

PAPER

View Article Online
View Journal | View Issue



Cite this: *React. Chem. Eng.*, 2025, 10, 1048

Received 16th August 2024,
Accepted 25th November 2024

DOI: 10.1039/d4re00394b

rsc.li/reaction-engineering

The “factory in a lab”: telescoping the Matteson and Matteson–Hoppe–Aggarwal boronate chemistry under flow conditions†‡

Florian Fricke,^a Gerald Dräger ^a and Andreas Kirschning ^{*ab}

The Matteson reaction and the related Matteson–Hoppe–Aggarwal variant were combined in a compartmentalized flow system and the doubly homologated resulting boronate was transformed into the corresponding alcohols after terminal oxidation. Terpenoids were included allowing the generation of new terpene alcohols in excellent yields which were evaluated for their olfactory properties.

One concept of why Nature appears to be such a “formidable chemist” is associated with the fact that it does rely on the concepts of modularity and iteration as manifested in polypeptides, oligonucleotides and oligosaccharides. Also, the biosyntheses of terpenes and polyketides are based on these synthetic concepts.¹ Strategically, such iterations can be combined very well with flow chemistry² by creating assembly line systems using modular flow elements specially designed for this purpose. Such assembly line systems are easier to handle in terms of rate control than corresponding single-pot batch processes and often lead to higher yields in much shorter process times.³

The study also revealed for the first time that transfer from batch to flow provides accurate data on reaction times and ideal temperatures for the individual steps (lithiation 1 → 2, I, boronate formation 2 → 4, II, and migration 4 → 5, III) of the Matteson reaction. These three steps can be conducted in less than 10 s in total.⁴

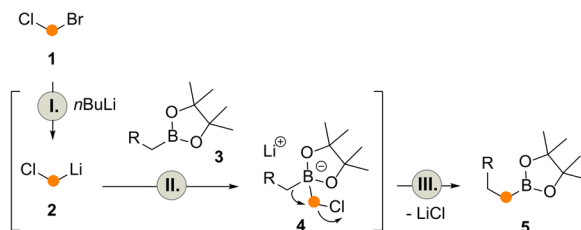
Flow chemistry is commonly associated with the term “lab on a chip”, which in our view does not fully reflect reality. Industrial reality would probably rather describe the possibilities and potential of flow chemistry with the term “factory in a lab”. Since the pioneering work of Yoshida and co-workers, it is well known that organolithium chemistry in combination with “flow” technology is perfectly suited to perform carbanion chemistry in high yield under highly optimized conditions.⁵ The easy handling of highly reactive organolithium species in flow devices⁶ was demonstrated in

the synthesis of the tricyclic antidepressant amitriptyline (Elavil).⁷ Besides carbanions, other reactive intermediates such as carbenes and radicals can be well controlled in flow reactors.⁸

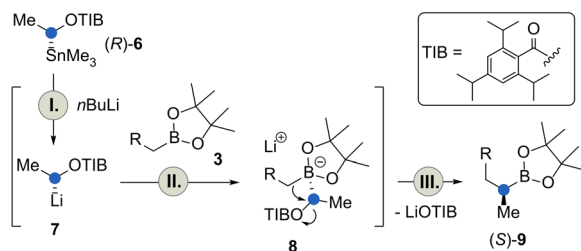
Also, the Matteson homologation reaction⁹ was found to be ideally suited for iterative operation. At each stage, a boronate ester is homologated by one carbon atom yielding a new boronate ester (Scheme 1, top).¹⁰ Recently, we disclosed a Matteson flow protocol that allowed (per-) homologation of terpenes in a controlled manner to yield homo-, bishomo- and trishomo-terpenols after oxidative workup.⁴

An extension of the Matteson reaction has recently been popularized by the group of Aggarwal.¹¹ Here, Matteson’s boronate chemistry is combined with the controlled

The Matteson homologation



The Matteson–Hoppe–Aggarwal homologation



Scheme 1 The Matteson and the Matteson–Hoppe–Aggarwal homologations.

^a Institute of Organic Chemistry, Leibniz University Hannover, Schneiderberg 1B, 30167 Hannover, Germany. E-mail: andreas.kirschning@oci.uni-hannover.de

^b Uppsala Biomedical Center (BMC), Uppsala University, Husargatan 3, 752 37 Uppsala, Sweden

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4re00394b>

‡ Dedicated to Dieter Hoppe († 20 March 2024).



formation of stable chiral organolithium intermediates developed by Hoppe and co-workers (Scheme 1, bottom).¹² Mechanistically, this reaction is very similar to the Matteson homologation (lithiation **6** → **7**, **I**, boronate formation **7** → **8**, **II**, and migration **8** → **9**, **III**) but it allows the introduction of side chains, mainly methyl groups, in a highly enantiocontrolled manner. Aggarwal and coworkers also devoted their studies to iterative applications¹³ and, more recently, to iterative automation under batch-type conditions in which they were able to prepare the core fragment of the natural product (+)-kalkitoxin.¹⁴

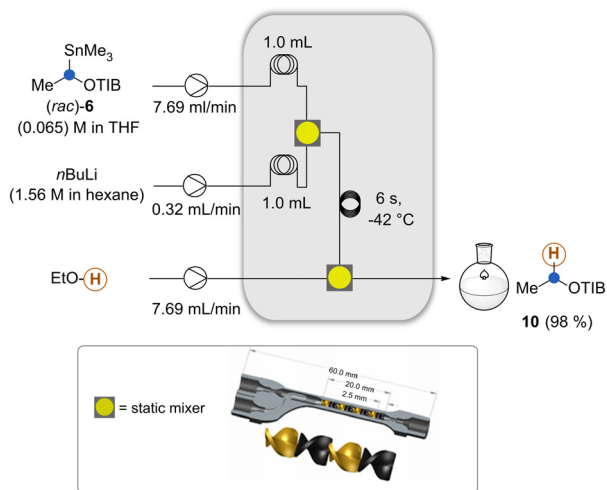
In the current work, we describe the combination of the classical Matteson reaction with the Matteson–Hoppe–Aggarwal protocol under flow conditions. Again, we included terpenes as substrates in our studies because organo-lithium flow chemistry offers great potential for “factory in the lab” production, and the flavour and fragrance industries could very well benefit from this enabling technology.^{15,16} Continuous flow processes can be controlled through flow rates and residence times and efficient mixing is a key to success, especially when the concentration of reactants or the flow rates in two streams to be mixed differ considerably.

We began our investigations with the conversion of the organotin compound **6** to the lithiated intermediate **7** by altering reaction parameters and in-line quenching with EtOH (Scheme 2). We kept the reactor system as compact as possible and decided to use moderate flow rates with residence times compatible with the second step. For optimal mixing, we employed a 3D-printed static mixer¹⁷ that was designed during the investigation of the Matteson reaction to prevent side reactions such as per-homologation¹⁸ and Wurtz coupling. It is important that the lithiation step has to be conducted below −42 °C (see the ESI†) as otherwise formation of substantial amounts of by-products was

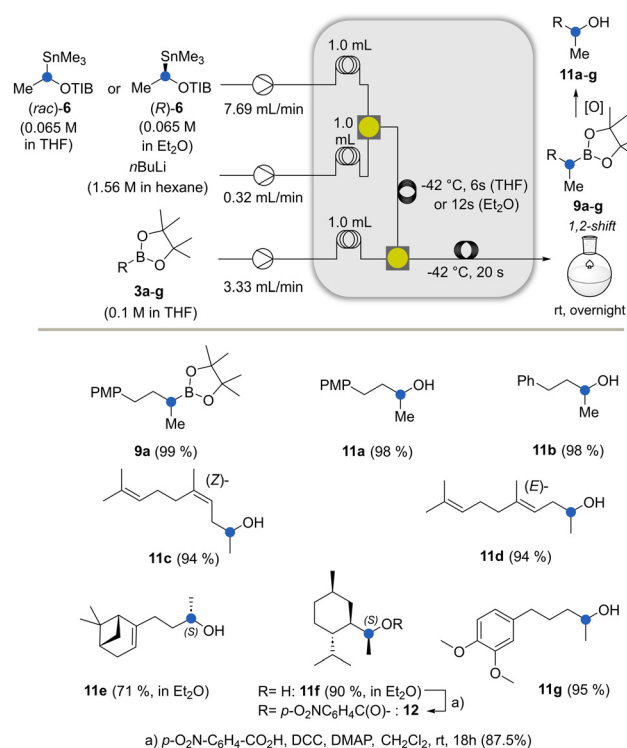
observed. Likely the lithiated species underwent degradation *e.g.* α-elimination. We then went on to introduce the boronic ester *via* a third stream (Scheme 3).

After the optimisation of the reaction parameters that included temperature, concentration, residence time and equivalents of reactants (for details, see the ESI†), we found the flow conditions that yielded the homologated boronate **9a** in excellent yields (Scheme 3). The spatial compartmentalisation of the lithiation step and the formation of the boronate complex led to an efficient suppression of side reactions. Except for the conversion of boronate **3a** to the homologous product **9a**, which served as a model reaction for the development of the Matteson–Hoppe–Aggarwal flow protocol, we generally terminated the process with the oxidation of the final boronic esters (aq. H₂O₂, (35%), 0 °C → rt). As such, the corresponding alcohols **11a–11g** were obtained from the corresponding intermediate boronates **9a–9g**.

Experiments using enantiopure **6** in THF with the boronic esters **3e** and **3f** led to the partial erosion of the integrity of the stereogenic center and the formation of a diastereomeric mixture of about 9:1. This problem was circumvented by generating the carbanion from (*R*)-configuration stannane **6** in Et₂O instead of THF. Afterwards, the lithiated species were mixed with the boronic ester dissolved in THF, leading to a single diastereomer. Clearly, a THF solution can be added to the carbenoid dissolved in a second solvent like Et₂O, which drastically enhances the rate of borylation while achieving



Scheme 2 Intercepting the *in situ* generated organolithium species **7** and formation of ester **10** to determine the residence time for the lithiation of **6**. Graphic presentation of the static mixer used here (see also ref. 4).



Scheme 3 The Matteson–Hoppe–Aggarwal homologation under flow conditions and oxidation of boronic esters (PMP = *p*-methoxybenzyl, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine).

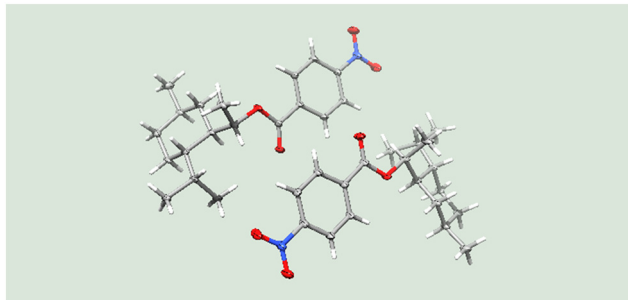


Fig. 1 Crystallographic analysis of *p*-nitrobenzoic ester **12**.

high ee values. In contrast, the exclusive use of THF leads to decreased ee values.¹⁹

Under these conditions, the residence time was found to be 12 s to achieve full conversion. The absolute configuration of the resulting alcohol **11f** was confirmed by X-ray crystallography of the *p*-nitrobenzoate **12** which was obtained under standard esterification conditions (Fig. 1).

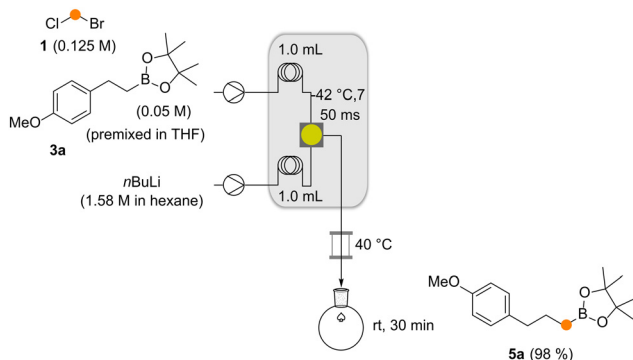
To fit the reaction parameters for coupling the aforementioned method with our previously reported Matteson homologation,⁴ we modified the original flow protocol (Scheme 4). By adjusting the substrate concentrations, equivalents and the individual flow rates in conjunction with the reactor length and the reactor temperature (see the ESI†), a flow module was created that delivered excellent yields of new boronates (Scheme 4). The module consists of two pumps, two cooling loops to cool the two input streams before they are efficiently mixed, and a reactor element where lithiation and boronate formation take place.

The two flow processes reveal differences between the Matteson homologation and the Matteson–Hoppe–Aggarwal variant. The most striking and important one is the ease of formation of the boronate complex **4** compared to the corresponding ate-complex **8** and the ease with which the rearrangement **4** → **5** versus the one from **8** to **9** occurs (Scheme 1). In the classical Matteson reaction, the lithium intermediate bears chloride, a very good leaving group and

usually it is not branched, so both steps can proceed very rapidly (within 250 ms at −40 °C for the first step and 9 s at 40 °C for the second step, according to ref. 4). In contrast, organolithium species **7** is branched with a methyl group creating a certain degree of steric hindrance but foremost the 2,4,6-triisopropylbenzoate group has poorer leaving group properties compared to chloride typically used in the Matteson homologation protocol. These factors explain the significant difference of 1,2-migration reaction rates observed for the two homologation protocols. While boronate formation is completed within 20 s at −40 °C, the rearrangement requires reaction times that are beyond the regime of seconds. The 1,2 migration can be monitored by ¹¹B-NMR spectroscopy and was reported to take place within 1–2 h at temperatures between 20 °C and 35 °C for selected boronate complexes containing the benzoate leaving group.^{13,20} With the optimized conditions for both reactions in hand, we set out to telescope the Matteson homologation flow protocol with the Matteson–Hoppe–Aggarwal homologation flow protocol developed here (Scheme 5) by connecting homologation module 1 with module 2. In module 1, the Matteson reaction was carried out by first forming the lithiated intermediate **2** by halogen lithium exchange.

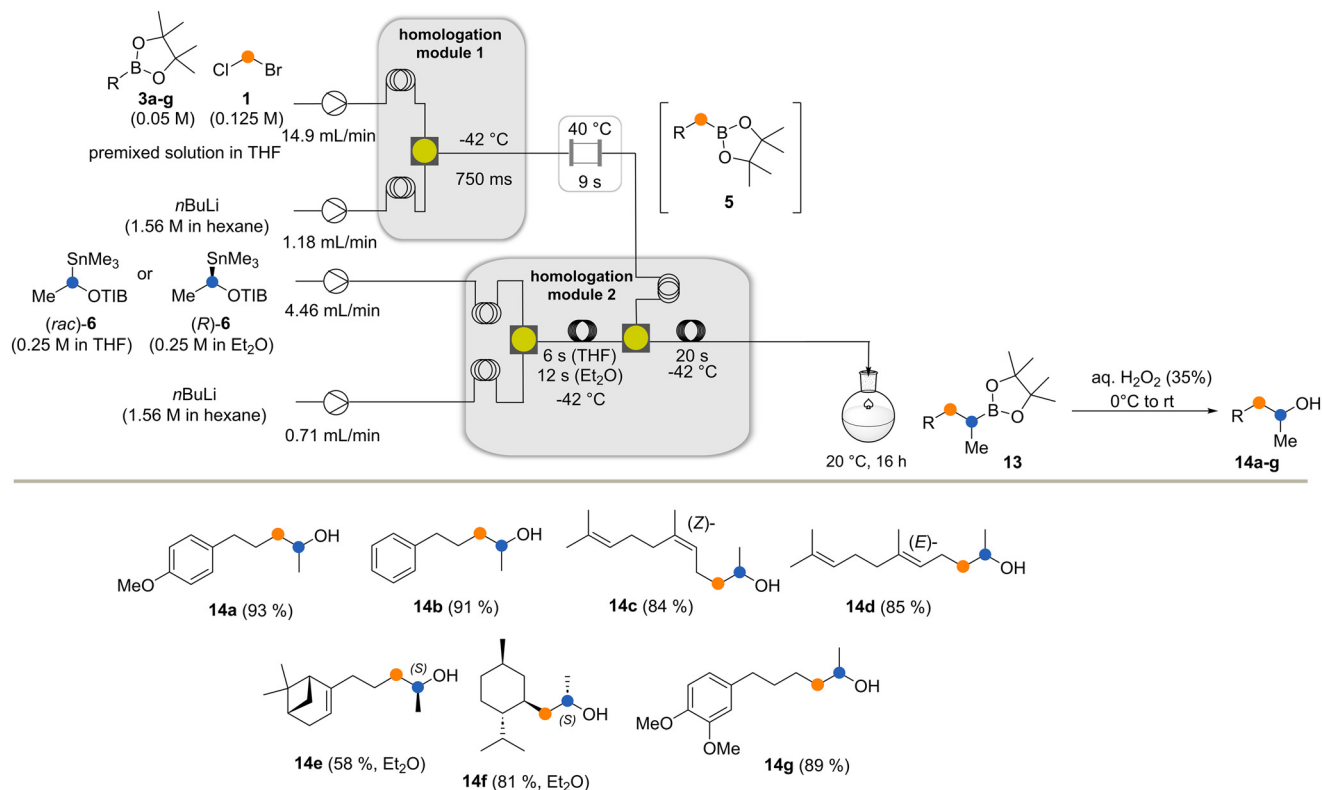
After boronation and rearrangement, the new boronates **5** were pumped into homologation module 2, where they reacted with lithiated species **7**. This was generated in a second compartment by tin lithium exchange prior to boronate formation. The resulting ate complexes that leave homologation module 2 were kept for up to 16 h at rt to guarantee complete rearrangement and formation of boronates **13a–g**. Finally, the boronic esters were directly oxidized with H₂O₂ to furnish the corresponding alcohols **14a–g** in overall very good yields.

Finally, the new alcohols **11a–g** and **14a–g** were examined for their olfactory profiles using GC–O (gas chromatography–olfactometry) (Table 1).²¹ Except for alcohol **14e**, all products showed interesting olfactory properties. Alcohols **11c** and **11d** exhibited a floral, rosy scent, with the (*Z*)-isomer outperforming the (*E*)-isomer. The −CH₂− homologated alcohols **14c** and **14d** showed similar profiles, with **14d** exhibiting an additional note of apple and pear. Alcohol **11b** exhibited a profile that can be described as flowery, herbal and green with additional notes of lavender and banana. The corresponding methylene elongated alcohol **14b** also revealed a strong scent, specifically fruity and green with a metallic note. Alcohol **11a** was judged to be woody and mossy with a hint of mold while the corresponding homologated alcohol **14a** exhibited a balsamic, powdery profile with notes of vanilla and maltol. Alcohol **11e** exhibited a weak scent with notes of lavender and muguet, whereas alcohol **14e** has an unpleasant odor profile. Alcohols **14f** and **11f** were found to have a scent linked to menthol and peppermint with a cooling touch, with **11f** showing an additional element of chamomile. Finally, the monohomologated alcohol **11g** exhibited a weak floral scent, and the doubly homologated analog **14g** showed a strong scent reminiscent of vanilla, dry fruits and rum.



Scheme 4 The Matteson homologation under flow (**3a** → **5a**). Conditions had to be optimized with respect to the protocol reported in ref. 4 for effective telescoping of this reaction with the Matteson–Hoppe–Aggarwal flow protocol.



**Table 1** Olfactory evaluation of alcohols **11a-f** and **14a-f**

Alcohol	Olfactory analysis	Alcohol	Olfactory analysis
11a	Woody, mossy with a hint of mold	14a	Balsamic, powdery profile with notes of vanilla and maltol
11b	Flowery, herbal and green; additional notes of lavender and banana	14b	Fruity and green with a metallic note
11c	Floral, rosy	14c	Floral, rosy
11d	Floral, rosy	14d	Floral, rosy with a note of apple and pear
11e	Weak scent with notes of lavender and muguet	14e	Strong, sulphurous, technical
11f	Menthol, peppermint with a cooling touch and a note of chamomile	14f	Menthol, peppermint with a cooling touch
11g	Weak, floral, salicyl-like	14g	Strong, vanilla, dry fruits, rum

Conclusions

In conclusion, we report on the development of a flow module for performing the Matteson-Hoppe-Aggarwal homologation protocol under continuous mode conditions. The use of a specially designed static mixer allowed us to carry out the homologation in a highly efficient manner with high yields. This sets the stage for combining this Matteson variant with the classical Matteson homologation by optimizing individual flow rates, residence times and reactor temperature and then linking two homologation flow modules. Double homologation and oxidation (1. Matteson, 2. Matteson-Hoppe-Aggarwal and 3. oxidation) also proceeded in very good yields. This work represents another example that organolithium chemistry and flow technology are a perfect match

being superior to the corresponding batch chemistry. This opens doors for expanding the synthetic opportunities for industrial applications which includes the fragrance and flavour industries as demonstrated in this work.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

F. F. conducted the research and performed the experiments. G. D. carried out the X-ray analysis. A.K. formulated the



overarching research goals and aims and supervised the research programme. The manuscript was written by all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Symrise AG, Holzminden, Germany and particularly Dr. J. Panten for financial support and Lara-Joy Kleine-Benne for the olfactory evaluation of new products.

Notes and references

- (a) G. Jürjens, A. Kirschning and D. Candito, Lessons from the Synthetic Chemist Nature, *Nat. Prod. Rep.*, 2015, **32**, 723; (b) J. Hartwig and A. Kirschning, Iterative Syntheses-The Gateway to New Automation Protocols, *Angew. Chem., Int. Ed.*, 2015, **54**, 10412.
- Selected reviews on flow chemistry: (a) A. Kirschning, L. Kupracz and J. Hartwig, New Synthetic Opportunities in Miniaturized Flow Reactors with Inductive Heating, *Chem. Lett.*, 2012, **41**, 562; (b) J. Wegner, S. Ceylan and A. Kirschning, Flow Chemistry - A Key Enabling Technology for (Multistep) Organic Synthesis, *Adv. Synth. Catal.*, 2012, **354**, 17; (c) D. T. McQuade and P. H. Seeberger, Applying Flow Chemistry: Methods, Materials, and Multistep Synthesis, *J. Org. Chem.*, 2013, **78**, 6384; (d) J. C. Pastre, D. L. Browne and S. V. Ley, Flow chemistry syntheses of natural products, *Chem. Soc. Rev.*, 2013, **42**, 8849; (e) I. R. Baxendale, The integration of flow reactors into synthetic organic chemistry, *J. Chem. Technol. Biotechnol.*, 2013, **88**, 519; (f) T. Fukuyama, T. Totoki and I. Ryu, Carbonylation in microflow: close encounters of CO and reactive species, *Green Chem.*, 2014, **16**, 2042; (g) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque and T. Noel, Liquid phase oxidation chemistry in continuous-flow microreactors, *Chem. Soc. Rev.*, 2016, **45**, 83; (h) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noel, Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment, *Chem. Rev.*, 2016, **116**, 10276; (i) M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, The Hitchhiker's Guide to Flow Chemistry, *Chem. Rev.*, 2017, **117**, 11796.
- (a) C. P. Gordon, The renaissance of continuous-flow peptide synthesis – an abridged account of solid and solution-based approaches, *Org. Biomol. Chem.*, 2018, **16**, 180, and references cited therein; (b) C. Battilocchio, F. Feist, A. Hafner, M. Simon, D. N. Tran, D. M. Allwood, D. C. Blakemore and S. V. Ley, Iterative reactions of transient boronic acids enable sequential C–C bond formation, *Nat. Chem.*, 2016, **8**, 360.
- C. Kuhwald and A. Kirschning, The Matteson reaction under flow conditions – iterative flash homologations of terpenes, *Org. Lett.*, 2021, **23**, 4300–4304.
- (a) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami and J. Yoshida, Generation and Reactions of o-Bromophenyllithium without Benzyne Formation Using a Microreactor, *J. Am. Chem. Soc.*, 2007, **129**, 11692; (b) A. Nagaki, E. Takizawa and J. Yoshida, Oxiranyl Anion Methodology Using Microflow Systems, *J. Am. Chem. Soc.*, 2009, **131**, 1654; (c) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi and J. Yoshida, Cross-coupling in a flow microreactor: space integration of lithiation and Murahashi coupling, *Angew. Chem., Int. Ed.*, 2010, **49**, 7543 (*Angew. Chem.*, 2010, **122**, 7705); (d) Y. Tomida, A. Nagaki and J. Yoshida, Asymmetric Carbolithiation of Conjugated Enynes: A Flow Microreactor Enables the Use of Configurationally Unstable Intermediates before They Epimerize, *J. Am. Chem. Soc.*, 2011, **133**, 3744; (e) H. Kim, A. Nagaki and J. Yoshida, A flow-microreactor approach to protecting-group-free synthesis using organolithium compounds, *Nat. Commun.*, 2011, **2**, 264; (f) A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki and J. Yoshida, Lithiation of 1,2-dichloroethene in flow microreactors: versatile synthesis of alkenes and alkynes by precise residence-time control, *Angew. Chem., Int. Ed.*, 2012, **51**, 3245 (*Angew. Chem.*, 2012, **124**, 3299); (g) A. Nagaki, Y. Takahashi and J. Yoshida, Extremely Fast Gas/Liquid Reactions in Flow Microreactors: Carboxylation of Short-Lived Organolithiums, *Chem. – Eur. J.*, 2014, **20**, 7931; (h) A. Nagaki, Y. Takahashi and J. Yoshida, Generation and Reaction of Carbamoyl Anions in Flow: Applications in the Three-Component Synthesis of Functionalized α -Ketoamides, *Angew. Chem., Int. Ed.*, 2016, **55**, 5327 (*Angew. Chem.*, 2016, **128**, 5413); (i) A. Nagaki, H. Yamashita, K. Hirose, Y. Tsuchihashi and J. Yoshida, Alkylolithiums Bearing Electrophilic Functional Groups: A Flash Chemistry Approach, *Angew. Chem., Int. Ed.*, 2019, **58**, 4027 (*Angew. Chem.*, 2019, **131**, 4067).
- A. Nagaki, Recent topics of functionalized organolithiums using flow microreactor chemistry, *Tetrahedron Lett.*, 2019, **60**, 150923.
- L. Kupracz and A. Kirschning, Multiple Organolithium Generation in the Continuous Flow Synthesis of Amitriptyline, *Adv. Synth. Catal.*, 2013, **35**, 3369.
- Reviews on “flash” chemistry: (a) J. Yoshida, A. Nagaki and T. Yamada, Flash Chemistry: Fast Chemical Synthesis by Using Microreactors, *Chem. – Eur. J.*, 2008, **14**, 7450; (b) J. Yoshida, Y. Takahashi and A. Nagaki, Flash chemistry: flow chemistry that cannot be done in batch, *Chem. Commun.*, 2013, **49**, 9896.
- D. S. Matteson and R. W. H. Mah, Neighboring Boron in Nucleophilic Displacement, *J. Am. Chem. Soc.*, 1963, **85**, 2599.
- (a) T. von Kreutz, D. Cantillo and C. O. Kappe, Flow Microreactor Technology for Taming Highly Reactive Chloriodomethylithium Carbenoid: Direct and Chemoselective Synthesis of α -Chloroaldehydes, *Org. Lett.*, 2020, **22**, 7537; (b) P. Musci, M. Colella, A. Sivo, G. Romanazzi, R. Luisi and L. Degennaro, Organomagnesium Based Flash Chemistry: Continuous Flow Generation and Utilization of Halomethylmagnesium Intermediates, *Org. Lett.*, 2020, **22**, 3623; (c) C. Stueckler, P. Hermsen, B. Ritzen, M. Vasiloiu, P.



- Poechlauer, S. Steinhof, A. Pelz, C. Zinganell, U. Felfer, S. Boyer, M. Goldbach, A. de Vries, T. Pabst, G. Winkler, V. LaVopa, S. Hecker and C. Schuster, Development of a continuous flow process for a Matteson reaction: from lab scale to full-scale production of a pharmaceutical intermediate, *Org. Process Res. Dev.*, 2019, **23**, 1069.
- 11 M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey and V. K. Aggarwal, Assembly-line synthesis of organic molecules with tailored shapes, *Nature*, 2014, **513**, 183.
 - 12 D. Hoppe and T. Hense, Enantioselective synthesis with lithium/(-)-sparteine carbanion pairs, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2282.
 - 13 S. Balieu, G. E. Hallett, M. Burns, T. Bootwicha, J. Studley and V. K. Aggarwal, Toward Ideality: The Synthesis of (+)-Kalkitoxin and (+)-Hydroxyphthioceranic Acid by Assembly-Line Synthesis, *J. Am. Chem. Soc.*, 2015, **137**, 4398–4403.
 - 14 V. Fasano, R. C. Mykura, J. M. Fordham, J. J. Rogers, B. Banecki, A. Noble and V. K. Aggarwal, Automated stereocontrolled assembly-line synthesis of organic molecules, *Nat. Synth.*, 2022, **1**, 902.
 - 15 A. Kirschning, W. Solodenko and K. Mennecke, Combining enabling techniques in organic synthesis: Continuous flow processes with heterogenized catalysts, *Chem. – Eur. J.*, 2006, **12**, 5972.
 - 16 (a) M. Kleoff, P. Kiler and P. Heretsch, Synthesis of odorants in flow and their applications in perfumery, *Beilstein J. Org. Chem.*, 2022, **18**, 754; (b) G. Gambacorta, J. S. Sharley and I. R. Baxendale, A comprehensive review of flow chemistry techniques tailored to the flavours and fragrances industries, *Beilstein J. Org. Chem.*, 2021, **17**, 1181.
 - 17 (a) O. S. Galaktionov, P. D. Anderson, G. W. M. Peters and H. E. H. Meijer, Analysis and optimization of Kenics static mixers, *Int. Polym. Process.*, 2003, **18**, 138–150; (b) D. S. Kim, I. H. Lee, T. H. Kwon and D.-W. Cho, A barrier embedded Kenics micromixer, *J. Micromech. Microeng.*, 2004, **14**, 1294.
 - 18 The perhomologation can occur when the first homologation product 5a reacts with a second equivalent of (chloromethyl) lithium (2), followed by rearrangement.
 - 19 R. C. Mykura, S. Veth, A. Varela, L. Dewis, J. J. Farndon, E. L. Myers and V. K. Aggarwal, Investigation of the Deprotonative Generation and Borylation of Diamine-Ligated α -Lithiated Carbamates and Benzoates by in Situ IR Spectroscopy, *J. Am. Chem. Soc.*, 2018, **140**, 14677.
 - 20 R. Larouche-Gauthier, C. J. Fletcher, I. Couto and V. K. Aggarwal, Use of alkyl 2,4,6-triisopropylbenzoates in the asymmetric homologation of challenging boronic esters, *Chem. Commun.*, 2011, **47**, 12592.
 - 21 Evaluation of the olfactoric profile was conducted at Symrise AG (Holzminden, Germany).

