

Invited Paper

Open Access

Leonardo Degennaro*, Aiichiro Nagaki, Yuya Moriwaki, Giuseppe Romanazzi, Maria Michela Dell'Anna, Jun-ichi Yoshida, Renzo Luisi

Flow microreactor synthesis of 2,2-disubstituted oxetanes via 2-phenyloxetan-2-yl lithium

DOI 10.1515/chem-2016-0041

received November 11, 2016; accepted December 29, 2016.

Abstract: A mild and sustainable synthesis of 2,2-disubstituted oxetanes has been achieved through the use of a flow microreactor system. By controlling the residence time a highly unstable intermediate such as 2-phenyloxetan-2-yl lithium can be generated and trapped with various electrophiles affording in moderate to good yields 2-substituted-2-phenyloxetanes at higher temperatures with respect to macrobatch-mode where $-78\text{ }^{\circ}\text{C}$ is required.

Keywords: oxetanes, organolithium, flow chemistry, microreactor system, residence time

1 Introduction

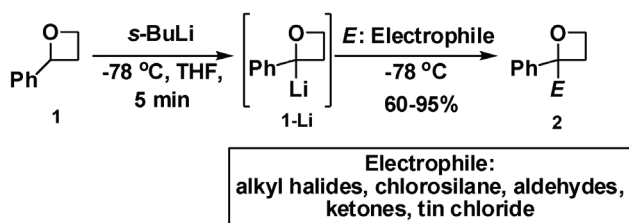
Oxetane rings have an important role as the main core in naturally occurring compounds as well as versatile motifs both in the total synthesis of natural products [1] and in synthetic organic chemistry. [2] They have also received considerable attention as versatile elements in drug discovery [3,4] and their preparation has offered opportunities for the discovery of novel chemical transformations [5]. Moreover, oxetanes are also versatile starting materials for a wide variety of ring-expansion reactions [6].

Among the strategies for accessing oxetane rings, there are generally two synthetic approaches that have the widest application, although some interesting alternative synthetic approaches have been recently suggested by Bull's group [7-11]. The first approach entails a ring-closing etherification reaction [12,13], namely an intramolecular Williamson ether synthesis, and the second one involves the Paternò-Büchi reaction [14,15], namely a photochemical [2+2] cycloaddition of carbonyl compounds to alkenes. Following these approaches, the preparation of more elaborated oxetanes bearing a higher degree of functionalization can be sometimes a very laborious work. Therefore, the study on synthesis of oxetane containing molecules is yet an open issue showing the need for new synthetic methods for the rapid preparation of valuable functionalized oxetanes. In this context, a recent work by Capriati and co-workers [16] (**scheme 1**) demonstrated, for the first time, a direct method to obtain 2-substituted-2-phenyloxetanes (**2**) by electrophilic quenching of the 2-lithiated derivative **1-Li**, although the latter was found to be thermally and configurationally unstable. In fact, at temperature higher than $-78\text{ }^{\circ}\text{C}$, **1-Li** was found to mainly undergo decomposition with the formation of a complex reaction mixture of unidentified products. However, it should be pointed out that in the reactivity of oxetanes towards alkyllithiums, it was already known that the nucleophilic substitution at C-2 can compete with α -lithiation [17] as well as oxetane moiety could undergo ring opening reactions [18,19].

More recently, Capriati's group [20], has shown that 2-substituted-2-phenyloxetanes, obtained as shown above, can be functionalized regioselectively on phenyl group via an ortho-lithiation reaction using *s*-BuLi as a base, opening new possibilities for the synthesis of oxetane derivatives. Next, Ley and co-workers [21], within this context, have successfully shown that oxetanes bearing a pyridine at C2 can be lithiated regioselectively on pyridine moiety using *n*-BuLi as a base affording new functionalized pyridine oxetane building blocks.

By taking in account the paucity of examples, employing 2-aryloxetanes as starting material for the

*Corresponding author: **Leonardo Degennaro**: Department of Pharmacy – Drug Sciences, University of Bari “A. Moro”; FLAME-Lab – Flow Chemistry and Microreactor Technology Laboratory, Via E. Orabona 4, 70125, Bari Italy, E-mail: leonardo.degennaro@uniba.it
Renzo Luisi: Department of Pharmacy – Drug Sciences, University of Bari “A. Moro”; FLAME-Lab – Flow Chemistry and Microreactor Technology Laboratory, Via E. Orabona 4, 70125, Bari Italy
Aiichiro Nagaki, Yuya Moriwaki, Jun-ichi Yoshida: Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan
Giuseppe Romanazzi, Maria Michela Dell'Anna: DICATEch, Politecnico di Bari, Via E. Orabona 4, 70125, Bari Italy



Scheme 1.

synthesis of 2,2-disubstituted oxetanes, and continuing our research interests [22-27] in the field of flow microreactor chemistry [28-30] and flash chemistry [31,32], we wondered if Capriati's protocol for the preparation of 2-substituted-2-phenyloxetanes (2) by electrophilic quenching of 1-Li, could be conducted under mild and sustainable conditions employing flow microreactor systems. We reasoned that within a microreactor system, we should have been able to control the thermal (and chemical) instability of 1-Li avoiding its decomposition. In fact, in the last decade microreactors and continuous flow technologies are emerging as a viable alternative to macrobatch processes both in academic research and in the industrial field, offering even more sustainable synthetic routes. Furthermore, organolithium compounds are generally very unstable and they have to be generated at very low temperatures and the reactions are sometimes difficult or impossible to control in batch-mode systems because they are often extremely fast and highly exothermic. In this context, flow chemistry could open new possibilities in organic synthesis involving organolithiums. Therefore, the use of a flow microreactor, by controlling residence time and temperature, allows the overcoming of these drawbacks [33,34]. The proper control of the residence time in microreactors can be fundamental to increase yields and selectivities in organic reactions compared to macrobatch-mode [35].

2 Experimental Procedure

Typical Procedure for Deprotonation Reaction of 2-Phenyloxetane Followed by Reaction with Electrophiles in Flow Microreactor Systems.

A flow microreactor system consisting of two T-shaped micromixers (M1 ($\varphi = 250 \mu\text{m}$) and M2 ($\varphi = 500 \mu\text{m}$)), two microtube reactors (R1 and R2 ($\varphi = 1000 \mu\text{m}$, $L = 200 \text{cm}$)) and three tube pre-cooling units (P1 ($\varphi = 1000 \mu\text{m}$, $L = 100 \text{cm}$),

P2 ($\varphi = 1000 \mu\text{m}$, $L = 50 \text{cm}$) and P3 ($\varphi = 1000 \mu\text{m}$, $L = 100 \text{cm}$)) was used. A solution of oxetane (0.05 M) in THF (flow rate: 6.00 mL min^{-1}) and a solution of *sec*-BuLi (0.40 M) in *n*-hexane (flow rate: 1.50 mL min^{-1}) were introduced to M1. The resulting solution was passed through R1 and was mixed with a solution of electrophile (0.30 M) in THF (flow rate: 1.75 mL min^{-1}) in M2. The resulting solution was passed through R2. After a steady state was reached, the product solution was collected for 60 s while being quenched with H_2O . Sat. aq. NH_4Cl (5 ml) and brine (20 ml) were added and the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extract was dried over Na_2SO_4 . Organic layer was analyzed by gas chromatography and isolated by flash chromatography.

Deprotonation of 2-Phenyloxetane (1) Followed by Reaction with Chlorotrimethylsilyl-ane in a Flow Microreactor System.

2-phenyl-2-trimethylsilyl oxetane (2a). The crude product was purified by flash chromatography (hexane/ethyl acetate 100:0 to 9:1); 85% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ , 0.02 (s, 9 H), 2.66-2.73 (m, 1 H), 3.06-3.12 (m, 1 H), 4.67-4.71 (m, 2 H), 7.06-7.33 (m, 5 H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ , -5.1, 31.6, 68.8, 86.8, 123.2, 125.1, 127.7, 147.8. Analytical data in agreement with those reported in the literature. [16]

Deprotonation of 2-Phenyloxetane (1) Followed by Reaction with Iodomethane in a Flow Microreactor System.

2-methyl-2-phenyloxetane (2b): the crude product was purified by flash chromatography (hexane/ethyl acetate 20:1 to 4:1); 78% yield, colorless oil; IR (neat) 2967, 2880, 1444, 1283, 965, 701 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ , 7.28-7.22 (m, 4H), 7.15-7.11 (m, 1H), 4.53-4.48 (m, 1H), 4.42-4.38 (m, 1H), 2.71-2.60 (m, 2H), 1.61 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3) δ , 148.2, 128.2, 126.6, 123.6, 86.6, 64.5, 35.6, 30.7. Analytical data in agreement with those reported in the literature. [36]

Deprotonation of 2-Phenyloxetane (1) Followed by Reaction with Pivaldehyde in a Flow Microreactor System.

2,2-dimethyl-1-(2-phenyloxetan-2-yl)propan-1-ol (2c). The crude product (anti:syn = 67:33 (determined

by ^1H NMR)) was purified by flash chromatography (hexane/ethyl acetate 20:1 to 4:1): inseparable mixture of diastereoisomers (dr = 67:33); 63% yield, yellow solid, mp 96 - 97 °C (Et_2O). ^1H NMR (400 MHz, CDCl_3) δ , 0.61 (s, 3 H minor), 0.64 (s, 3 H major), 2.52 - 2.59 (m, 1 H minor), 2.72 - 2.78 (m, 1 H major), 2.98 (d, $J = 8.4$ Hz, 1 H minor, exchanges with D_2O), 3.22 (d, $J = 2.8$ Hz, 1 H major, exchanges with D_2O), 3.29 - 3.43 (m, 1 H minor + 1 H major), 3.52 (d, $J = 2.8$ Hz, 1 H major, s after exchange with D_2O), 3.61 (d, $J = 8.4$ Hz, 1 H minor, s after exchange with D_2O), 4.39 - 4.52 (m, 2 H minor + 2 H major), 7.27 - 7.43 (m, 5 H minor + 5 H major); ^{13}C NMR (100 MHz, CDCl_3) δ , 27.2 (minor), 27.4 (major), 28.6 (major), 31.6 (minor), 33.9 (minor), 34.6 (major), 66.0 (minor), 66.3 (major), 83.0 (minor), 83.7 (major), 91.5 (minor), 91.9 (major), 125.3 (minor), 126.0 (major), 126.9 (minor), 127.5 (major), 127.9 (minor), 127.9 (major), 143.9 (major), 144.5 (minor). The spectral data were identical to those reported in the literature [16].

Deprotonation of 2-Phenyloxetane (1) Followed by Reaction with Acetone in a Flow Microreactor System.

2-(2-phenyloxetan-2-yl)propan-2-ol (2d). The crude product was purified by flash chromatography (hexane/ethyl acetate 20:1 to 4:1). Colorless oil, 55% yield. ^1H NMR (600 MHz, CDCl_3) δ , 0.97 (s, 3 H), 1.15 (s, 3 H), 2.53 - 2.57 (m, 1 H), 3.40 - 3.45 (m, 1 H), 4.43 - 4.47 (m, 1 H), 4.50 - 4.54 (m, 1 H), 7.34 - 7.38 (m, 5 H); ^{13}C NMR (150 MHz, CDCl_3) δ , 21.8, 23.1, 29.5, 65.6, 73.8, 93.3, 125.9, 126.8, 127.4, 144.0. ^1H and ^{13}C data in agreement with those reported in the literature. [16]

Deprotonation of 2-Phenyloxetane (1) Followed by Reaction with Benzophenone in a Flow Microreactor System.

Diphenyl(2-phenyloxetan-2-yl)methanol (2e). The crude product was purified by flash chromatography (hexane/ethyl acetate 20:1 to 4:1); white solid, mp 98 °C (Et_2O), 70% yield. ^1H NMR (400 MHz, CDCl_3) δ , 2.56 - 2.63 (m, 1 H), 3.20 - 3.27 (m, 1 H), 4.06 - 4.12 (m, 1 H), 4.38 - 4.43 (m, 1 H), 7.15 - 7.31 (m, 11 H), 7.58 - 7.61 (m, 2 H), 7.75 - 7.77 (m, 2 H); ^{13}C NMR (150 MHz, CDCl_3) δ , 32.4, 66.1, 80.5, 93.1, 126.9, 127.0, 127.1, 127.2, 127.3, 127.47, 127.50, 127.8, 142.9, 143.0, 143.6; GC-MS (70 eV) m/z (%) 316 (M^+ , 2), 270 (5), 183 (47), 133 (100), 105 (90), 77 (47). Analytical data in agreement with those reported in the literature. [16]

3 Results and Discussion

On the basis of previous experience of generating highly unstable oxiranyl [37-39] and aziridinyl lithium species [40,41] under flow chemistry, our study began by assembling a flow microreactor system that consisted of two T-shaped micromixers (M1 and M2) and two microtube reactors (R1 and R2) as shown in **figure 1**. A solution of 2-phenyloxetane **1** and a solution of *s*-BuLi were introduced to micromixer M1 by syringe pumps. The mixture passed through microtube reactor R1, with variable length; the resulting solution of generated 2-phenyloxetan-2-yl lithium **1-Li** and a solution of chlorotrimethylsilane were respectively introduced to micromixer M2. The resulting mixture was then passed through microtube reactor R2 with fixed length ($t^{\text{R}2} = 2.20$ s) affording the desired product **2a**.

In particular, the reaction was carried out by varying the residence time ($t^{\text{R}1}$) from 0.38 to 25 s changing the length of microtube reactor R1, while maintaining a fixed flow rate, and varying the temperature of cooling bath from -50 to -20 °C. Therefore, both deprotonation and quenching with chlorotrimethylsilane were conducted at the same temperature. The effects of an accurate control of both reaction temperature (T) and residence time ($t^{\text{R}1}$) on the yield of **2a** are highlighted in **Figure 2**.

By conducting the reaction using shorter residence times (i.e. between 0.38 and 2.5 s), we obtained low or moderate yields of **2a**. On the other hand, employing higher residence times (i.e. between 2.5 and 25 s), at temperatures between -50 and -30 °C, **2a** was obtained from moderate to high yield, but at temperatures higher than -30 °C the yields decreased significantly. The assembled flow microreactor system has indeed provided an effective reactor for the generation and reactions of 2-phenyloxetan-2-yl lithium **1-Li** without decomposition by using a residence time of 12.5 s and efficient temperature control at -40 °C, which is an impracticable temperature in batch-mode. In particular, the systematic tuning of

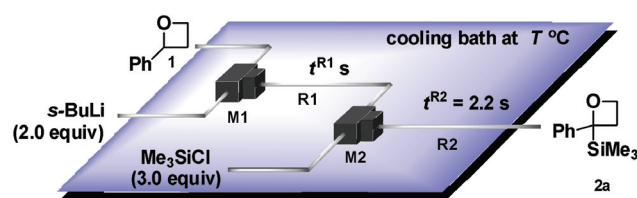


Figure 1: A flow microreactor system for the deprotonation of 2-Phenyloxetane (**1**) with *s*-BuLi followed by reaction with chlorotrimethylsilane. M1, M2: T-shaped micromixer. R1, R2: microtube reactor.

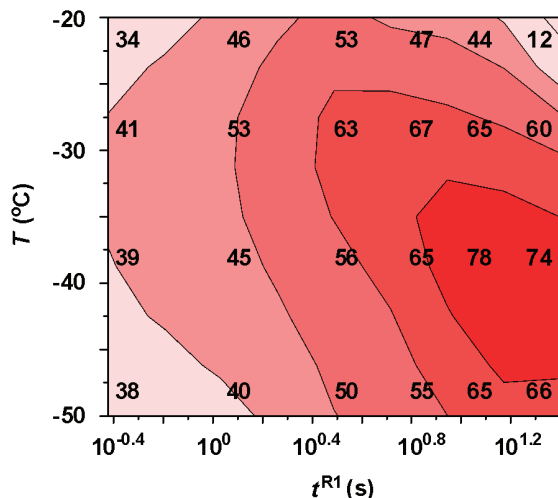


Figure 2: Effects of reaction temperature (T) and residence time (t^{R1}) on the yield of **2a** under the flow conditions reported in figure 1.

Table 1: Deprotonation of 2-phenyloxetane **1** followed by reactions with electrophiles using a flow microreactor system under the optimized conditions.

Entry	Electrophile	Product	Yield ^a
1			85
2	MeI		78
3			63 ^b
4			55
5			36

^a Isolated yield after column chromatography. ^b Overall isolated yield of inseparable mixture of diastereomers; diastereomeric ratio = 67:33 (determined by ¹H NMR spectroscopy).

the residence time (t^{R1}) has proved, as generally expected in flash chemistry, to be a key parameter for achieving a reaction with good yield and selectivity.

In order to increase the yield of **2a**, we attempted a further tuning of the reaction conditions by changing the molarity of a solution of *s*-BuLi (from 0.5 M to 0.6 M). We found that the yield of **2a** slightly depends on the amount of the base. However, with 3 equiv of *s*-BuLi, **2a** was obtained in 85% yield.

Next, on the basis of the optimized conditions (1.0 equiv of **1**, 3.0 equiv of *s*-BuLi, 3.0 equiv of electrophile, $t^{R1} = 12.50$ s, $t^{R2} = 2.20$ s at -40 °C), we examined the nucleophilicity of **1-Li** towards various electrophiles in order to prepare different 2,2-disubstituted-oxetane derivatives as reported in **Table 1**.

By using electrophiles such as chlorotrimethylsilane and MeI (entry 1 and 2), the corresponding 2-substituted-2-phenyloxetanes **2a** and **2b** were obtained in good yield. An aliphatic aldehyde such as pivalaldehyde (entry 3) also reacted affording the expected addition product **2c** in good yield although, with diastereoselectivity poor (*dr* = 67:33) as observed in batch. [16] With an acetone (entry 4), the corresponding hydroxyalkylated products **2d** was obtained in moderate yield suggesting that enolisation could in principle compete with the addition reaction. On the other hand, when enolisation is not possible as in the case of benzophenone (entry 5), the corresponding hydroxyarylated products **2e** was even obtained in lower yield.

4 Conclusions

The use of a flow microreactor system, enabled the generation of 2-lithiated oxetane species such as **1-Li** and its trapping with representative electrophiles. In particular, by controlling the residence time, the highly unstable intermediate **1-Li** could be generated and trapped with electrophiles at higher temperatures with respect to batch-mode (i.e. -40 °C instead of -78 °C) obtaining 2,2-disubstituted oxetanes (**2a-e**) in moderate to good yields. Under flow conditions, it is worth noting that the accurate control of reaction parameters such as residence time and temperature proved to be fundamental for achieving a more sustainable reaction, that normally need to be carried out in bath-mode at much lower temperatures. This work could eventually open the possibility for a sustainable flow synthesis of substituted oxetanes in pharmaceutical field.

Acknowledgements: This work has been realized under the framework of the National Project “FIRB - Futuro in Ricerca” (code: CINECA RBFRO83M5N) coordinated by R.L.

References

- [1] Mahal A., Oxetanes as versatile building blocks in the total synthesis of natural products: An overview, *Eur. J. Chem.*, 2015, 6, 357–366.
- [2] Bull, J. A., Croft, R. A., Davis, O. A., Doran, R., Morgan K. F. Oxetanes: Recent Advances in Synthesis, Reactivity and Medicinal Chemistry, *Chem. Rev.* 2016, 116, 12150–12233.
- [3] Wuitschik G., Carreira E. M., Wagner B., Fischer H., Parrilla I., Schuler F., Rogers-Evans M., and Müller K., Oxetanes in Drug Discovery: Structural and Synthetic Insights, *J. Med. Chem.*, 2010, 53, 3227–3246.
- [4] Burkhard J. A., Wuitschik G., Rogers-Evans M., Müller K., and Carreira E. M., Oxetanes as Versatile Elements in Drug Discovery and Synthesis, *Angew. Chem., Int. Ed.*, 2010, 49, 9052–9067.
- [5] Malapit C. A., and Howell A. R., Recent Applications of Oxetanes in the Synthesis of Heterocyclic Compounds, *J. Org. Chem.*, 2015, 80, 8489–8495.
- [6] Smith D. T., and Njardarson J.T., Ring Expansions of Oxiranes and Oxetanes, *Top. Heterocycl. Chem.*, 2016, 41, 281–310.
- [7] Davis O. A., and Bull J. A., Recent Advances in the Synthesis of 2-Substituted Oxetanes, *Synlett*, 2015, 26, 1283–1288.
- [8] Davis O. A., and Bull J. A., Synthesis of Di-, Tri-, and Tetrasubstituted Oxetanes by Rhodium-Catalyzed O–H Insertion and C–C Bond-Forming Cyclization, *Angew. Chem. Int. Ed.* 2014, 53, 14230–14234.
- [9] Davis O. A., Croft R. A., and Bull J. A., Synthesis of diversely functionalised 2,2-disubstituted oxetanes: fragment motifs in new chemical space, *Chem. Commun.*, 2015, 51, 15446–15449.
- [10] Morgan K. F., Hollingsworth I. A., and Bull J. A., Studies on the synthesis, stability and conformation of 2-sulfonyl-oxetane fragments, *Org. Biomol. Chem.*, 2015, 13, 5265–5272.
- [11] Morgan K. F., Doran R., Croft R. A., Hollingsworth I. A., and Bull J. A., 2-Sulfinyl Oxetanes: Synthesis, Stability and Reactivity, *Synlett*, 2016, 27, 106–110.
- [12] Aftab T., Carter C., Christlieb M., Hart J., and Nelson A., Stereospecific conversion of (1*R**,3*S**)- and (1*R**,3*R**)-3-cyclohexyl-1-phenylpropane-1,3-diol into the corresponding 2,4-disubstituted oxetanes, *J. Chem. Soc. Perkin Trans. 1*, 2000, 711–722.
- [13] Jenkinson S. F., and Fleet G. W. J., Oxetanes from the Ring Contraction of α -Triflates of γ -Lactones: Oxetane Nucleosides and Oxetane Amino Acids, *Chimia*, 2011, 65, 71–75.
- [14] Abe M., Recent Progress Regarding Regio-, Site-, and Stereoselective Formation of Oxetanes in Paternò-Büchi Reactions, *J. Chin. Chem. Soc.* 2008, 55, 479–486.
- [15] D'Auria M., and Racioppi R., Oxetane Synthesis through the Paternò-Büchi Reaction, *Molecules*, 2013, 18, 11384–11428.
- [16] Coppi D. I., Salomone A., Perna F. M., and Capriati V., 2-Lithiated-2-phenyloxetane: a new attractive synthon for the preparation of oxetane derivatives, *Chem. Commun.*, 2011, 47, 9918–9920.
- [17] Schakel M., Vrieland J. J., and Klumpp G. W., Enhanced reactivity of 3-(methoxymethyl)- and 3-(dimethylaminomethyl)oxetanes towards alkylolithiums, *Tetrahedron Lett.*, 1987, 28, 5147–5750.
- [18] Yamaguchi H., Nobayashi Y., and Hirao I., A ring opening reaction of oxetanes with lithium acetylides promoted by boron trifluoride etherate, *Tetrahedron*, 1984, 40, 4261–4266 and reference there in.
- [19] Thurner A., Faigl F., Mordini A., Bigi A., Reginato G., and L. Töke, A New Base Promoted Rearrangement of (E)-l-Benzyloxy-2,3-Epoxyalkanes, *Tetrahedron*, 1998, 54, 11597–11602.
- [20] Coppi D. I., Salomone A., Perna F. M., and Capriati V., Exploiting the Lithiation-Directing Ability of Oxetane for the Regioselective Preparation of Functionalized 2-Aryloxetane Scaffolds under Mild Conditions, *Angew. Chem. Int. Ed.*, 2012, 51, 7532–7536.
- [21] Rouquet G., Blakemore D. C., and Ley S. V., Highly regioselective lithiation of pyridines bearing an oxetane unit by n-butyllithium, *Chem. Commun.*, 2014, 50, 8908–8911.
- [22] Giovine A., Musio B., Degennaro L., Falcicchio A., Nagaki A., Yoshida J., and Luisi R., Synthesis of 1,2,3,4-Tetrahydroisoquinolines by Microreactor-Mediated Thermal Isomerization of Laterally Lithiated Arylaziridines, *Chem.–Eur. J.*, 2013, 19, 1872–1876.
- [23] Carroccia L., Musio B., Degennaro L., Romanazzi G., and Luisi R., Microreactor-Mediated Organocatalysis: Towards the Development of Sustainable Domino Reactions, *J. Flow Chem.*, 2013, 3, 29–33.
- [24] Degennaro L., Fanelli F., Giovine A., and Luisi R., External Trapping of Halomethylithium Enabled by Flow Microreactors, *Adv. Synth. Catal.*, 2015, 357, 21–27.
- [25] De Angelis S., De Renzo M., Carlucci C., Degennaro L., and Luisi R., A convenient enantioselective CBS-reduction of arylketones in flow-microreactor systems, *Org. Biomol. Chem.*, 2016, 14, 4304–4311.
- [26] Degennaro L., Maggiulli D., Carlucci C., Fanelli F., Romanazzi G., and Luisi R., A direct and sustainable synthesis of tertiary butyl esters enabled by flow microreactors, *Chem. Commun.*, 2016, 52, 9554–9557.
- [27] Degennaro L., Carlucci C., De Angelis S., and Luisi R., Flow technology for organometallic-mediated synthesis, *J. Flow Chem.*, 2016, 6, 136–166.
- [28] Reschetilowski W. (Ed.), *Microreactors in Preparative Chemistry*, Wiley-VCH, Weinheim, Germany, 2013.
- [29] Wirth T. (Ed.), *Microreactors in Organic Synthesis and Catalysis*, 2nd ed., Wiley-VCH, Weinheim, Germany, 2013.
- [30] Yoshida J., *Basics of Flow Microreactor Synthesis*, Springer, Tokyo, 2015.
- [31] Yoshida J., *Flash Chemistry: Fast Organic Synthesis in Microsystems*, John Wiley & Sons, Chichester, 2008.
- [32] Yoshida J., Takahashi Y. and Nagaki A., Flash Chemistry: Flow Chemistry That Cannot Be Done in Batch, *Chem. Commun.* 2013, 49, 9896–9904.
- [33] Nagaki A., and Yoshida J., Preparation and Use of Organolithium and Organomagnesium Species in Flow, *Top. Organomet. Chem.*, 2016, 57, 137–176.
- [34] Nagaki A., and Yoshida J., Microreactor Technology in Lithium Chemistry, In: Luisi R., Capriati V. (Eds.), *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*, Wiley-VCH, Weinheim, Germany, 2014.

- [35] Mándity I. M., Ötvös S. B., and Fülöp F., Strategic Application of Residence-Time Control in Continuous-Flow Reactors, *ChemistryOpen* 2015, 4, 212–223.
- [36] Toshihiko S., Gang L., Shigeki M., and Masakatsu S., Catalytic Asymmetric Synthesis of 2,2-Disubstituted Oxetanes from Ketones via One-pot Sequential Addition of Sulfur Ylide, *Angew. Chem. Int. Ed.*, 2009, 48, 1677–1680.
- [37] Nagaki A., Takizawa E., and Yoshida J., Oxiranyl Anion Methodology Using Microflow Systems, *J. Am. Chem. Soc.*, 2009, 131, 1654–1655.
- [38] Nagaki A., Takizawa E., and Yoshida J. Generation and Reactions of Oxiranyllithiums by Use of a Flow Microreactor System, *Chem. Eur. J.* 2010, 16, 14149–14158.
- [39] Nagaki A., Takizawa E., and Yoshida J., Generation and Reactions of α -Silyloxiranyllithium in a Microreactor, *Chem. Lett.*, 2009, 38, 486–487.
- [40] Nagaki A., Takizawa E., and Yoshida J., Generations and Reactions of N-(*t*-Butylsulfonyl)aziridinyllithiums Using Microreactors, *Chem. Lett.*, 2009, 38, 1060–1061.
- [41] Takizawa E., Nagaki A., and Yoshida J., Flow microreactor synthesis of tricyclic sulfonamides via *N*-tosylaziridinyllithiums, *Tetrahedron Lett.*, 2012, 53, 1397–1400.