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Utilizing microfluidic devices for organic synthesis

Ứng dụng thiết bị vi lưu trong tổng hợp hữu cơ

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Abstract

In the last twenty years, microfluidic devices have been employed extensively in organic synthesis as strong tools for performing reactions with safety, high efficiency, high selectivity, low cost, and low environmental impact. These devices, which have excellent mass and heat transfers and can be fabricated into different shapes by using different materials, are widely employed in several organic synthetic transformations such as oxidation, organometallic, isomerization, and aldol reactions. This review focuses on the applications of microfluidic devices in such processes.

Keywords: Microfluidic devices; organic syntheses; oxidation; organometallic reaction.

Tóm tắt

Trong hai thập niên qua, thiết bị vi lưu được sử dụng rộng rãi như một công cụ trong tổng hợp hữu cơ để thực hiện các chuyển hóa an toàn, chọn lọc, hiệu quả, kinh tế và ít ảnh hưởng lên môi trường. Với tính năng ưu việt trong khuếch tán khối và nhiệt, có thể được chế tạo bằng nhiều loại vật liệu dưới nhiều mẫu mã, thiết bị vi lưu được dùng khá phổ biến trong một số quá trình tổng hợp hữu cơ như oxi hóa, phản ứng cơ kim loại, đồng phân hóa và aldol hóa. Bài tổng quan này đề cập đến ứng dụng của thiết bị vi lưu trong các quá trình này.

Từ khóa: Thiết bị vi lưu; tổng hợp hữu cơ; oxi hóa; phản ứng cơ kim loại.

1. Introduction

Finding a technology for improving performances of transformations is a central development of chemical synthesis. Main issues of the development are selectivity, efficiency, safety, and waste. Recent advancement of microfluidic devices has contributed to the enhancements of chemical transformations. The technology allowing extremely fast mixing times has offered many advantages such as safety, selectivity, short reaction time, low costs, low environmental impact, high efficiency and

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easy scale-up [1-14]. In addition, such devices can be used in reactions involving reactive intermediates with short life-times to produce desired products with high chemoselectivity. This review highlights the applications of microfluidic devices in several organic processes including oxidation, organometallic, isomerization, and aldol reactions.

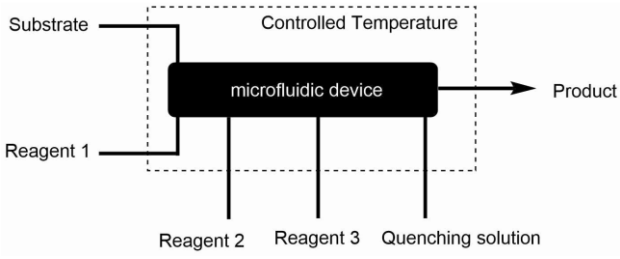


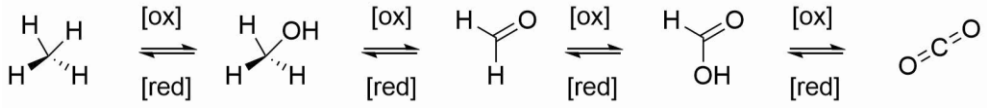
Figure 1. A model for a reaction in a microfluidic device

2. Microfluidics in organic synthesis

2.1. Oxidation reactions

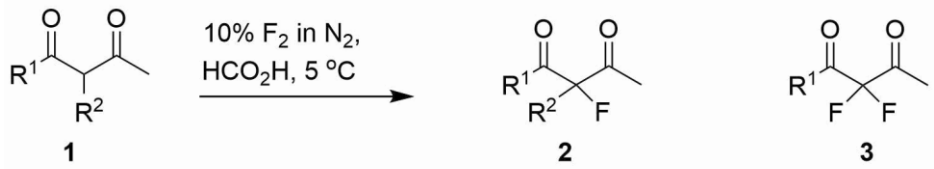
Organic oxidations are fundamental transformations in organic chemistry and essential tools for constructing organic molecules. The oxidations involve in formation of bonds between carbon atoms with more electronegative elements, typically oxygen and nitrogen. For example, in Swern, Corey Kim or Dess-Martin oxidation a sigma C-H bond of an alcohol is converted to a pi C-O bond of a carbonyl compound (Scheme 1). In chemical industry, oxidations are employed to prepare fine chemicals such as adipic acid, acrylic acid, acetaldehyde, cumene peroxide, terephthalic acid and benzoid acid.

However, development of organic oxidations is still limited because several issues are associated with these transformations. In general, such reactions are extremely exothermic and toxic as they require strong oxidative reagents. Conventional methods for conducting these reactions pose serious concerns about safety and health, which make large scale production unlikely. Therefore, strict procedures for handling oxidants are required to ensure safety. Moreover, efficiency and selectivity of such oxidation processes are usually low because the highly reactive intermediates of these reactions, which are sensitive to high temperature, decompose very quickly.



Scheme 1. Organic oxidations involving bonds of carbon and oxygen

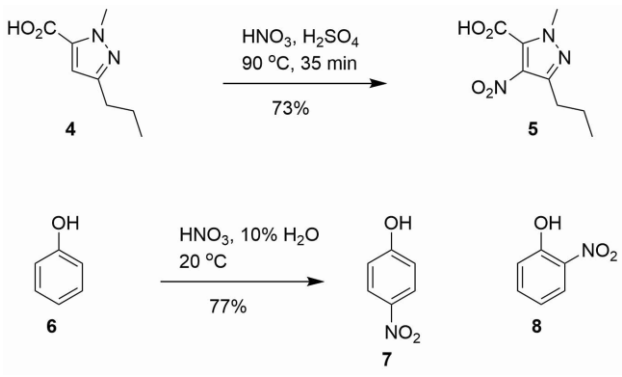
Despite many challenges associated with oxidative processes, many of those requiring harsh conditions and hazardous reagents have been successfully carried out in microfluidic devices. In many cases, the technology significantly improved safety, selectivity and efficiency of oxidative processes. In 2001 Chambers *et al.* reported selective direct fluorination in microreactors [15]. Several 1,3-dicarbonyl compounds including acyclic and cyclic ones were effectively fluorated with good yields. Moreover, direct fluorination in microreactors is much safer than conventional techniques.



1	R^1	R^2	Yield (%) 2	Yield (%) 3
a	OEt	H	71	12
b	OEt	CH_3	49	11
c		$-OCH_2-CH_2-$	95	4
d		$-(CH_2)_4-$	78	9

Scheme 2. Direct fluorination in microreactors

Nitration is one of fundamental transformation in organic synthesis. However, this reaction is extremely exothermic and difficult to control. In 2003 Taghavi-Moghadam *et al.* described a continuous-flow nitration using microreactors [16]. This method introduced a safe and controllable way for the nitration of aromatic compounds. For instance, the nitration of pyzarole-5-carboxylic acid **4** in microreactors allowed temperature control at 90 °C with 73% yield. In the batch system, undesired decarboxylation is occurred in such highly exothermic condition. In 2005 Ducry *et al.* reported a similar nitration of phenol in a glass microreactor with high efficiency [17].



Scheme 3. Nitration in microreactors

Swern oxidation is one of the reliable methods for converting primary and secondary alcohol to carbonyl compounds. The conventional oxidation requires low temperatures (-50°C and below) in order to avoid side reactions such as Pummerer rearrangement driven by formation of highly active intermediate thionium ion. In addition, this oxidation employs hazardous reagents such as DMSO, oxalyl chlorides and TFAA which pose safety issues when carrying out this reaction in normal laboratory condition. In 2005 Yoshida *et al.* reported the Swern oxidation of alcohols in microfluidic devices which could be performed safely at higher temperatures (-20 °C to 20 °C) with excellent yields [18]. This is a strong example that shows the effectiveness of microfluidic devices in a highly exothermic oxidation.

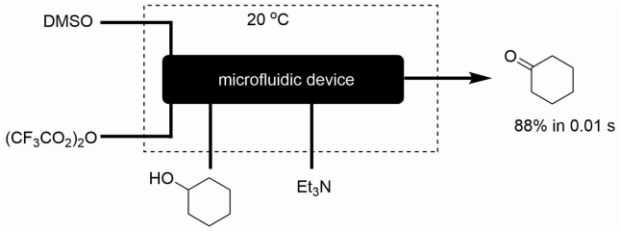
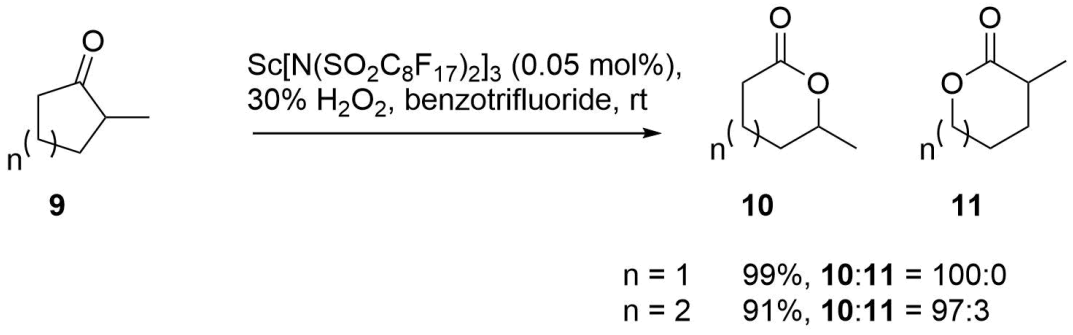


Figure 2. Swern oxidation of cyclohexanol at 20°C in microreactors

In 2006 Mikami *et al.* described the Baeyer-Villiger reaction of cyclicketones catalyzed by a small amount of the fluorous lanthanide catalyst (<< 0.1 mol%), $Sc[N(SO_2C_8F_{17})_2]_3$, in a microreactor. This process generated lactone products in excellent yields and regioselectivily with the residence time of 8.1 s [19].



Scheme 4. Baeyer-Villiger reaction in microfluidic devices

In 2012 Boyle *et al.* reported a photo-oxidation reaction in a photosensitizer-immobilized microfluidic device [20]. The reactor functionalized with photoactive porphyrins had small reaction volumes (nL) which enhanced safety in handling hazardous reagents. The device also provided a simple separation of photosensitizer from products and remaining reagents and leaded to simple purification process.

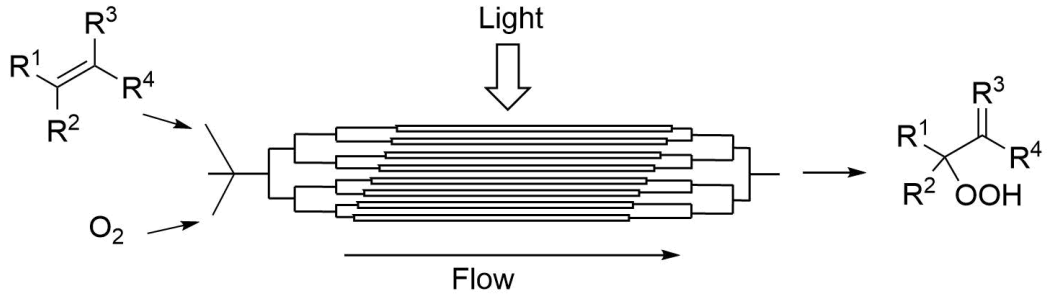


Figure 3. Photo-oxidation in a photosensitizer-immobilized microfluidic device

2.2. Organometallic reactions

In 2004 Hessel *et al.* investigated a phenylation of a boronic ester in microreactors with high chemoselectivity, high yield and energy saving [21]. This process generated phenyl boronic acid **7** with 89% yield at ambient temperature. For such extremely exothermic process, reaction yield is significantly decreased when being carried out at high temperature. In a batch process, this reaction was carried out at -35°C and many byproducts such as diphenyl boronic acid, benzene and phenol were also formed.

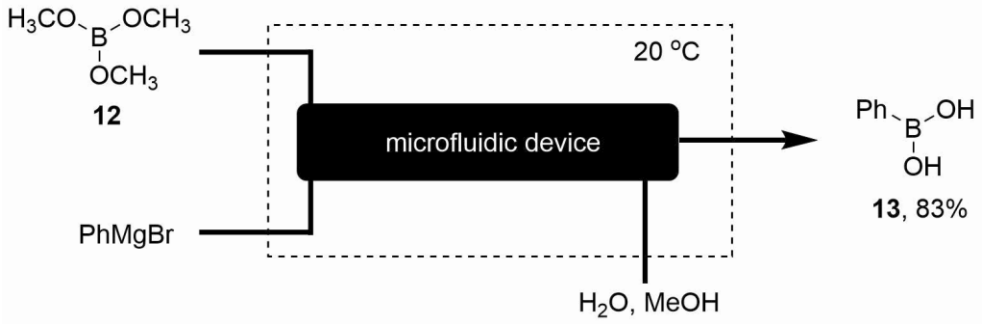
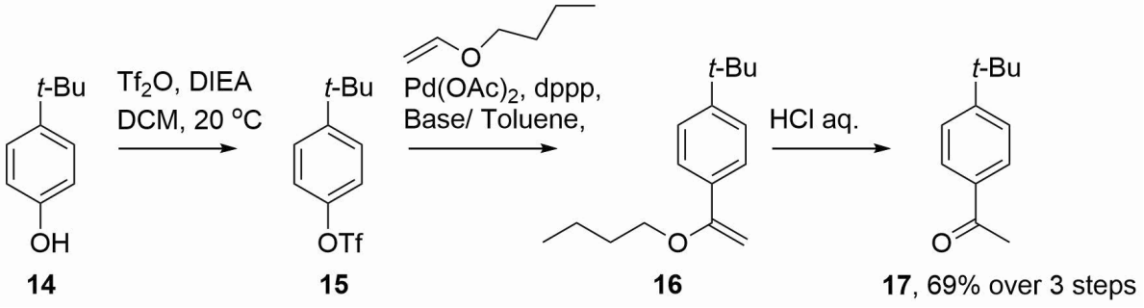


Figure 4. Synthesis of **13** in a microreactor

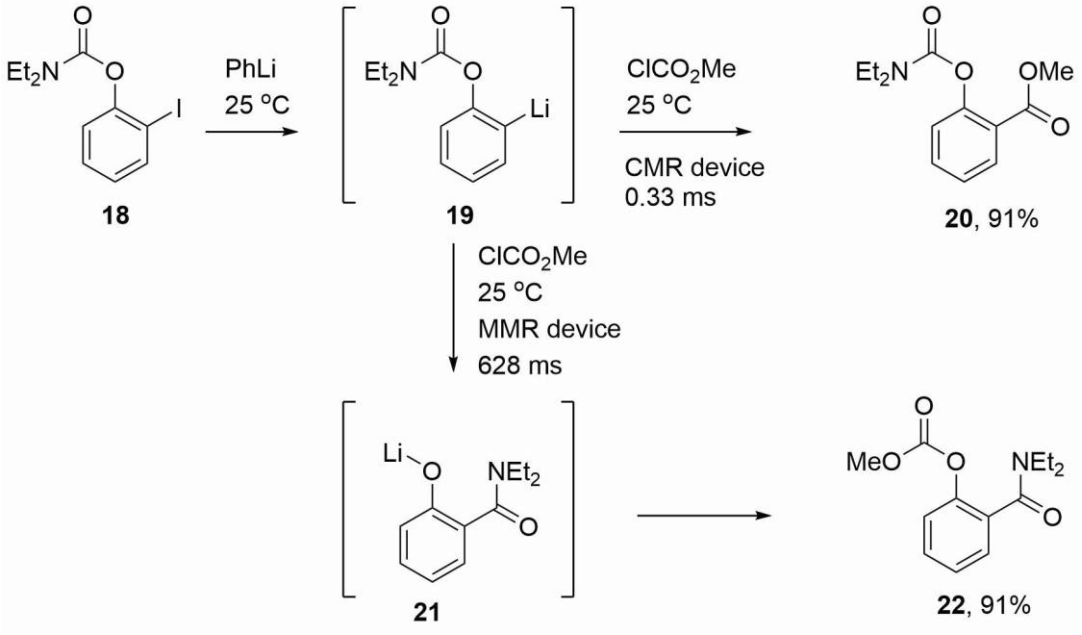
In 2010 Jensen *et al.* employed a microfluidic distillation to exchange reaction solvents in a multistep synthesis [22]. In the microreactors, triflate **15** was synthesized in DCM, which was distilled out of the reaction mixture. In the second step (**15** → **16**),

a palladium-catalyzed Heck reaction in toluene generated the coupling product **16** which was hydrolyzed to produce **17** in 69% yield. The distillation was successfully performed by utilizing excellent heat transfer properties of microfluidic devices and a major difference in boiling temperature of DCM (40°C) and Toluene (110°C).



Scheme 5. Synthesis of **17** by employing microreactors

In 2016 Yoshida *et al.* demonstrated a chemoselective submillisecond Fries rearrangement by utilizing microfluidic devices [23]. In this process, designed microreactors including a polymer-based chip microreactor (CMR) and a modular microreactor (MMR) were developed to control the resident time of the reaction which significantly affected the outcome. When the resident time was 0.33ms, the unrearranged product **20** was formed solely in 91% yield by the direct attack of an electrophile to the intermediate. However, when the resident time was 628ms, the electrophile reacted with the intermediate **19** and generated the rearranged product **22** in the same yield.

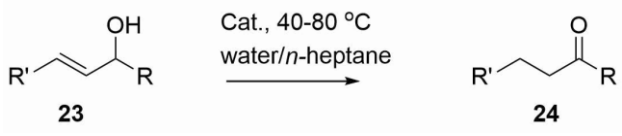


Scheme 6. Outpacing Fries rearrangement through microfluidic rapid mixing

2.3. Isomerization, aldol, ring-expansion, and carboxylation reactions

In 2000 Bellefon *et al.* reported a high throughput screening of fluid/liquid molecular catalysis in a microfluidic device [24]. In this process, 18 tests for the liquid/liquid isomerization (**23** → **24**) were conducted by using one to two micromoles of metal over a

total screening time of one hour. Compared to traditional parallel batch operations, this method used a small amount of samples and had a broader range of operating conditions.



Scheme 7. High throughput screening of catalysts for the isomerization

In 2001 Haswell *et al.* described the aldol reaction of silyl enol ethers within a microreactor [25]. Silyl enol ether **25** was mixed with tetrabutylammonium fluoride (TBAF) to generate enolate which react with aldehyde **26** to form beta-hydroxyketone **27** (Figure 5). The reaction was reached to quantitative conversion in 20 min. This process in the microreactor was much faster than the one in traditional batch systems, which required 24h to obtain the same conversion.

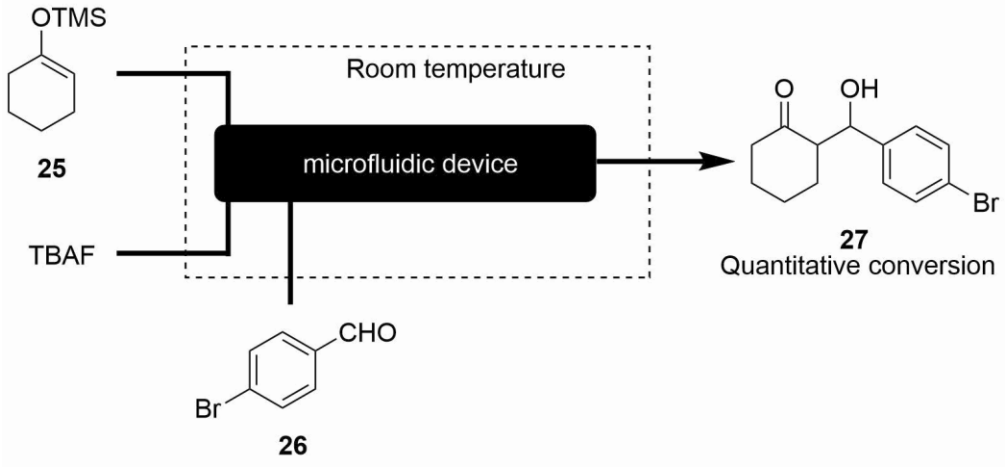
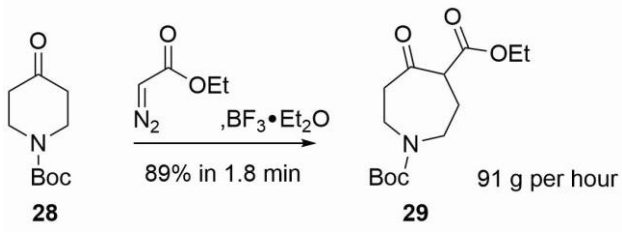


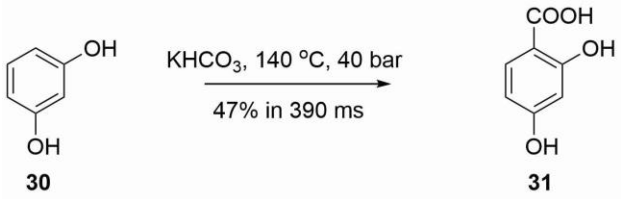
Figure 5. Synthesis of **27** in a microreactor

Also in 2004 Zhang *et al.* performed a ring-expansion reaction involving diazoacetate, a hazardous reagent, in a microreactor [26]. In normal batch condition, a large scale operation of this reaction (**28** → **29**) seriously poses safety concerns because it is highly exothermic and generates nitrogen gas. However, in a microreactor the reaction proceeded smoothly and safely to generate the desired product in 89% yield within 1.8 min. This process produced 91g of product **29** per hour.



Scheme 8. Synthesis of **29** in a microreactor

In 2005 Hessel *et al.* reported aqueous Kolbe-Schmitt synthesis using resorcinol in a microreactor under high-pressure, temperature conditions [27]. This process (**30** → **31**) improved significantly the space-time yield and reduced the reaction time. It also allowed a simple and flexible modulation for high-throughput experimentation.



Scheme 9. Synthesis of **31** in a microreactor

3. Conclusion and outlook

This mini review has shown that several organic synthesis processes, including oxidation,

organometallic, isomerization, and aldol reactions, were successfully performed in microfluidic devices with improvement of efficiency, selectivity, safety, and green. With those significant advantages, microfluidic devices are promising tools for overcoming challenges of organic syntheses. Although the number of reports of utilizing microfluidic devices for organic syntheses is still limited, this area of research will emerge in the near future.

References

[1] M. G. Clerici and O. A. Kholdeeva, Liquid Phase Oxidation via Heterogeneous Catalysis: Organic Synthesis and Industrial Applications, John Wiley & Sons, Hoboken, 2013.

[2] J. C. J. Bart and S. Cavallaro, *Ind. Eng. Chem. Res.*, 2015, *54*, 1–46.

[3] J. C. J. Bart and S. Cavallaro, *Ind. Eng. Chem. Res.*, 2015, *54*, 567–576.

[4] G. M. Whitesides, *Nature*, 2006, *442*, 368-373.

[5] K. S. Elvira, X. C. Solvas, R. C. R. Wootton, A. J. deMello *Nature Chemistry*, 2013, 5, 905-915.

[6] K. F. Jensen, B. J. Reizman, S. G. Newman *Lab Chip*, 2014, *14*, 3206-3212.

[7] K. Geyer, T. Gustafsson, P. H. Seeberger, Y. Bayon *Synlett*, 2009, *15*, 2382-2391.

[8] T. Wirth *Angew. Chem. Int. Ed.*, 2016, 55, 2-5.

[9] J. KovYahi, Y. Mori, S. Kobayashi, *Chem. Asian J.*, 2006, *1-2*, 22-35.

[10] H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel *Chem. Soc. Rev.*, 2016, *45*, 83-117.

[11] T. Illg, P. Lob, V. Hessel *Bioorg. Med. Chem.*, 2010, *18*, 3707-3719.

[12] S. V. Ley, D. E. Fitzpatrick, R. M. Myers, C. Battilocchio, R. J. Ingham, D. *Angew. Chem. Int. Ed.*, 2015, *54*, 10122-10137.

[13] C. Lee, G. Sui, A. Elizarov, C. J. Shu, Y. Shin, A. N. Dooley, J. Huang, A. Daridon, P. Wyatt, D. Stout, H. C. Kolb, O. N. Witte, N. Satyamurthy, J. R. Heath, M. E. Phelps, S. R. Quake, H. Tseng *Science*, 2005, *310*, 1793-1796.

[14] J. Pelleter, F. Renaud *Org. Process Res. Dev.*, 2009, *13*, 698-705.

[15] R. D. Chambers, D. Holling, R. C. H. Spink, G. Sandford *Lab Chip*, 2001, *1*, 132-137.

[16] G. Panke, T. Schwalbe, W. Stirner, S. Taghavi-Moghadam, G. Wille *Synthesis*, 2003, 2827-2830.

[17] L. Ducry, D. M. Roberge *Angew. Chem. Int. Ed.*, 2005, 7972-7975.

[18] T. Kawaguchi, H. Miyata, K. Ataka, K. Mae, J. Yoshida *Angew. Chem. Int. Ed.*, 2005, 2413-2416.

[19] K. Mikami, M. Yamanaka, N. Islam, T. Tonoi, Y. Itoh, M. Shinoda, K. Kudo *J. Fluor. Chem.*, 2006, *127*, 592-596.

[20] E. K. Lumley, C. E. Dyer, N. Pamme, R. W. Boyle *Org. Lett.*, 2012, *14*, 5724-5727.

[21] V. Hessel, C. Hofmann, H. Lowe, A. Meudt, S. Scherer, F. Schonfeld, B. Werner *Org. Process Res. Dev.* 2004, *8*, 511-523.

[22] R. L. Hartman, J. R. Naber, S. L. Buchwald, K. F. Jensen *Angew. Chem. Int. Ed.*, 2010, *49*, 899-903.

[23] H. Kim, K. Min, K. Inoue, D. J. Im, D. Kim, J. Yoshida *Science*, 2016, *352*, 691-694.

[24] C. D. Bellefone, N. Tanchoux, S. Caravieilhes, P. Grenouillet, V. Hessel *Angew. Chem. Int. Ed.*, 2000, *39*, 3442-3445.

[25] C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar *Lab Chip* 2001, *1*, 100-101.

[26] X. Zhang, S. Stefanick, F. J. Villani *Org. Process Res. Dev.* 2004, *8*, 455-460.

[27] V. Hessel, C. Hofmann, P. Lob, J. Lohndorf, H. Lowe, A. Ziogas *Org. Process Res. Dev.* 2005, *9*, 479-489.