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Article / Book Information

Title	Integrated Micro-Flow Synthesis Based on Photochemical Wolff Rearrangement
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Citation	European Journal of Organic Chemistry, Volume 2017, Issue 44, pp. 6466-6473
Pub. date	2017, 8
Note	This is the peer reviewed version of the following article: European Journal of Organic Chemistry, Volume 2017, Issue 44, pp. 6466-6473, which has been published in final form at https://doi.org/10.1002/ejoc.201700789 . This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Integrated Micro-flow Synthesis Based on Photochemical Wolff Rearrangement

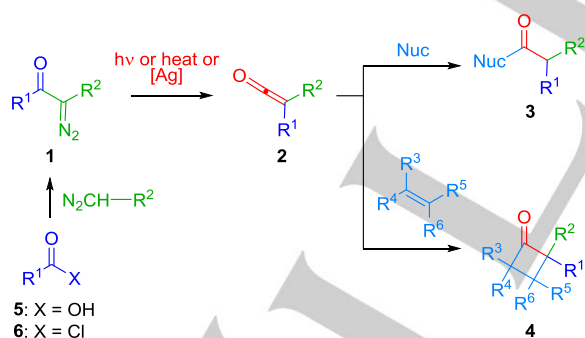
Shinichiro Fuse,* Yuma Otake, and Hiroyuki Nakamura

Abstract: Wolff rearrangement of α -diazo carbonyl compounds has remained important in organic synthesis since its development more than 115 years ago. The risk in treating diazo compounds can be minimized by utilizing micro-flow technology. In addition, photochemical Wolff rearrangement can be carried out efficiently by utilizing micro-flow technology. Therefore, integrated micro-flow synthesis is well suited to the preparation of α -diazo carbonyl compounds and their photochemical Wolff rearrangement. In this review article, recently reported micro-flow photochemical Wolff rearrangements and their application in integrated micro-flow syntheses are summarized.

1. Introduction

1.1. Photochemical Wolff Rearrangement

Wolff rearrangement was developed by Ludwig Wolff in 1902.^[1] Although 115 years have passed since its development, Wolff rearrangement has not lost its usefulness in synthetic organic chemistry.^[2-4] In Wolff rearrangement, α -diazocarbonyl compound **1** is converted to ketene **2** via photoirradiation, heating, or silver-mediated conditions (Scheme 1). Subsequent additions of various nucleophiles against **2** afford a variety of carbonyl compounds **3**. If R^1 and R^2 in **1** are directly linked and form a ring structure, a one-carbon, ring-contracted product is obtained via the Wolff rearrangement/nucleophilic addition sequence. This sequence is



Scheme 1. Wolff rearrangement of α -diazocarbonyl compounds **1** to ketene **2** and a subsequent nucleophilic addition to afford **3** or a [2+2] cycloaddition to afford **4**.

particularly useful for the homologation of carboxylic acids **5**. Namely, the chlorination of **5**/nucleophilic acyl substitution of **6** with the diazomethane compounds/Wolff rearrangement of **1**/nucleophilic addition of water against ketene **2** affords one-carbon elongated carboxylic acid **3** ($Nuc = OH$). This sequence is referred to as Arndt-Eistert homologation.^[5, 6] In addition, the [2+2] cycloaddition of reactive ketene **2** with unsaturated compounds affords the 4-membered ring compound **4**.

Due to the potential explosibility of diazo compounds, it is desirable that α -diazocarbonyl compound **1** is prepared *in situ* for use in subsequent reactions without isolation.^[7, 8] In addition, in order to reduce the risk in handling dangerous compounds, the reactor should be as small as possible.^[9] From this point of view, integrated micro-flow synthesis^[10-17] is ideal for the preparation of **1** and its Wolff rearrangement.

Thermolysis of α -diazocarbonyl compounds **1** is the oldest method that is used to generate ketenes **2**. Although this involves only simple manipulation, it usually requires high temperatures ($> 100^\circ C$) that sometimes cause undesired reactions.^[4] Therefore, silver (silver benzoate/triethyl amine^{[18])}-mediated ketene formation has long been the primary option. However, freshly prepared silver reagent, a long reaction time, and high temperatures are usually required to obtain the desired compounds in high yields.^[18-20] Another choice is photolysis that requires no catalyst. With this process, however, the photochemical reactors are usually expensive, and photochemical reactions usually require high-dilution conditions that are ill-suited for large-scale syntheses. Photochemical micro-flow synthesis can solve these problems.^[21-28]

1.2. Advantages of Micro-flow Synthesis over Conventional Batch Synthesis

Micro-flow synthesis has many advantages over conventional batch synthesis, as shown below.^[10-17, 21-38]

- (1) Precise control of short reaction time (< 1 sec) can be achieved.
- (2) Reaction temperature can be precisely controlled.
- (3) Light penetration efficiency is higher than batch synthesis in photochemical reactions.
- (4) The risk in handling dangerous compounds can be minimized.
- (5) Scale-up can be readily achieved.
- (6) Catalyst poisoning by reaction products can be avoided.

(1) Control of the short reaction time can be achieved by fast mixing in a micro mixer due to its short diffusion length and generation of turbulence flow. (2) The large surface-to-volume ratio of a micro-flow reactor enables rapid heat transfer for precise reaction temperature control. The advantages of (1) and (2)

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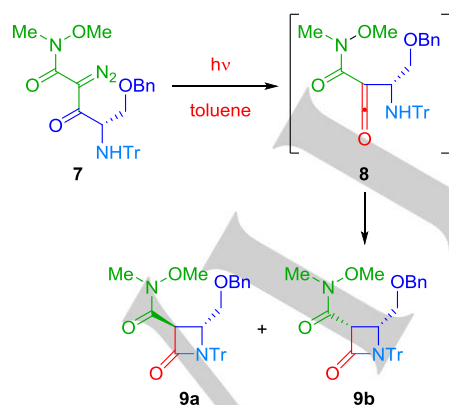
enable the use of highly reactive and unstable chemical species in organic synthesis.^[29] (3) According to the Lambert-Beer law, the intensity of light decreases exponentially with the length of the light path. The thinness of a micro-flow photoreactor improves the light-penetration efficiency. (4) A micro-flow reactor has a small reaction space, which allows only a small amount of compounds and minimizes the risk in treating explosive and/or toxic compounds. (5) Scale-up is readily carried out either by continuous operation or by increasing the number of reactors.^[33] (6) The reaction products are continuously removed from the reaction space in micro-flow synthesis. In this way, catalyst poisoning by reaction products can be avoided.

In consideration of these advantages, the preparation of α -diazocarbonyl compounds **1** and its photochemical Wolff rearrangement using an integrated micro-flow system is an ideal synthetic process for obtaining useful carbonyl compounds. Herein, we summarize recently reported micro-flow photochemical Wolff rearrangements and describe their applications in integrated micro-flow syntheses. In this microreview, "micro-flow" is defined as having reaction channels equal to, or less than, an inner diameter of 1 mm.

3. Micro-flow, Photochemical Wolff Rearrangement

3.1. The First Report of Continuous-flow, Photochemical Wolff Rearrangement

The first example of a continuous-flow photochemical Wolff rearrangement was reported by Konopelski and co-workers in 2010.^[39] They conducted the photochemical Wolff rearrangement of α -diazob- β -ketoamide **7** and the subsequent lactamization of *in situ*-generated **8** to afford β -lactam **9** (Scheme 2).



Scheme 2. Photochemical Wolff rearrangement of α -diazob- β -ketoamide **7** and a subsequent lactamization to afford β -lactam **9**.

The continuous-flow photoreactor used in this study is shown in Figure 1. A toluene solution of α -diazob- β -ketoamide **7** was placed in a three-neck, round-bottom flask that was then

degassed by bubbling N_2 . A fluorinated ethylene propylene (FEP) tube (inner diameter: 1.6 mm) was looped around a light source. The solution was passed through the FEP tube via a liquid chromatography pump then returned to the three-neck flask. The solution was allowed to circulate during the photoreaction.

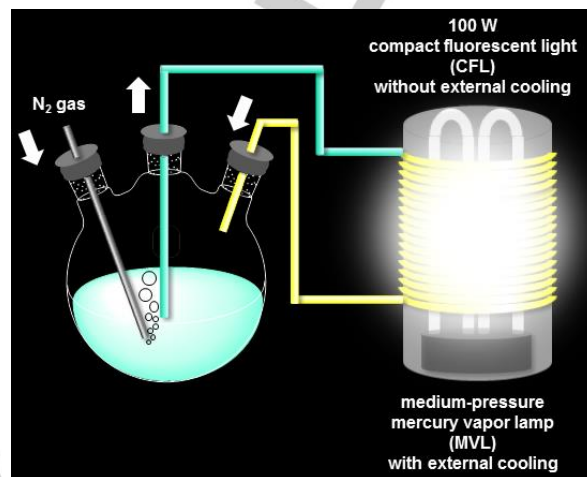


Figure 1. Continuous-flow photoreactor used for the Wolff rearrangement and intramolecular cyclization of α -diazob- β -ketoamide **7**.

At first, a medium-pressure mercury vapor lamp (MVL) was employed as the light source. In this case, an external cooling system was necessary to cool the reaction mixture. The reaction time of the continuous-flow conditions was shortened to half that of the batch conditions (Table 1, entry 1 vs. 2). The observed *cis/trans* ratio was not significantly changed (entry 1 vs. 2). To avoid the risk of using a high-power light source with strong heat and UV radiation, the use of a 100 W compact fluorescent light (CFL) was examined for the photochemical Wolff rearrangement. Due to the decreased heat generation by the CFL, external cooling was unnecessary. Both the yield of **9** and the ratio of **9a/9b** were improved by using a CFL instead of an MVL, although the reaction time was lengthened (entries 1 and 2 vs. 3 and 4). Slightly higher yields of **9** were observed in batch conditions (entries 1 and 3) compared with those of flow conditions (entries 2 and 4). However, Konopelski and co-workers preferred the flow conditions to the batch conditions because of the ease of scale-up.

Table 1. Photochemical Wolff rearrangement of α -diazob- β -ketoamide **7** using a continuous-flow photoreactor.

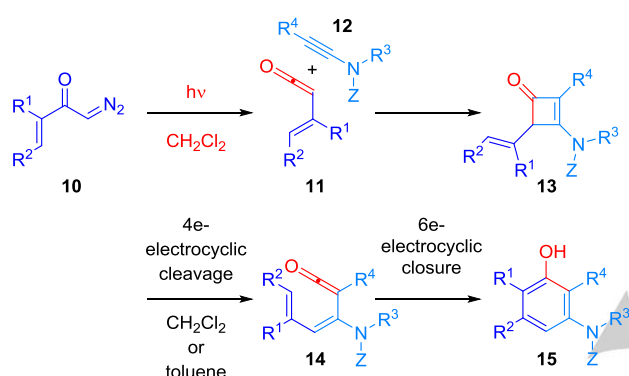
entry	light source	reactor	scale	time	yield	9a/9b
1	MVL	batch	0.6 g	7 h	90%	64%/26%
2	MVL	flow	1.0 g	3.5 h	81%	61%/20%

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3	CFL	batch	0.1 g	18 h	95%	75%/20%
4	CFL	flow	1.0 g	48 h	91%	70%/21%

3.2. The Micro-flow, Photochemical Wolff Rearrangement/[2+2] Cycloaddition Sequence

Danheiser and co-workers reported the synthesis of aromatic compound **15** from ketene **11** and amino alkyne **12** (Scheme 3).^[40] In this synthesis, ketene **11** was prepared by the micro-flow photochemical Wolff rearrangement of α -diazoketone **10**.



Scheme 3. Photochemical Wolff rearrangement/[2+2] cycloaddition to afford cyclobutenone **13** and a subsequent 4-electron electrocyclic cleavage and 6-electron electrocyclic closure to afford **15**.

The micro-flow photoreactor used in this study is shown in Figure 2. The light source for the reactor was a 450 W medium-pressure mercury lamp with a water jacket and a Pyrex filter, which was necessary in order to reduce the undesired polymer generation on the wall of the reaction tube. The solution of **10** and **12** was introduced to the FEP tube (inner diameter: 0.76 mm) at a flow rate of 0.025–0.32 mL/min. The irradiation time was 21 to 33 min (the corresponding batch reaction required 3 to 8 h to complete), and the throughput of this reactor was around 0.9 mmol/h. The obtained solution was heated in a batch reactor to proceed the following 4-electron, electrocyclic cleavage/6-electron, electrocyclic closure sequence to obtain **15**.

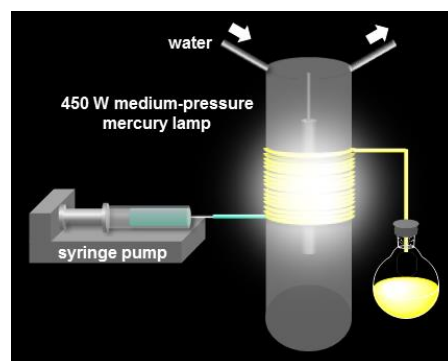
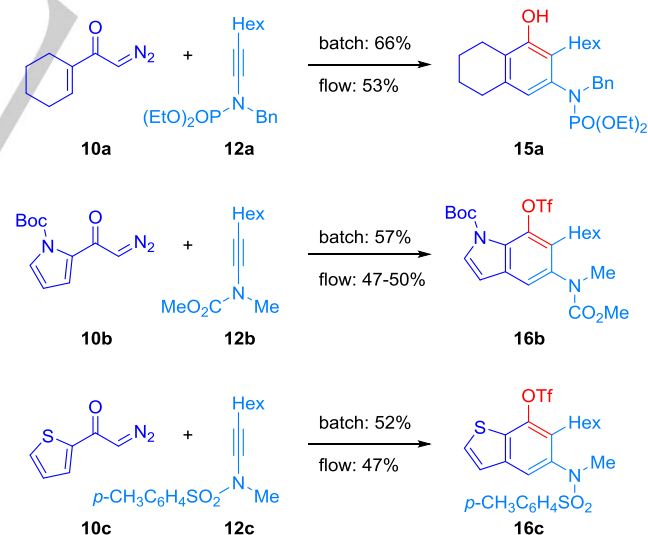


Figure 2. Micro-flow photoreactor used for a Wolff rearrangement/[2+2] cycloaddition sequence.

Selected results are shown in Scheme 4. The observed yields of micro-flow conditions were comparable to those of batch conditions. In the synthesis of **16b** and **16c**, the products were purified after converting the phenols to the corresponding triflates in order to avoid an undesired oxidation of the phenols. In the synthesis of **16c**, a uranium filter (>340 nm) was used instead of a Pyrex filter (>280 nm) in order to suppress the decomposition of **16c**. Use of the uranium filter required a prolonged reaction time (from 3–8 to 50 h) for batch conditions, whereas a complete consumption of the substrates was accomplished with a slight extension of the reaction time (from 21 to 33 min) in the case of the micro-flow conditions. The use of micro-flow conditions allowed a ready synthesis of the desired product on multigram scale.

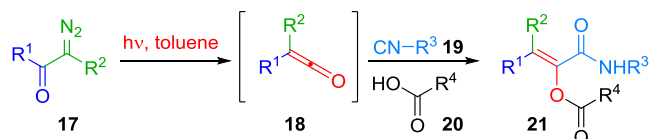


Scheme 4. Comparing the yields of **15a**, **16b**, and **16c** from batch and micro-flow conditions.

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3.3. The Continuous-flow, Photochemical Wolff Rearrangement/Nucleophilic Addition/Carboxylation Sequence

Basso and coworkers demonstrated a three-component coupling reaction of ketene **18**, isonitrile **19**, and carboxylic acid **20** to obtain acyloxyacrylamide **21** (Scheme 5).^[41] The authors attempted to prepare ketene **18** via a silver-mediated Wolff rearrangement of **17**, but the desired product was not afforded, probably due to an undesired coordination of isonitrile **19** with the silver reagent. Therefore, **18** was prepared via the continuous-flow photochemical Wolff rearrangement of α -diazoketone **17**.



Scheme 5. Photochemical Wolff rearrangement/nucleophilic addition/carboxylation to afford acyloxyacrylamide **21**.

The continuous-flow photoreactor used in this study is shown in Figure 3. A hollow cylinder was surrounded by 8 W UV lamps (emission maximum wavelength: 365 nm) and an FEP tube (diameter: 1.6 mm) was looped around the hollow cylinder. A solution of α -diazoketone **17**, isonitrile **19**, and carboxylic acid **20** was introduced into the FEP tube.

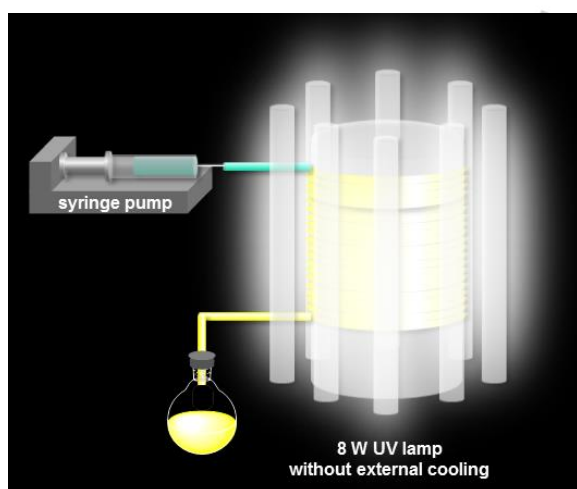
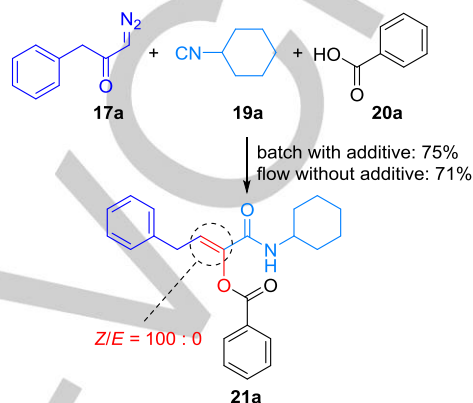


Figure 3. Continuous-flow photoreactor used for the Wolff rearrangement/nucleophilic addition/carboxylation sequence to obtain acyloxyacrylamide **21**.

In the batch synthesis of acyloxyacrylamide **21**, the product was obtained as a mixture of *Z/E* isomers. In this reaction, a *Z*-isomer was generated first, however, photoirradiation of the generated *Z*-isomer caused undesired isomerization of the alkene to afford the *E*-isomer. In order to avoid this undesired isomerization, an addition of *trans*-stilbene (0.2 equiv.) was required under batch conditions. On the other hand, continuous-

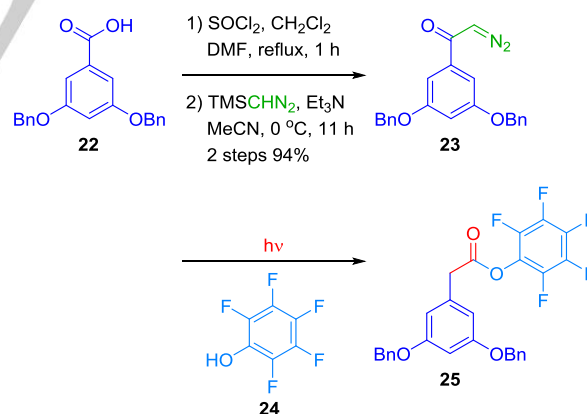
flow conditions suppressed the isomerization without adding *trans*-stilbene because the product was continuously removed from the photoreaction space. A selected example of the reaction is shown in Scheme 6. In this example, continuous-flow conditions dominantly afforded the desired **21a** without the additive. The observed yield of **21a** was comparable to that from batch conditions.



Scheme 6. Selective synthesis of (*Z*)-acyloxyacrylamide via a three-component coupling reaction under either batch or flow conditions.

3.4. The Micro-flow, Photochemical Wolff Rearrangement/Nucleophilic Sequence

Fuse and coworkers reported an Arndt-Eistert homologation of carboxylic acid **22** to obtain ester **25**.^[42] In this synthesis, **25**



Scheme 7. Arndt-Eistert homologation of carboxylic acid **23** to afford α -aryl ester **25**.

was synthesized from the micro-flow, photochemical Wolff rearrangement of α -diazoketone **23**.

In this study, various photo reactors were examined, as shown in Table 2. The irradiation time required for the complete consumption of **23** was shortened via the use of micro-flow

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conditions (entries 1-3) compared with the time required for batch conditions (entry 4). A 4 W portable UV lamp that was inexpensive, readily available, and safe to use resulted in a yield (entry 3) that was comparable to the photoreaction using a 400 W high-pressure mercury lamp (entries 1 and 2), although a longer irradiation time was required for the consumption of **23**.

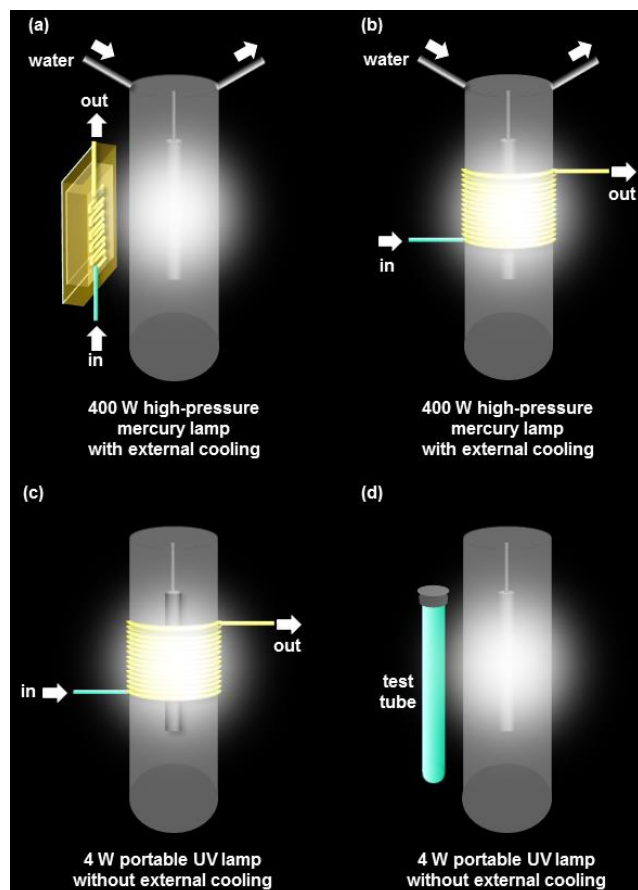


Table 2. Photochemical Wolff rearrangement of α -diazoketone **23** using various photoreactors.

entry	reactor	irradiation time	yield
1	a ^[a] (flow)	30 sec	58% ^[e]
2	b ^[b] (flow)	60 sec	51% ^[e]
3	c ^[c] (flow)	300 sec	57% ^[e] (82%) ^[f]
4	d ^[d] (batch)	1.5 h	75% ^[f]

[a] 400 W high-pressure mercury lamp with external cooling and a quartz-derived micro-flow cell reactor (depth: 200 μ m; width: 1 mm; length: 250 mm; volume: 50 μ L). [b] 400 W high-pressure mercury lamp with external cooling

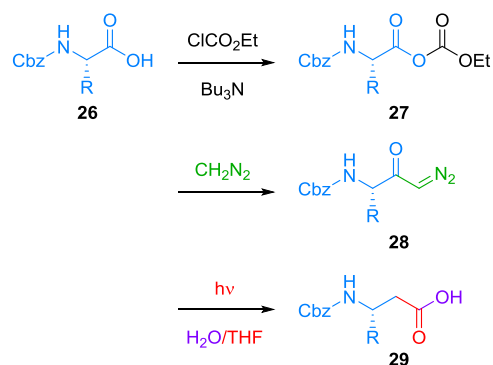
and a FEP tube (inner diameter: 1.0 mm). [c] 4 W portable UV lamp without external cooling and a FEP tube (inner diameter: 1.0 mm). [d] 4 W portable UV lamp without external cooling and a quartz-derived test tube. [e] 1.5 equiv. of **24** was used. [f] 3.0 equiv. of **24** was used.

4. Integrated Micro-flow Synthesis based on Photochemical Wolff Rearrangement

4.1. Integrated Micro-flow Synthesis of β -amino acids via Arndt-Eistert Homologation

Kappe and coworkers first reported an integrated micro-flow synthesis based on a photochemical Wolff rearrangement.^[43] They successfully demonstrated an Arndt-Eistert homologation of α -amino acid **26** to β -amino acid **29**.

In this synthesis, both preparation of α -diazoketone **28** and its use for photochemical Wolff rearrangement were carried out in a micro-flow reactor, as shown in Figure 4. α -Amino acid **26** and base were injected into a T-shape mixer. Ethyl chloroformate was also introduced into the T-shape mixer to generate mixed anhydride **27**. The mixed anhydride was introduced to an outer chamber of a tube-in-tube reactor. Explosive and toxic diazomethane was safely generated by reacting Diazald and KOH.^[44, 45] The diazomethane-containing mixture was introduced to an inner tube of the tube-in-tube reactor. The inner tube (inner diameter: 0.8 mm) was made of a hydrophobic, gas-permeable Teflon AF-2400 membrane. Thus, only gaseous diazomethane diffused through the wall of the inner tube to the outer chamber and reacted with the mixed anhydride **27** to generate α -diazoketone **28**. Aqueous waste from the inner tube of the tube-in-tube reactor was removed. The reaction solution in the outer chamber of the tube-in-tube reactor was then introduced to a gas-permeable AF-2400 tube that was immersed in acetic acid to remove the remaining diazomethane. Otherwise, diazomethane can cause undesired



Scheme 8. Arndt-Eistert homologation of α -amino acid **26** to afford β -amino acid **29**.

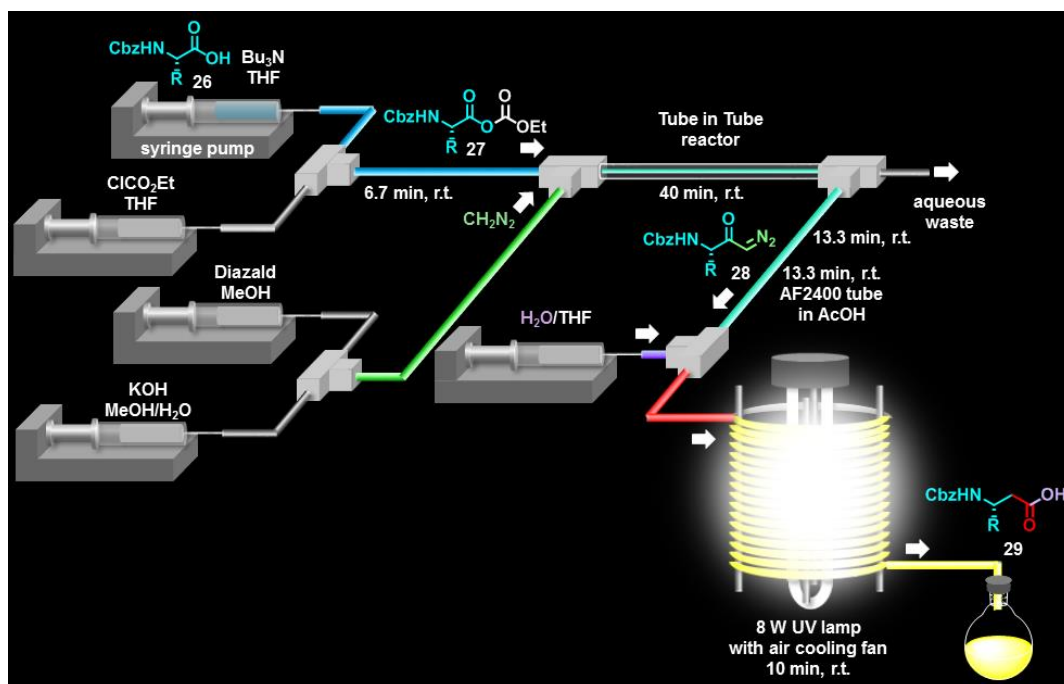


Figure 4. Integrated micro-flow system for β -peptide synthesis via Arndt-Eistert homologation.

reactions and/or N_2 generation that disturbs flow rate in a subsequent photochemical Wolff rearrangement. Then H_2O/THF was mixed with a solution of **28**, and the resultant solution was introduced into a photoreactor (8 W germicide compact fluorescent UV lamp was surrounded by perfluoroalkoxy alkane

(PFA) tube (inner diameter: 1.6 mm). The desired β -amino acid **29** was obtained from α -amino acid **26** without the isolation of any intermediates.

Six β -amino acids **29a–29f** and two β -amino acid ethyl esters **30a** and **30b** were successfully synthesized from the corresponding α -amino acids, as shown in Figure 5, using the developed integrated micro-flow system.

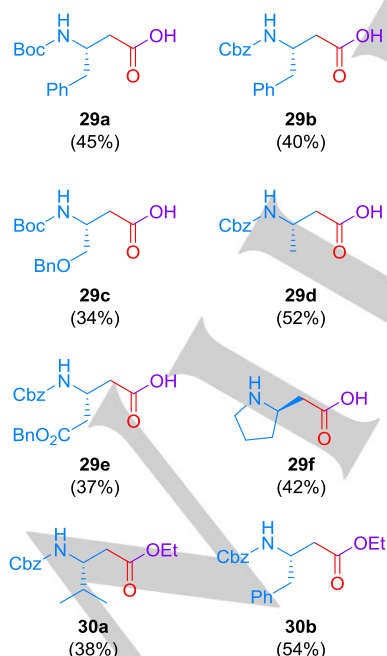
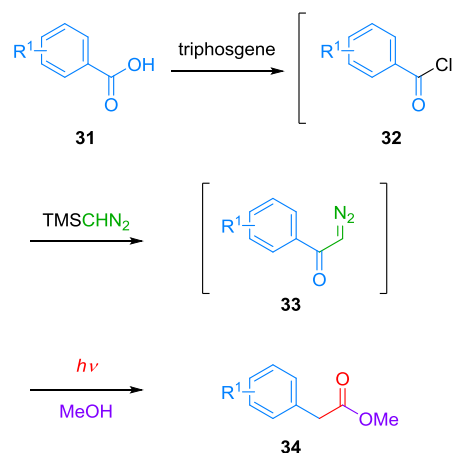


Figure 5. Arndt-Eistert homologation of α -amino acid **26** to afford β -amino acid **29** and β -amino acid ester **30**.

4.2. Integrated Micro-flow Synthesis of α -aryl carboxylic acid via Arndt-Eistert Homologation

Fuse and coworkers recently reported integrated micro-flow synthesis based on a photochemical Wolff rearrangement.^[46]



Scheme 9. Synthesis of α -aryl ester **34** via Arndt-Eistert homologation.

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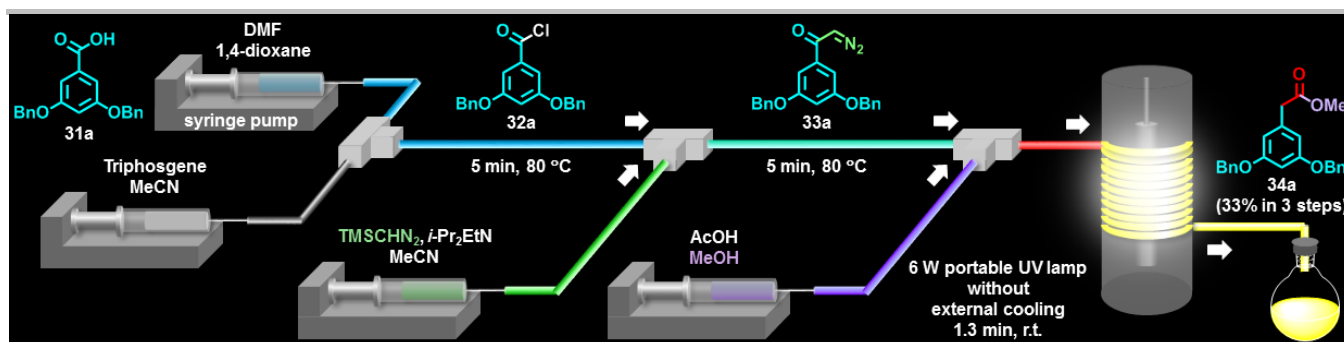
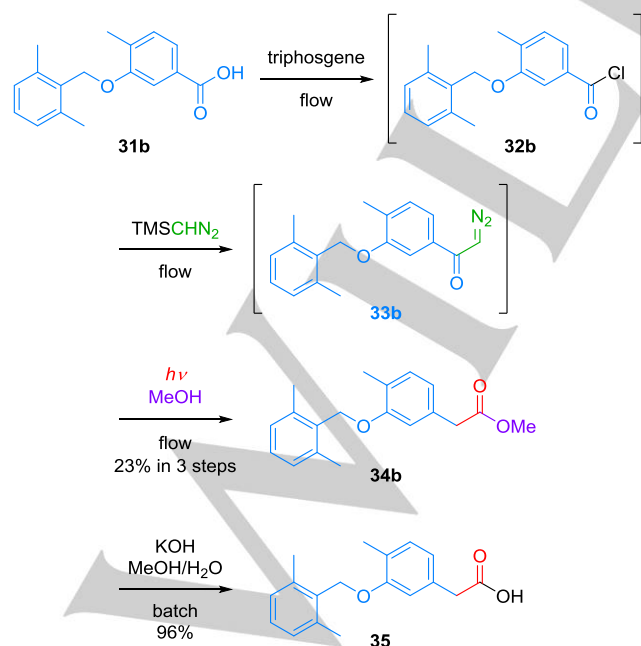


Figure 6. Integrated micro-flow synthesis of α -aryl carboxylic acid via Arndt-Eistert homologation.

They synthesized α -aryl ester **34** from benzoic acid derivative **31** via Arndt-Eistert homologation (Scheme 9).

In detail, α -diazoketone **33a** was prepared and directly used for photochemical Wolff rearrangement in a micro-flow reactor, as shown in Figure 6. Benzoic acid derivative **31a** (with a catalytic amount of DMF) and triphosgene were injected into a T-shaped mixer to obtain acid chloride **32a**. The acid chloride was introduced to another T-shaped mixer and reacted with trimethylsilyl diazomethane to generate α -diazoketone **33a**. The α -diazoketone was mixed with AcOH and MeOH. AcOH decomposed unreacted trimethylsilyl diazomethane. The resultant solution was introduced into a photoreactor (6 W portable UV lamp surrounded by a FEP tube (inner diameter: 1.0 mm)). The desired α -aryl ester **34a** was obtained in a 33% yield from benzoic acid derivative **31a** in a one-flow reaction. This integrated micro-flow system rapidly produced a one-carbon homologated product (total residence time: 11 min 20 s).

Biologically active α -aryl carboxylic acid **35** was synthesized utilizing the developed method, as shown in Scheme 10. α -Aryl ester **34b** was synthesized in the integrated micro-flow system from benzoic acid derivative **31b**. Hydrolysis of the obtained α -aryl ester in a batch reactor afforded the desired α -aryl carboxylic acid **35**.



Scheme 10. Synthesis of biologically active α -aryl carboxylic acid **35** via Arndt-Eistert homologation.

Conclusions and Outlook

Wolff rearrangement is regarded as one of the most useful transformations in organic synthesis. In particular, photochemical Wolff rearrangement is potentially very useful because it requires no addition of reagents. Use of micro-flow reactors for the photochemical Wolff rearrangement further increases its utility due to improved light penetration efficiency. The micro-flow photochemical process employs higher concentration conditions, which decreases the amount of solvent waste and shortens the reaction time. In addition, the integrated micro-flow system enables the safe generation and consumption of potentially hazardous diazo compounds. Moreover, scale-up is readily carried out either by continuous operation or by increasing the number of reactors. This integrated micro-flow system is ideal for industrial processing. It is highly possible that many integrated micro-flow syntheses including photochemical Wolff rearrangement, will be used in industrial fields in the near future. The authors anticipate that more examples of integrated micro-flow syntheses based on photochemical Wolff rearrangement will be reported in further advancements in this field.

Shinichiro Fuse was born in 1977 in Japan. He earned a BS in Chemical Engineering from Tokyo Institute of Technology in 2000, and a PhD in Applied Chemistry from Tokyo Institute of Technology under the supervision of Prof. Takashi Takahashi in 2005. He was a researcher at ChemGenesis Incorporated from 2005 to 2006, and a postdoctoral fellow with Prof. Daniel E. Kahne at Harvard University from 2006 to 2008. In 2008, he joined the faculty at the Tokyo Institute of Technology as an assistant professor. He moved to Chemical Resources Laboratory at the same university as an associate professor in 2015. The affiliation name was changed to Laboratory for Chemistry and Life Science in 2016.

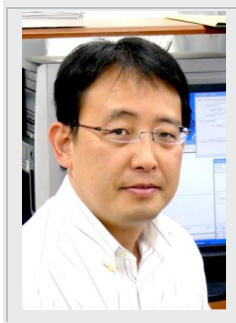


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Yuma Otake was born in 1992 in Japan. He earned a BS in Chemical Engineering from Tokyo Institute of Technology in 2015, and he is currently pursuing doctoral studies under the supervision of Dr. Shinichiro Fuse, and Prof. Hiroyuki Nakamura at Tokyo Institute of Technology.



Hiroyuki Nakamura was born in 1967 in Japan. He received his PhD from Tohoku University under the supervision of Prof. Yoshinori Yamamoto in 1996. He became an assistant professor at Kyushu University (1995–1997) and at Tohoku University (1997–2002). He worked as a visiting assistant professor at University of Pittsburgh with Prof. Dennis Curran (2000–2001). In 2002, he was appointed as an associate professor at Gakushuin University and promoted as a professor in 2006. In 2013, he was appointed as a professor at Tokyo Institute of Technology. He received the Chemical Society of Japan Award for Young Chemists in 1999 and the Award of the Japanese Society for Molecular Target Therapy of Cancer in 2007. His research interests include synthetic methodology, medicinal chemistry, chemical biology, and neutron capture therapy.



Acknowledgements

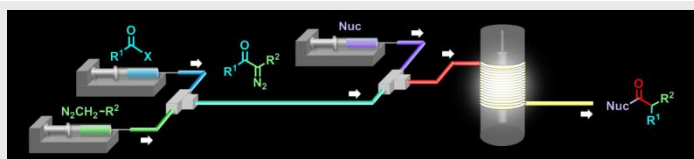
The authors are thankful for a Grant-in-Aid for Young Scientists (B) for Scientific Research on Innovative Areas of “Organic Synthesis Based on Reaction Integration, Development of New Methods and Creation of New Substances” (No. 2105); and, to The Naito Foundation Natural Science Scholarship for financial support.

Keywords: microreactors • photochemistry • carbonyl compound • Wolff rearrangement • Arndt-Eistert homologation

- [1] L. Wolff, *Justus Liebigs Ann. Chem.* **1902**, 325, 129.
- [2] W. Kirmse, *Eur. J. Org. Chem.* **2002**, 2002, 2193.
- [3] A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKevey, *Chem. Rev.* **2015**, *115*, 9981.
- [4] N. R. Candeias, R. Paterna, P. M. P. Gois, *Chem. Rev.* **2016**, *116*, 2937.
- [5] F. Arndt, B. Eistert, *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 200.
- [6] Z. Wang, in *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc., **2010**.
- [7] B. J. Deadman, S. G. Collins, A. R. Maguire, *Chem. Eur. J.* **2015**, *21*, 2298.
- [8] S. T. R. Müller, T. Wirth, *ChemSusChem* **2015**, *8*, 245.
- [9] F. Cavani, G. Centi, S. Perathoner, F. Trifiro, *Sustainable Industrial Chemistry*, WILEY-VCH, Weinheim, **2009**.
- [10] J. P. McMullen, K. F. Jensen, *Annu. Rev. Anal. Chem.* **2010**, *3*, 19.
- [11] D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675.
- [12] C. Jiménez-González, P. Poehlauer, Q. B. Broxterman, B.-S. Yang, D. am Ende, J. Baird, C. Bertsch, R. E. Hannah, P. Dell’Orco, H. Noorman,

- S. Yee, R. Reintjens, A. Wells, V. Massonneau, J. Manley, *Org. Process Res. Dev.* **2011**, *15*, 900.
- [13] J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17.
- [14] I. R. Baxendale, *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519.
- [15] M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2015**, *11*, 1194.
- [16] R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2.
- [17] J. Britton, C. L. Raston, *Chem. Soc. Rev.* **2017**, *46*, 1250.
- [18] M. S. Newman, P. F. Beal, *J. Am. Chem. Soc.* **1950**, *72*, 5163.
- [19] J.-Y. Winum, M. Kamal, A. Leydet, J.-P. Roque, J.-L. Montero, *Tetrahedron Lett.* **1996**, *37*, 1781.
- [20] A. R. Katritzky, S. Zhang, A. H. M. Hussein, Y. Fang, P. J. Steel, *J. Org. Chem.* **2001**, *66*, 5606.
- [21] M. Oelgemöller, O. Shvydkiv, *Molecules* **2011**, *16*, 7522.
- [22] J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025.
- [23] M. Oelgemöller, *Chem. Eng. Technol.* **2012**, *35*, 1144.
- [24] E. M. Schuster, P. Wipf, *Isr. J. Chem.* **2014**, *54*, 361.
- [25] Y. Su, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Eur. J.* **2014**, *20*, 10562.
- [26] D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276.
- [27] K. Loubière, M. Oelgemöller, T. Aillet, O. Dechy-Cabaret, L. Prat, *Chem. Eng. Process.* **2016**, *104*, 120.
- [28] K. Mizuno, Y. Nishiyama, T. Ogaki, K. Terao, H. Ikeda, K. Kakiuchi, *J. Photochem. Photobiol. C Photochem. Rev.* **2016**, *29*, 107.
- [29] J.-i. Yoshida, *Chem. Rec.* **2010**, *10*, 332.
- [30] M. Baumann, I. R. Baxendale, S. V. Ley, *Mol. Divers.* **2011**, *15*, 613.
- [31] J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, 47, 4583.
- [32] J.-i. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331.
- [33] N. G. Anderson, *Org. Process Res. Dev.* **2012**, *16*, 852.
- [34] K. S. Elvira, X. C. i Solvas, R. C. R. Wootton, A. J. deMello, *Nature Chem.* **2013**, *5*, 905.
- [35] V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem* **2013**, *6*, 746.
- [36] J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849.
- [37] L. N. Protasova, M. Bulut, D. Ormerod, A. Buekenhoudt, J. Berton, C. V. Stevens, *Org. Process Res. Dev.* **2013**, *17*, 760.
- [38] R. M. Myers, D. E. Fitzpatrick, R. M. Turner, S. V. Ley, *Chem. Eur. J.* **2014**, *20*, 12348.
- [39] Y. S. M. Vaske, M. E. Mahoney, J. P. Konopelski, D. L. Rogow, W. J. McDonald, *J. Am. Chem. Soc.* **2010**, *132*, 11379.
- [40] T. P. Willumstad, O. Haze, X. Y. Mak, T. Y. Lam, Y.-P. Wang, R. L. Danheiser, *J. Org. Chem.* **2013**, *78*, 11450.
- [41] S. Garbarino, L. Banfi, R. Riva, A. Basso, *J. Org. Chem.* **2014**, *79*, 3615.
- [42] Y. Mifune, S. Fuse, H. Tanaka, *J. Flow Chem.* **2014**, *4*, 173.
- [43] V. D. Pinho, B. Gutmann, C. O. Kappe, *RSC Advances* **2014**, *4*, 37419.
- [44] F. Mastronardi, B. Gutmann, C. O. Kappe, *Org. Lett.* **2013**, *15*, 5590.
- [45] V. D. Pinho, B. Gutmann, L. S. M. Miranda, R. O. M. A. de Souza, C. O. Kappe, *J. Org. Chem.* **2014**, *79*, 1555.
- [46] S. Fuse, Y. Otake, Y. Mifune, H. Tanaka, *Aust. J. Chem.* **2015**, *68*, 1657.

MICROREVIEW

**Micro-flow Synthesis***

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Page No. – Page No.
Integrated Micro-flow Synthesis
Based on Photochemical Wolff
Rearrangement

Wolff rearrangement is regarded as one of the most useful transformations in organic synthesis. *In situ* preparation of α -diazo carbonyl compounds and their use in photochemical Wolff rearrangement in integrated micro-flow systems is particularly valuable. Because the risk in the treatment of potentially hazardous diazo compounds can be minimized, photochemical reactions can be accelerated due to increases in the light penetration efficiency of micro-flow photoreactors.