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Matteson Reaction under Flow Conditions: Iterative Homologations of Terpenes

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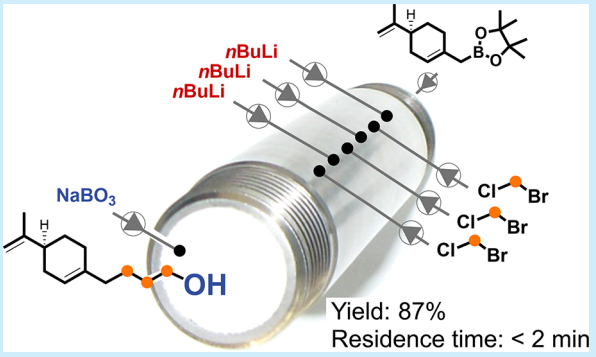
ABSTRACT: The Matteson reaction is ideally suited for flow chemistry since it allows iterative homologation of boronate esters. The present study provides accurate data on reaction times of the individual steps of the Matteson reaction, which occurs in less than 10 s in total. The protocol allows terpenes to be (per-)homologated in a controlled manner to yield homo-, bishomo-, and trishomo-terpenols after oxidative workup. The new terpene alcohols are validated with respect to their olfactoric properties.



Conceptually, modularity and iteration are common concepts that occur in nature and manifest themselves in polypeptides, oligonucleotides, and oligosaccharides as well as in secondary metabolites such as terpenes and polyketides.[1] Strategically, iteration is still in its infancy in many areas of synthesis. This includes the development of continuously operated multistep syntheses with microreactors.[2]

The performance of flow chemistry and microstructured reactor devices[3] is particularly evident in reactions that take place under energetically unusual or extreme conditions (high temperature, high pressure,[4] irradiation, or electrochemical[5]) or that are based on highly reactive reagents (e.g., fluorine, diazomethane) or intermediates (radicals, carbene, and carbanions[6]). Related to this is the fact that continuous flow processes can be precisely controlled via the residence time, so that highly reactive intermediates can be intercepted at the moment of their formation.

Yoshida et al. have shown in a series of elegant studies[7] that organolithium reagents are formed within fractions of a second and can be intercepted immediately by continuous addition of an electrophile.[8,9] Consequently, his insights have been used for the synthesis of pharmaceutically relevant molecules such as the tricyclic antidipressant amitriptyline (Elavil).[10]

Recently, several flow processes have been reported that start with chloroiodomethane and produce (chloromethyl) lithium (**2**) or its magnesium analog. They have been reacted with aldehydes and ketones, respectively.[13] Lately, an industrial consortium reported on the remarkable large-scale synthesis of an intermediate to the β-lactamase inhibitor vaborbactam, in which a flow protocol played a key role, consisting of the generation of (dichloro-methyl)lithium which served in a variant of the Matteson reaction.[14]

In view of these developments, we report on a flow protocol for the Matteson reaction with bromochloromethane as the starting point that includes controlled multihomologation and oxidation using a highly modular flow device.[11,12] For the first time, we apply our studies specifically to the synthesis of terpene-derived alcohols, which are of great importance in the fragrance industry. In developing the protocol, we particularly aimed at achieving high yields for each homologation step and short reaction times.

Pinacol boronate **3a** was chosen as the model substrate to transfer and optimize the Matteson homologation from batch to continuous flow conditions. The batch synthesis was conducted on a 0.5 mmol scale by mixing (chloromethyl) lithium (**2**) (obtained from **1** and *n*BuLi) and boronate **3a** at 78 °C in Et_2O (0.25 M).[15] The temperature was raised to rt over 30 min before workup to yield the homologated boronate **5a** (80%). Initial attempts to shorten reaction times under batch conditions, which would open the door to establish a flow protocol, showed that both yield and selectivity were significantly reduced at short reaction times. These can only be achieved under batch conditions by very rapid mixing of the reagents. Therefore, an acceptable yield of **5a** (45%) within 30 s was obtained by vigorous stirring. However, the selectivity of the reaction decreased, yielding bishomo- and trishomo-

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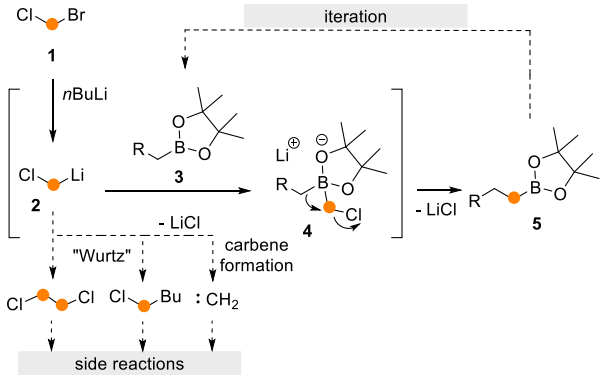
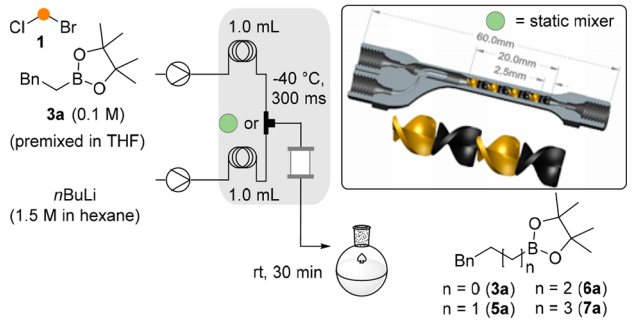
boronates (**6a**, **7a**) as byproducts judged by GC-MS (see also Scheme 2). The undesired overhomologation can occur when

Scheme 1. Concept of the (Iterative) Matteson Homologation and Possible Side Reactions



Scheme 2. Comparison of Mixer Systems for the Model Reaction (3a → 5a–7a) (Yields Determined by GC-MS); the Graphic Presentation of the Mixer Is Also Shown; Internal Cross-section of the 3D Model and Enlarged Kenics Mixer Module of 180° Clockwise and 180° Counterclockwise Spiral Structure

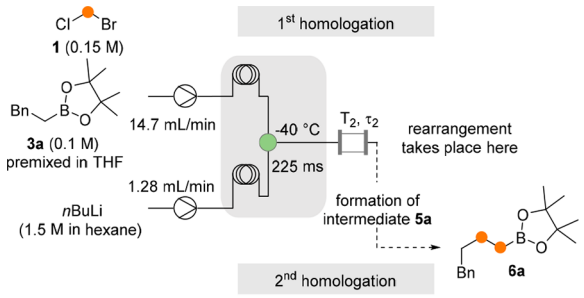


reagents ClBrCH$_2$/*n*BuLi	yield **3a** : **5a** : **6a** : **7a** [%]		
	T-mixer ID=750 μm	T-mixer ID=250 μm	Kenics-mixer
3.0 eq./2.5 eq.	11 : 83 : 5 : 1	8 : 87 : 4 : 1	3 : 96 : 1 : 0
2.0 eq./1.5 eq.	42 : 55 : 3 : 0	12 : 85 : 2 : 1	4 : 96 : 1 : 0
1.5 eq./1.3 eq.	77 : 21 : 2 : 0	46 : 53 : 1 : 0	**5 : 95 : 0 : 0**

the first homologation product **5a** reacts with a second equivalent of (chloromethyl)lithium (**2**), followed by rearrangement.

Engineered devices such as micromixers, as well as controlling reaction times by adjusting flow rates, are powerful tools for controlling ultrafast reactions under very mild conditions Thus, we started with 30 s as a guideline from above for developing a flow protocol. The optimization of the continuous Matteson reaction was divided into two separate steps: (a) the generation of the carbanion with the formation of the boronate complex and (b) then the 1,2-aniotropic rearrangement of the ate complex in a flask located at the outlet of the flow reactor. To prevent precipitation of lithium salts the solvent had to be changed from Et_2O to THF. The premixed solution containing boronate **3** and chloromethyl bromide (**1**) in THF and the *n*BuLi solution were transferred into two precooled loop reactors (V = 1 mL, ID = 1 mm), using a syringe pump. From there, the two cooled streams were mixed in a T piece (ID = 750 μm) and then fed into a

Scheme 3. Flow System for Optimizing the Conditions (Temperature = T_2, Residence Time = τ_2) of the 1,2-Aniotropic Rearrangement by Determining the Yield of the Second Homologation Product 6a[a]



6a: 98%	**6a**: 96%
τ_2 = 30 s for T_2 = 20, 30 and 40 °C	τ_2 = 20 s for T_2 = 20 °C
τ_2 = 20 s for T_2 = 30 and 40 °C	τ_2 = 8 s for T_2 = 40 °C
τ_2 = 10 s for T_2 = 30 and 40 °C	**6a**: 93%
τ_2 = 9 s for T_2 = 40 °C	τ_2 = 9 s for T_2 = 30 °C

[a]Details on the second homologation are found in Scheme 4 and the SI; yields determined by GC-MS.

microtube (V = 0.1 mL, ID = 1 mm). Downstream of the outlet, the reaction solution was passed into a glass flask where the 1,2-aniotropic rearrangement took place at elevated temperature over a period of 30 min (Scheme 2). First experiments showed that residence times greater than 1 s are not practical, presumably due to the low stability of the lithiated species **2** (Scheme 1). Thus, residence times between 1 s and 100 ms and a temperature range of −78 °C and −30 °C were chosen for optimization. The best yields were found for residence times of 200 to 300 ms and temperatures between −40 and 30 °C. Under these conditions, the yield for the homologation product **5a** was found to be 83% with 11% of starting boronate **3a** and 5% of doubly homologated product **6a**.

The per-homologation could not be suppressed by lowering the temperature. We also observed the formation of the Wurtz product from the excess of bromochloromethane (**1**), as determined by GC MS analysis. One reason for these unsatisfactory results may be insufficient mixing; initial indications of this were already provided by the batch experiments. Therefore, we planned to replace the specified T-piece.

Since the flow in microflow systems is mostly laminar, which drastically reduces efficient mixing, two approaches can be taken to overcome this problem. Either one can reduce the inner diameter of the T-piece as well as the tubing. However, this would lead to a sharp increase in pressure, which we tried to avoid. Alternatively, static or dynamic mixers can be used. We decided to use a Kenics mixing module to eliminate per-homologation and Wurtz coupling. The static mixer used here contains eight helical mixing elements, rotated alternately left and right, which divide the flow into thin layers to increase mixing speed and efficiency.[16] The mixer was designed using a CAD program and 3D printed from 1.4404 stainless steel using the SLM (selective laser melting) process (Scheme 2).

The performance of this static mixer was compared with T-mixers (ID = 750 mm and 250 mm) for the model reaction (Scheme 2), and it proved to be clearly superior to the T-mixers. The homologation product **5a** was obtained in 96%

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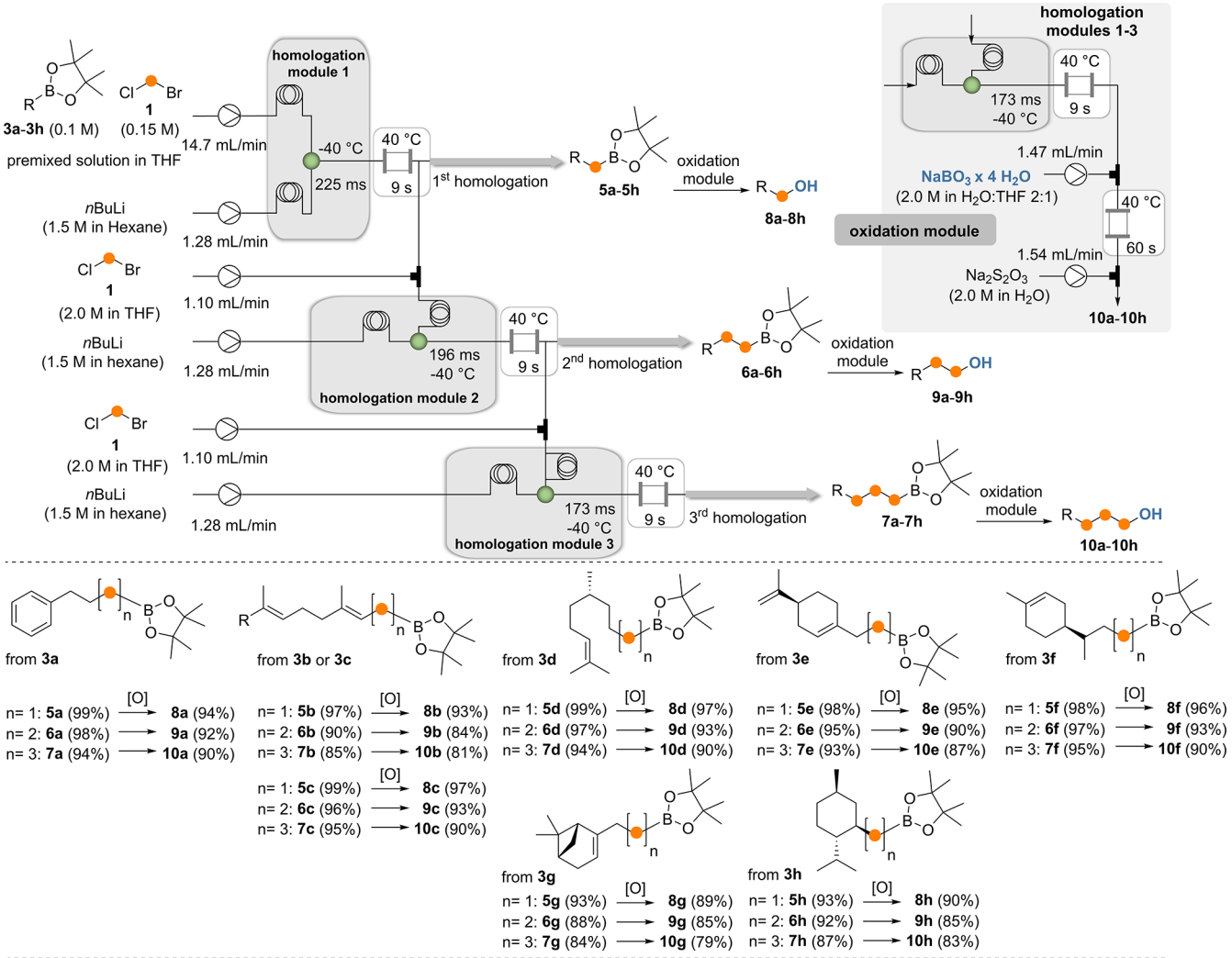
Scheme 4. Oligo-homologation of Pinacol Boronates 3a−h, Oxidation and Formation of 5−10[a]



[a]The flow set up for all three homolog-ation protocols and the oxidation is shown (isolated yields are given).

yield with reduced byproduct formation. In addition, the excess of reagents could be substantially reduced.

Optimization using 1.5 equiv of $ClBrCH_2$ (**1**) and 1.3 equiv of *n*BuLi confirmed that a residence time of 200 ms at −40 °C is ideal and resulted in 99% yield for **5a** with excellent selectivity (see Supporting Information (SI)). These optimizations were further supported by DoE revealing that temperature variations in the range −35 °C to −45 °C are principally possible with residence times between 150 and 250 ms (see SI).

We also sought to determine the best conditions in terms of residence time and temperature for the 1,2-aniotropic rearrangement that follows lithiation and boronate formation. For this purpose, we designed a flow setup that allowed flexible reactor volumes (V = 8.0, 5.3, 2.7, 2.4, and 2.1 mL) at different temperatures (T = 20, 30, and 40 °C) while the flow rate was kept constant. The rearranged product was then pumped directly into a second flow device where another homologation step occurred. This experimental setup provided us with an indication of the efficiency of the first aniotropic rearrangement via the yield of the doubly homologated product **6a** (Scheme 3). After having collected these data, we decided to perform the aniotropic rearrangement at 40 °C and a residence time of 9 s in the following studies.

In terms of substrates, we focused on the boronates **3b−3h** derived from geraniol → **3b**, farnesol → **3c**, (−)-citronellol → **3d**, (−)-perillyl alcohol → **3e**, limonene → **3f**, α-pinene → **3g**, and menthol → **3h**, as the resulting homologation products after boronic ester oxidation are of particular importance to the fragrance industry. The corresponding pinacol boronates **3b−3h** were prepared on a multigram scale (for details on their synthesis, see SI).

With the optimized protocols in hand, we developed a modular flow setup that allows mono-, di- and trihomologations to be performed under flow conditions. In addition, the boronate esters formed were converted into the corresponding alcohols **8−10** in a separate oxidation module. In this module, the last formed boronate of the modular flow synthesis was first combined with sodium perborate, while a second solution containing thiosulfate was combined with the reaction product at the outlet of the reactor. The oxidation is completed within 1 min at 40 °C. As summarized in Scheme 4, these continuously run multistep modular processes can be carried out in very high yields, generally above 95% for individual

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homologations. Thus, they are well above the reported yields for the batch reactions.

Products **5**−**10** were evaluated for their olfactory properties. We found that alcohol **8d** has a fragrance with a citrus and menthol note with an additional slightly floral component. The next homologous alcohol **9d** exhibits a turpentine and woody scent. Alcohol **9b** was found to have a strong fruity, melon-like scent. Finally, the menthol-derived pinacolboronates, especially the triple homologue **7h**, show a rather sweet slightly apple-like fruity odor. Homologous terpenes, such as homofarnesol, are also an important precursor for the synthesis of (−) ambrox, a prototype of all ambergris odorants.[17] Ambergris is a metabolic product of the sperm whale (*Physeter macrocephalus*) and is considered one of the most valuable animal perfumes.

In summary, we developed a flow protocol for the controlled homologation of pinacol boronates. As shown and exploited by Yoshida and co-workers before,[7] flow protocols with organolithium species also provide insight into lithium formation and individual reaction times at different temperatures, as also found in the present work. For example, organolithium formation from **1** is completed within ms at −40 °C, while ate formation, accompanied by the 1,2-aniotropic rearrangement, proceeds in less than 10 s at 40 °C. Overall, single Matteson homologation can be completed in less than 20 s under flow conditions, while triple homologation is remarkably accomplished in less than a minute at very high yields, with the corresponding homologated alcohols accomplished in less than 2 min.

We also show that these flow protocols succeed well with the structurally more challenging terpenoids even starting from α-branched pinacol boronates such as **3h** derived from menthol and, after oxidation, yield the alcohols that possess potential as ingredients for fragrance compositions or starting material for scents. Indeed, we believe that, in addition to the pharmaceutical industry, those industries dealing with fragrances and flavors should also benefit from flow technologies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01222.

Detailed assembly guides, experimental procedures, and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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