (**6**): Prepared according to the general procedure A. 2-Bromopyridine (**5**; 0.79 g, 5 mmol) and fenchone (**4**; 0.76 g, 5 mmol) were reacted with *n*-BuLi (4 mL, 6 mmol) to give **6** (1.14 g, 99%) as a white solid; mp 73 °C; $[\alpha]_D^{20}$ –39.9 (*c* = 2.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.42 (s, 3 H), 0.97 (s, 3 H), 1.00 (s, 3 H), 1.13 (m, 1 H), 1.35 (dd, ^1J = 10.8 Hz, ^2J = 1.5 Hz, 1 H), 1.47 (m, 1 H), 1.79 (m, 1 H), 1.84 (m, 1 H), 2.23 (m, 1 H), 2.34 (m, 1 H), 5.79 (br, 1 H), 7.17 (ddd, ^1J = 7.2 Hz, ^2J = 4.2 Hz, ^3J = 1.0 Hz, 1 H), 7.49 (td, ^1J = 8.2 Hz, ^2J = 1.0 Hz, 1 H), 7.67 (m, 1 H), 8.45 (ddd, ^1J = 4.2 Hz, ^2J = 1.8 Hz, ^3J = 1.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1, 22.2, 24.3, 29.2, 32.5, 42.0, 46.1, 48.9, 51.9, 83.8, 121.6, 123.4, 135.7, 146.2, 162.1. HRMS (EI): *m*/*z* calcd for $C_{15}H_{21}NO$: 231.162; found: 231.162.
(1*R*,2*R*,4*S*)-2-(Thiazol-2-yl)-1,3,3-trimethyl-

bicyclo[2.2.1]heptan-2-ol (**10**): Prepared according to general procedure A. 2-Bromothiazole (**9**; 0.33 g, 2 mmol) and fenchone (**4**; 0.30 g, 2 mmol) were reacted with *n*-BuLi (1.27 mL, 2.4 mmol) to afford **10** (0.437 g, 92%) as a pale yellow solid; mp 43 °C; $[\alpha]_D^{20}$ 84.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.69 (s, 3 H), 0.92 (s, 3 H), 1.02 (s, 3 H), 1.17–1.23 (m, 1 H), 1.29 (dd, ^1J = 10.0 Hz, ^2J = 2.0 Hz, 1 H), 1.45–1.52 (m, 1 H), 1.73–1.79 (m, 1 H), 1.79–1.80 (m, 1 H), 1.95–2.01 (m, 1 H), 2.68 (dd, ^1J = 10.0 Hz, ^2J = 2.0 Hz, 1 H), 2.95 (br, 1 H), 7.20 (d, *J* = 3.0 Hz, 1 H), 7.72 (d, *J* = 3.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.0, 21.8, 25.2, 28.5, 30.6, 40.8, 46.1, 48.6, 53.8, 86.4, 118.0, 141.4, 177.0. MS (EI, 70 eV): *m*/*z* (%) = 237 (15), 156 (100), 140 (35), 126 (20), 86 (70), 59 (25). HRMS (EI): *m*/*z* calcd for $C_{13}H_{19}NOS$: 237.1187; found: 237.1185. Anal. Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07; N, 5.90. Found: C, 65.77; H, 8.08; N, 5.87.

(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-(pyridin-2-yl)cyclohexanol (**14**): Prepared according to general procedure B. 2-Bromopyridine (**5**; 0.79 g, 5 mmol) and menthone (**13**; 0.77 mg, 5 mmol) were reacted with *t*-BuLi (7.7 mL, 10 mmol) to afford **14** (0.68g, 58%) as a white solid; mp 70–71 °C; $[\alpha]_D^{20}$ –23.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.63 (d, *J* = 6.8 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.93–1.26 (m, 2 H), 1.33 (d, *J* = 11.9 Hz, 1 H), 1.47–2.03 (m, 6 H), 5.20 (br, 1 H), 7.13 (dd, ^1J = 4.9 Hz, ^2J = 1.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.65 (td, ^1J = 8.0 Hz, ^2J = 2.0 Hz, 1 H), 8.46 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 21.9, 22.3, 23.6, 27.4, 28.4, 35.2, 50.0, 50.7, 77.1, 119.2, 121.5, 136.7, 146.9, 165.3. HRMS (EI): *m*/*z* calcd for $C_{15}H_{23}NO$: 233.1779; found: 233.178. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.06; H, 9.94; N, 6.08.

(1*R*,2*R*,4*S*)-2-(6-Bromopyridine-2-yl)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (**26**): Prepared according to general procedure A. 2,6-Dibrompyridine (**25**; 2.37 g, 10.0 mmol) and fenchone (**4**; 1.61 mL, 10.0 mmol) were reacted with *n*-BuLi (7.7 mL, 12.0 mmol) to afford **26** (3.04 g, 9.8 mmol, 98%) as a colorless solid; $[\alpha]_D^{20}$ –40.4 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 55 °C): δ = 0.46 (s, 3 H), 0.98 (s, 3 H), 0.99 (s, 3 H), 1.14 (dt, ^1J = 8.3 Hz, ^2J = 16.9 Hz, 1 H), 1.34 (d, *J* = 10.5 Hz, 1 H), 1.48 (m, 1 H), 1.78–1.83 (m, 2 H), 2.28 (m, 1 H, H-6), 5.45 (s, 1 H), 7.32–7.48 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1, 22.1, 24.4, 29.2, 32.5, 41.9, 46.2, 48.9, 52.2, 84.0, 121.7, 125.6, 127.1, 137.6, 140.9. Anal. Calcd for $C_{15}H_{20}NOBr$: C, 58.07; H, 6.50; N, 4.51. Found: C, 58.14; H, 6.53; N, 4.40.

Synthesis of 26 on a 50-gram Scale Using a Microreactor: Stock solutions of reactants were prepared as follows:
A: 2,6-Dibromopyridine (**25**; 94.76 g, 0.405 mol) and fenchone (**4**; 76.08 g, 0.50 mol) were dissolved and diluted with anhyd THF to a volume of 1000 mL.
B: *n*-BuLi (330 mL, 0.52 mol, 1.58 M in hexane) was diluted with anhyd hexane to a volume of 1000 mL.
A microreactor system (Cytos from CPC systems) equipped with a 2-mL microreactor cell and a 15-mL residence unit was flushed with anhyd THF and cooled by means of a cryostat to a temperature of –17 °C. With a flow rate of approximately 1.5 mL/min (each) the two reactant solutions (A and B) were then pumped (parallel) into the reactor. The system was stopped after 6 h. At this time 510 mL of solution A and 570 mL of solution B had been consumed. The collected product solution was carefully quenched by addition of ice-water. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic solutions were then washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by Kugelrohr distillation (120 °C/0.4 mbar) to yield **26** (51.90 g, 82%).

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