CORNING

Advanced-Flow™ Reactors

AFR-related publications

Complete list of published scientific papers that utilize Corning® Advanced-Flow™ Reactor Technology

Publication Date: August 2022

This list compiles scientific papers published that utilize Corning® Advanced-Flow™ Reactor (AFR) Technology. Corning expresses our thanks to all authors who used our technology in their experiments. If you would like to include your published paper using AFR Technology, please contact us at reactors@corning.com and we will be pleased to review your submission for inclusion in this document.

1. Reactors: Goal, Design & Characterization

Corning developed AFR technology to support the synthetic industry as an ongoing effort toward process intensification.[1] For this, switching the synthetic paradigm[2] from traditional batch to flow chemistry was pursued.[3] The reactors were designed towards high scale production[4–10] with a variety of applications.[11]

2. Reactors Engineering & Characterization

Using Corning's expertise, reactors were designed either in resistant glass[12] or Silicon Carbide (no chemical limitation found yet).[13] The mass transfer properties,[14] heat exchange,[15] pressure drop[16] and residence time distribution[17] were fully characterized for single[18,19] or dual phase systems.[20–22] The hydrodynamic properties of liquid and gas liquid[23] flow were published.[24,25] The same work was also carried out for the Corning® Low-Flow Reactor.[26] Light was also characterized in photochemical reactors.[27]

To help with industrialization, the design of Corning's reactors ensured a scalable system such as liquid/liquid systems from Low-Flow to G1[28], and up to production.[29,30] The concept behind flow reactors and scale-up has been summarized.[31]

3. Published applications in Corning AFR

3.1. Photochemistry

Photochemistry is possible due to an LED system, used from laboratory to industrial scale.[32–34] While each individual wavelength was characterized,[27] the behavior of a multiphasic system with photochemistry was also characterized.[35]

3.1.1. Gas photochemistry: Oxygen oxidation.

For alpha-terpinene oxidation, optimizing photochemistry guidelines were published.[36] β-dicarbonyl compounds were enantioselectively oxidated.[37] Sulfured Methionine amino acid was oxidisized[38] and the protocol was extended so that mustard gas can be neutralized by air.[39] The generation of hypochlorite for this work can be performed continuously.[40] Use of sensitizer on nanoparticles was compared to batch for an oxygen oxidation.[41] Function of terminal N-Methyl groups into aldehydes could also be performed without metals.[42]

3.1.2. Materials

Gold nanoparticles can be synthesized, showing the multi-purpose possibility of the reactor.[43] On top of it, daily use of *aqua regia* showed the chemical tolerance of the reactor.

3.1.3. Halogen Photo-Chemistry

Iodoperlfuoroalkylation of alkenes were carried out.[44] Benzylic bromination reaction was also successfully performed[45]. Another example on G1 scale using NBS was successful.[46] An atom-economical selective chlorination was also performed.[47] Synthesis of Thiomorpholine at 4 M via a Telescoped Photochemical Thiol–Ene/ Cyclization Sequence was performed.[48]

3.1.4. Potentially hazardous species "in situ"

Potentially hazardous species can be generated and used *in situ*, leveraging the inherently safer technology used in continuous manufacturing. Amongst them, Bromine can be generated and reacted *in situ* at laboratory[49] and industrial scales.[50,51] Similarly, nitrosyl chloride can perform photonitrisation.[52] N-Chloroamines were synthesized metal-free by radical addition reactions in continuous flow.[53,54] Hypochlorites were also synthesized *in situ*.[40]

3.1.5. Cycloaddition

Selective photoredox transformation can be performed.[55] [2+2] Cycloaddition reaction, supported *in silico*, were performed in G1 reactors .[56] Cerium also catalyzed Cycloalkanols Cycloaddition[57] and functionalize alkanes.[58]

Using renewable source chemicals, γ-butyrolactone were synthesized.[59]

3.1.6. Organometallics

Using Nickel as a catalyst, arylhydrazines were synthesized.[60] Using inline NMR monitoring, Nickel Negishi coupling reactions were also carried out.[61] An API intermediate was synthesized this way.[62]

3.1.7. Green Chemistry

Direct metal free organocatalytic arylation coupling to aryl bromide was performed.[63]

3.2. Thermal Chemistry

3.2.1. Classical Chemistry/Batch to Flow

Plant design and economic study of Ibuprofen and artemisinin was evaluated in flow.[64] The use of the appropriate analytical tools (such as Raman spectroscopy) is an asset to ensure a full optimization of process in flow.[65]

Collecting internal data, a Moffat-Swern oxidation was translated from Batch to Flow Chemistry.[66] This showcase highlights the number of possible reactions which can be used in flow. The exothermic chlorination of a compound with thionyl chloride was performed from laboratory to industrial scale both in simulation and experimentally.[67]

3.2.2. Synthesis of potentially hazardous chemicals

Using flow reactors, potentially hazardous species can be synthesized using inherently safer technology.

3.2.2.1. Nitric acid use.

Alcohol esterification with nitrous acid, while being an exothermic process, could be carried out successfully in G1 Reactors and turned into synthetically useful alkyl nitrites.[68] Similar nitration reactions can be performed effectively.[69]

3.2.2.2. Nitrogen/Azide compounds,

While potentially hazardous but synthetically interesting, these reactions have been successfully implemented in AFR technology. Monomethylhydrazine was synthesised.[70] Despite the risks associated with hydrazoic acid, there is a synthesis of Diphenylphosphoryl azide.[71] Using azides, Ritalin was synthesized.[72] Similarly, *in situ*, generated diazomethane was used in a synthetic way.[73] Cyclopropanation was successfully implemented through Design of Experiment strategy.[74]

Benzoic acid alkylation reaction, generating and consuming *in situ* dangerous intermediate species, was performed in flow.[75] Tetrazole coupling reaction was performed, keeping in check all parameters in typically unstable condition.[76]

3.2.2.3. Oxidation

Peracids, unstable species formed in conditions where their stability depends upon a reliable set of unstable conditions, were synthesized effectively.[77] Synthesis of Modafinil was performed smoothly with Hydrogen Peroxide as an oxidant.[78]

3.2.2.4. Use of Gas.

Using oxygen, benzylic oxidation was carried out in metal free and reagent recyclable conditions.[79] Oxygen was also helped with the hydroxylation of ketones and ketamine synthesis.[80]

Ozonolysis, which is potentially hazardous even at a trace level, was performed in a Low Flow Reactor.[81] A successful case was published at kilo lab scale.[82]

On the other hand, reduction via hydrogenation could be performed, too.[83,84] For a hydrogenation reaction, a system with Pd allowed a temporary Pd deposit in situ.[85]

Challenging Bunsen reaction (Gas SO_2/liquid) requiring precise mixing was industrially implemented. [86,87]

Synthesis of an anti-bacterial agent performic peracid was successfully carried out.[77]

The electrophilic α-aminohydroxylation of ketones was carried out by preparing *in situ* the 1-chloro-1-nitrosocyclopentane reagent.[88]

3.2.3. Green Process

Using flow chemistry, a strong emphasis on Green Chemistry is pushed.[89,90]

3.2.3.1. Greener conditions

First, existing applications are optimized in a more ecofriendly way. Tertiary Ketone were hydroxylated without need for metal.[91]

Cyclic organic carbonates were synthesized[92] and solvent-free options were also developed.[93]

Solvent free biphasic alcohol oxidation was carried out and scaled up in a Low Flow Reactor .[94] Using bleach, alcohol was oxidized and scale up in a biphasic mixture in a metal free process.[95] LAH reduction of esters into aldehyde was performed in mild conditions.[96] Epoxide nucleophilic opening was used for a coupling en route to the synthesis of an API, telescoping steps and removing DCM as a solvent.[97]

3.2.3.2. Sustainable Material

Synthesis from green glycerol towards oxiranes was performed. Biodiesel could be synthesized from cooking oil.[98] Similarly, biodiesel additive STBE was synthesized from bio-sourced glycerol.[99,100] Total synthesis of Modafinil was entirely performed in flow in 3 steps.[78]

3.2.3.3. Biosynthesis

The bioprocess of lipase β-catalyzed isoamyl acetate synthesis was carried out in flow.[101]

3.2.4. Material Chemistry/Nanoparticles

Iron oxide nanoparticles were synthesized.[102] Further characterization of the equipment and synthesis of iron nanoparticles was successfully carried out.[19] Micro-encapsulation led to smooth, monodisperse and stable components.[103]

Working on asteroids, valuable metals were extracted.[104]

4. Bibliography

(1) Chevalier, B. Corning Microreaction Technology, a Process Intensification Solution Designed for Industrial Production. *Chemistry Today* **2008**, *26* (5), 6–7.

(2) Gérardy, R.; Emmanuel, N.; Toupy, T.; Kassin, V.-E.; Tshibalonza, N. N.; Schmitz, M.; Monbaliu, J.-C. M. Continuous Flow Organic Chemistry: Successes and Pitfalls at the Interface with Current Societal Challenges. *Eur. J. Org. Chem.* **2018**, *2018* (20–21), 2301–2351. https://doi.org/10.1002/ejoc.201800149.

(3) Calabrese, G. S.; Pissavini, S. From Batch to Continuous Flow Processing in Chemicals Manufacturing. *AIChE J.* **2011**, *57* (4), 828–834. https://doi.org/10.1002/aic.12598.

(4) Lavric, D.; Lobet, O.; Guidat, R.; Vizza, A.; Jiang, Y. Corning® Advanced-Flow™ Reactors: Innovation Drives Continuous Flow Manufacturing of Chemicals. *Pharma Tech Japan* **2017**, *33* (12), 68–77.

(5) Schmidt, F.; Chevalier, B. The Future Flows Through Corning® Advanced-Flow™ Glass Reactors. Engineered to Move You to Market Faster and More Efficiently. *Chemistry Today* **2009**, *27* (2), 4–5.

(6) Roberge, D. M.; Gottsponer, M.; Eyholzer, M.; Kockmann, N. Industrial Design, Scale-up and Use of Microreactors. *Chemistry Today* **2009**, *27* (4), July-August.

(7) Barthe, P.; Guermeur, C.; Lobet, O.; Moreno, M.; Woehl, P.; Roberge, D. M.; Bieler, N.; Zimmermann, B. Continuous Multi-Injection Reactor for Multipurpose Production - Part I. *Chem. Eng. Technol.* **2008**, *31* (8), 1146–1154. https://doi.org/10.1002/ceat.200800132.

(8) Roberge, D. M.; Bieler, N.; Mathier, M.; Eyholzer, M.; Zimmermann, B.; Barthe, P.; Guermeur, C.; Lobet, O.; Moreno, M.; Woehl, P. Development of an Industrial Multi-Injection Microreactor for Fast and Exothermic Reactions - Part II. *Chem. Eng. Technol.* **2008**, *31* (8), 1155–1161. https://doi.org/10.1002/ceat.200800131.

(9) Dann, E.; Schmidt, F.; Chevalier, B. Corning® Advanced-Flow™ Glass

Reactors: Now It Is Simple to Scale up Production. *Chemistry Today* **2010**, *28* (1), 24–25.

(10) Dann, E.; Schmidt, F.; Chevalier, B. Corning® Advanced-Flow™ Glass Reactors - the Benefits Are Clear. *Chemistry Today* **2009**, *27* (4), 12–13.

(11) Guidat, R.; Vizza, A.; Jiang, Y. Advanced-Flow Reactor Technologies Makes Continuous-Flow Industrial Production Real. *Specialty Chemical Magazine* **2015**, *35* (11), 30–32.

(12) Chevalier, B.; Lavric, E. D.; Cerato-Noyerie, C.; Horn, C. R.; Woehl, P. Microreactors for Industrial Multi-Phase Applications. Test Reactions to Develop Innovative Glass Microstructure Designs. *Chemistry Today* **2008**, *26* (2), 38–42.

(13) Lobet, O.; Vizza, A. SiC Advanced-Flow Reactors for Highly Corrosive Media. *Specialty Chemical Magazine* **2016**, *36* (08), 32–35.

(14) Lavric E. D.; Cerato-Noyerie C. Mass Transfer in Gas-Liquid Flow in Corning® Advanced-Flow™ Reactors. *Chemical Engineering Transactions* **2012**, *29*, 979–984. https://doi.org/10.3303/CET1229164.

(15) Lavric, D. Thermal Performance of Corning Glass Microstructures, Heat Transfer and Fluidic Flow in Microscale III. *Conference, Hilton Whistler, BC, Canada, ECI international* **2008**.

(16) Moreau, M.; Di Miceli Raimondi, N.; Le Sauze, N.; Cabassud, M.; Gourdon, C. Pressure Drop and Axial Dispersion in Industrial Millistructured Heat Exchange Reactors. *Chemical Engineering and Processing: Process Intensification* **2015**, *95*, 54–62. https://doi.org/10.1016/j.cep.2015.05.009.

(17) Mikhail Chivilikhin; Lev Kuandykov; Carine Cerato-Noyerie; Pierre Woehl; Elena Daniela Lavric. Residence Time Distribution in Corning® Advanced-Flow™ Reactor. Experiment and Modelling. *Chemical Engineering Transactions* **2011**, *25*, 791–796. https://doi.org/10.3303/CET1125132.

(18) Nieves-Remacha, M. J.; Kulkarni, A. A.; Jensen, K. F. OpenFOAM Computational Fluid Dynamic Simulations of Single-Phase Flows in an Advanced-Flow Reactor. *Ind. Eng. Chem. Res.* **2015**, *54* (30), 7543–7553. https://doi.org/10.1021/acs.iecr.5b00232.

(19) Yang, M.; Yang, L.; Zheng, J.; Hondow, N.; Bourne, R. A.; Bailey, T.; Irons, G.; Sutherland, E.; Lavric, D.; Wu, K.-J. Mixing Performance and Continuous Production of Nanomaterials in an Advanced-Flow Reactor. *Chemical Engineering Journal* **2021**, 128565. https://doi.org/10.1016/j.cej.2021.128565.

(20) Nieves-Remacha, M. J.; Yang, L.; Jensen, K. F. OpenFOAM Computational Fluid Dynamic Simulations of Two-Phase Flow and Mass Transfer in an Advanced-Flow Reactor. *Ind. Eng. Chem. Res.* **2015**, *54* (26), 6649–6659. https://doi.org/10.1021/acs.iecr.5b00480.

(21) Nieves-Remacha, M. J.; Kulkarni, A. A.; Jensen, K. F. Hydrodynamics of Liquid–Liquid Dispersion in an Advanced-Flow Reactor. *Ind. Eng. Chem. Res.* **2012**, *51* (50), 16251–16262. https://doi.org/10.1021/ie301821k.

(22) Chivilikhin M. S.; Soboleva V.; Kuandykov L.; Woehl P.; Lavric E. D. CFD Analysis of Hydrodynamic and Thermal Behaviour of Advanced-Flow™ Reactors. *Chemical Engineering Transactions* **2010**, *21*, 1099–1104. https://doi.org/10.3303/CET1021184.

(23) Nieves-Remacha, M. J.; Kulkarni, A. A.; Jensen, K. F. Gas–Liquid Flow and Mass Transfer in an Advanced-Flow Reactor. *Ind. Eng. Chem. Res.* **2013**, *52* (26), 8996–

9010. https://doi.org/10.1021/ie4011707.

(24) Wu, K.-J.; Nappo, V.; Kuhn, S. Hydrodynamic Study of Single- and Two-Phase Flow in an Advanced-Flow Reactor. *Ind. Eng. Chem. Res.* **2015**, *54* (30), 7554–7564. https://doi.org/10.1021/acs.iecr.5b01444.

(25) Nieves-Remacha, M. J.; Jensen, K. F. Mass Transfer Characteristics of Ozonolysis in Microreactors and Advanced-Flow Reactors. *Journal of Flow Chemistry* **2015**, *5* (3), 160–165. https://doi.org/10.1556/1846.2015.00010.

(26) Zhang, F.; Carine Cerato Noyerie; Pierre Woehl; Elena Daniela Lavric. Intensified Liquid/Liquid Mass Transfer in Corning® Advanced-Flow™ Reactors. *Chemical Engineering Transactions* **2011**, *24*, 1369–1374. https://doi.org/10.3303/CET1124229.

(27) Roseau, M.; Chausset-Boissarie, L.; Gremetz, S.; Roth, P. M. C.; Penhoat, M. Multiple Wavelength (365–475 Nm) Complete Actinometric Characterization of Corning® Lab Photo Reactor Using Azobenzene as a Highly Soluble, Cheap and Robust Chemical Actinometer. *Photochem Photobiol Sci* **2022**. https://doi.org/10.1007/s43630-022-00171-w.

(28) Woitalka, A.; Kuhn, S.; Jensen, K. F. Scalability of Mass Transfer in Liquid–Liquid Flow. *Chemical Engineering Science* **2014**, *116*, 1–8. https://doi.org/10.1016/j.ces.2014.04.036.

(29) J. Jorda; Vizza, A. From Laboratory to Production: A Seamless Scale-Up. *Speciality Chemicals Magazine* **2012**, No. Nov., 19–21.

(30) Lavric, E. D.; Woehl, P. Advanced-Flow™ Glass Reactors for Seamless Scale-Up. *Chemistry Today* **2009**, *27* (3), 45–48.

(31) Dong, Z.; Wen, Z.; Zhao, F.; Kuhn, S.; Noël, T. Scale-up of Micro- and Milli-Reactors: An Overview of Strategies, Design Principles and Applications. *Chemical Engineering Science: X* **2021**, 100097. https://doi.org/10.1016/j.cesx.2021.100097.

(32) Gauron, G.; Ao, J.; Gremetz, S.; Horn, C. R. Powerful Scalable Photochemistry: The Efficient Use of Light. *Chemistry Today* **2018**, *36* (4), 12–15.

(33) Elgue, S.; Aillet, T.; Loubiere, K.; Conté, A.; Dechy-Cabaret, O.; Prat, L.; Horn, C. R.; Lobet, O.; Vallon, S. Flow Photochemistry: A Meso-Scale Reactor for Industrial Applications. *Chemistry Today* **2015**, *33* (5), 58–61.

(34) Stankiewicz, A. I.; Nigar, H. Beyond Electrolysis: Old Challenges and New Concepts of Electricity-Driven Chemical Reactors. *React. Chem. Eng.* **2020**, *5* (6), 1005–1016. https://doi.org/10.1039/D0RE00116C.

(35) Roibu, A.; Horn, C. R.; Van Gerven, T.; Kuhn, S. Photon Transport and Hydrodynamics in Gas-Liquid Flow Part 2: Characterization of Bubbly Flow in an Advanced-Flow Reactor. *ChemPhotoChem* **2020**, *4* (10), 5193–5200. https://doi.org/10.1002/cptc.202000066.

(36) Horn, C. R.; Gremetz, S. A Method to Determine the Correct Photocatalyst Concentration for Photooxidation Reactions Conducted in Continuous Flow Reactors. *Beilstein J. Org. Chem.* **2020**, *16*, 871–879. https://doi.org/10.3762/bjoc.16.78.

(37) Tang, X.-F.; Zhao, J.-N.; Wu, Y.-F.; Zheng, Z.-H.; Feng, S.-H.; Yu, Z.-Y.; Liu, G.-Z.; Meng, Q.-W. Enantioselective Photooxygenation of β-Dicarbonyl Compounds in Batch and Flow Photomicroreactors. *Org. Biomol. Chem.*

2019, *17* (34), 7938–7942. https://doi.org/10.1039/C9OB01379B.

(38) Emmanuel, N.; Mendoza, C.; Winter, M.; Horn, C. R.; Vizza, A.; Dreesen, L.; Heinrichs, B.; Monbaliu, J.-C. M. Scalable Photocatalytic Oxidation of Methionine under Continuous-Flow Conditions. *Org. Process Res. Dev.* **2017**, *21* (9), 1435–1438. https://doi.org/10.1021/acs.oprd.7b00212.

(39) Emmanuel, N.; Bianchi, P.; Legros, J.; Monbaliu, J.-C. M. A Safe and Compact Flow Platform for the Neutralization of a Mustard Gas Simulant with Air and Light. *Green Chem.* **2020**, *22* (13), 4105–4115. https://doi.org/10.1039/D0GC01142H.

(40) Kassin, V.-E. H.; Silva-Brenes, D. V.; Bernard, T.; Legros, J.; Monbaliu, J.-C. M. A Continuous Flow Generator of Organic Hypochlorites for the Neutralization of Chemical Warfare Agent Simulants. *Green Chem.* **2022**, *24* (8), 3167–3179. https://doi.org/10.1039/D2GC00458E.

(41) Lancel, M.; Gomez, C.; Port, M.; Amara, Z. Performances of Homogeneous and Heterogenized Methylene Blue on Silica Under Red Light in Batch and Continuous Flow Photochemical Reactors. *Front. Chem. Eng.* **2021**, *3*, 752364. https://doi.org/10.3389/fceng.2021.752364.

(42) Mandigma, M. J.; Zurauskas, J.; MacGregor, C. I.; Edwards, L.; Shahin, A.; d'Heureuse, L.; Yip, P.; Birch, D. J. S.; Gruber, T.; Heilmann, J.; John, M. P.; Barham, J. P. An Organophotocatalytic Late-Stage *N* -CH_3 Oxidation of Trialkylamines to *N* -Formamides with O_2 in Continuous Flow. *Chem. Sci.* **2022**, 10.1039.D1SC05840A. https://doi.org/10.1039/D1SC05840A.

(43) Bianchi, P.; Petit, G.; Monbaliu, J.-C. M. Scalable and Robust Photochemical Flow Process towards Small Spherical Gold Nanoparticles. *React. Chem. Eng.* **2020**, *5* (7), 1224–1236. https://doi.org/10.1039/D0RE00092B.

(44) Rosso, C.; Williams, J. D.; Filippini, G.; Prato, M.; Kappe, C. O. Visible-Light-Mediated Iodoperfluoroalkylation of Alkenes in Flow and Its Application to the Synthesis of a Key Fulvestrant Intermediate. *Org. Lett.* **2019**, *21* (13), 5341–5345. https://doi.org/10.1021/acs.orglett.9b01992.

(45) Chen, Y.; de Frutos, O.; Mateos, C.; Rincon, J. A.; Cantillo, D.; Kappe, C. O. Continuous Flow Photochemical Benzylic Bromination of a Key Intermediate in the Synthesis of a 2-Oxazolidinone. *ChemPhotoChem* **2018**, *2* (10), 906–912. https://doi.org/10.1002/cptc.201800114.

(46) Waterford, M.; Saubern, S.; Hornung, C. H. Evaluation of a Continuous-Flow Photo-Bromination Using N-Bromosuccinimide for Use in Chemical Manufacture. *Aust. J. Chem.* **2021**. https://doi.org/10.1071/CH20372.

(47) Radjagobalou, R.; Imbratta, M.; Bergraser, J.; Gaudeau, M.; Lyvinec, G.; Delbrayelle, D.; Jentzer, O.; Roudin, J.; Laroche, B.; Ognier, S.; Tatoulian, M.; Cossy, J.; Echeverria, P.-G. Selective Photochemical Continuous Flow Benzylic Monochlorination. *Org. Process Res. Dev.* **2022**, acs.oprd.2c00065. https://doi.org/10.1021/acs.oprd.2c00065.

(48) Steiner, A.; Nelson, R. C.; Dallinger, D.; Kappe, C. O. Synthesis of Thiomorpholine via a Telescoped Photochemical Thiol–Ene/Cyclization Sequence in Continuous Flow. *Org. Process Res. Dev.* **2022**, acs.oprd.2c00214. https://doi.org/10.1021/acs.oprd.2c00214.

(49) Steiner, A.; Williams, J. D.; de Frutos, O.; Rincón, J. A.; Mateos, C.; Kappe, C. O. Continuous Photochemical Benzylic Bromination Using *in Situ* Generated Br

$_2$: Process Intensification towards Optimal PMI and Throughput. *Green Chem.* **2020**, *22* (2), 448–454. https://doi.org/10.1039/C9GC03662H.

(50) Steiner, A.; Roth, P. M. C.; Strauss, F. J.; Gauron, G.; Tekautz, G.; Winter, M.; Williams, J. D.; Kappe, C. O. Multikilogram per Hour Continuous Photochemical Benzylic Brominations Applying a Smart Dimensioning Scale-up Strategy. *Org. Process Res. Dev.* **2020**, *24* (10), 2208–2216. https://doi.org/10.1021/acs.oprd.0c00239.

(51) Williams, J. D.; Gauron, G. Harnessing the Photochemistry of Bromine for Sustainable Manufacturing. *RO* **2020**, No. 119. https://doi.org/10.32907/RO-119-9093.

(52) Lebl, R.; Cantillo, D.; Kappe, C. O. Continuous Generation, in-Line Quantification and Utilization of Nitrosyl Chloride in Photonitrosation Reactions. *React. Chem. Eng.* **2019**, *4* (4), 738–746. https://doi.org/10.1039/C8RE00323H.

(53) González-Esguevillas, M.; Fernández, D. F.; Rincón, J. A.; Barberis, M.; de Frutos, O.; Mateos, C.; García-Cerrada, S.; Agejas, J.; MacMillan, D. W. C. Rapid Optimization of Photoredox Reactions for Continuous-Flow Systems Using Microscale Batch Technology. *ACS Cent. Sci.* **2021**, acscentsci.1c00303. https://doi.org/10.1021/acscentsci.1c00303.

(54) Steiner, A.; de Frutos, O.; Rincón, J. A.; Mateos, C.; Williams, J. D.; Kappe, C. O. *N* -Chloroamines as Substrates for Metal-Free Photochemical Atom-Transfer Radical Addition Reactions in Continuous Flow. *React. Chem. Eng.* **2021**, *6* (12), 2434–2441. https://doi.org/10.1039/D1RE00429H.

(55) Steiner, A.; Williams, J. D.; Rincón, J. A.; de Frutos, O.; Mateos, C.; Kappe, C. O. Implementing Hydrogen Atom Transfer (HAT) Catalysis for Rapid and Selective Reductive Photoredox Transformations in Continuous Flow: *Eur. J. Org. Chem.* **2019**, *2019* (33), 5807–5811. https://doi.org/10.1002/ejoc.201900952.

(56) Williams, J. D.; Nakano, M.; Gérardy, R.; Rincón, J. A.; de Frutos, Ó.; Mateos, C.; Monbaliu, J.-C. M.; Kappe, C. O. Finding the Perfect Match: A Combined Computational and Experimental Study toward Efficient and Scalable Photosensitized [2 + 2] Cycloadditions in Flow. *Org. Process Res. Dev.* **2019**, *23* (1), 78–87. https://doi.org/10.1021/acs.oprd.8b00375.

(57) Hu, A.; Chen, Y.; Guo, J.-J.; Yu, N.; An, Q.; Zuo, Z. Cerium-Catalyzed Formal Cycloaddition of Cycloalkanols with Alkenes through Dual Photoexcitation. *J. Am. Chem. Soc.* **2018**, *140* (42), 13580–13585. https://doi.org/10.1021/jacs.8b08781.

(58) Hu, A.; Guo, J.-J.; Pan, H.; Zuo, Z. Selective Functionalization of Methane, Ethane, and Higher Alkanes by Cerium Photocatalysis. *Science* **2018**, *361* (6403), 668–672. https://doi.org/10.1126/science.aat9750.

(59) Gérardy, R.; Winter, M.; Horn, C. R.; Vizza, A.; Van Hecke, K.; Monbaliu, J.-C. M. Continuous-Flow Preparation of γ-Butyrolactone Scaffolds from Renewable Fumaric and Itaconic Acids under Photosensitized Conditions. *Org. Process Res. Dev.* **2017**, *21* (12), 2012–2017. https://doi.org/10.1021/acs.oprd.7b00314.

(60) Mata, A.; Tran, D. N.; Weigl, U.; Williams, J. D.; Kappe, C. O. Continuous Flow Synthesis of Arylhydrazines via Nickel/Photoredox Coupling of Tert-Butyl Carbazate with Aryl Halides. *Chem. Commun.* **2020**, 10.1039.D0CC06787C. https://doi.org/10.1039/D0CC06787C.

(61) Abdiaj, I.; Horn, C. R.; Alcazar, J. Scalability of Visible-Light-Induced Nickel Negishi Reactions: A Combination of Flow Photochemistry, Use of Solid Reagents, and In-Line NMR Monitoring. *J. Org. Chem.* **2019**, *84* (8), 4748–4753. https://doi.org/10.1021/acs.joc.8b02358.

(62) Cordell, M. J.; Adams, M. R.; Vincent-Rocan, J.-F.; Riley, J. G. Total Synthesis of Entrectinib with Key Photo-redox Mediated Cross-coupling in Flow. *Eur. J. Org. Chem.* **2021**, ejoc.202101143. https://doi.org/10.1002/ejoc.202101143.

(63) Pallini, F.; Sangalli, E.; Sassi, M.; Roth, P. M. C.; Mattiello, S.; Beverina, L. Selective Photoredox Direct Arylations of Aryl Bromides in Water in a Microfluidic Reactor. *Org. Biomol. Chem.* **2021**, *19* (13), 3016–3023. https://doi.org/10.1039/D1OB00050K.

(64) Jolliffe, H. G.; Gerogiorgis, D. I. Plantwide Design and Economic Evaluation of Two Continuous Pharmaceutical Manufacturing (CPM) Cases: Ibuprofen and Artemisinin. *Computers & Chemical Engineering* **2016**, *91*, 269–288. https://doi.org/10.1016/j.compchemeng.2016.04.005.

(65) Roberto, M. F.; Dearing, T. I.; Martin, S.; Marquardt, B. J. Integration of Continuous Flow Reactors and Online Raman Spectroscopy for Process Optimization. *J Pharm Innov* **2012**, *7* (2), 69–75. https://doi.org/10.1007/s12247-012-9128-8.

(66) Bleie, O.; Roberto, M. F.; Dearing, T. I.; Branham, C. W.; Kvalheim, O. M.; Marquardt, B. J. Moffat-Swern Oxidation of Alcohols: Translating a Batch Reaction to a Continuous-Flow Reaction. *Journal of Flow Chemistry* **2015**, *5* (3), 183–189. https://doi.org/10.1556/1846.2015.00025.

(67) Dobrosavljevic, I.; Schaer, E.; Commenge, J. M.; Falk, L. Intensification of a Highly Exothermic Chlorination Reaction Using a Combined Experimental and Simulation Approach for Fast Operating Conditions Prediction. *Chemical Engineering and Processing: Process Intensification* **2016**, *105*, 46–63. https://doi.org/10.1016/j.cep.2016.04.007.

(68) Monbaliu, J.-C. M.; Jorda, J.; Chevalier, B.; Stevens, C. V.; Morvan, B. Continuous-Flow Production of Alkyl Nitrites. *Chemistry Today* **2011**, *29* (3), 50–52.

(69) Braune, S.; Pochlauer, P.; Reintjens, R.; Steinhofer, S.; Winter, M.; Lobet, O.; Guidat, R.; Woehl, P.; Guermeur, C. Selective Nitration in a Microreactor for Pharmaceutical Production under CGMP Conditions. *Chemistry Today* **2009**, *27*, 26–29.

(70) Le, D. M.; Bougrine, A. J.; Duclos, O.; Pasquet, V.; Delalu, H. A New Strategy for the Synthesis of Monomethylhydrazine Using the Raschig Process. 2: Continuous Synthesis of Stoichiometric Monochloramine Using the Microreactor Technology. *Reac Kinet Mech Cat* **2020**, *130* (1), 17–34. https://doi.org/10.1007/s11144-020-01761-4.

(71) Born, S. C.; Edwards, C. E. R.; Martin, B.; Jensen, K. F. Continuous, on-Demand Generation and Separation of Diphenylphosphoryl Azide. *Tetrahedron* **2018**, *74* (25), 3137–3142. https://doi.org/10.1016/j.tet.2018.01.026.

(72) Gérardy, R.; Winter, M.; Vizza, A.; Monbaliu, J.-C. M. Assessing Inter- and Intramolecular Continuous-Flow Strategies towards Methylphenidate (Ritalin) Hydrochloride. *React. Chem. Eng.* **2017**, *2* (2), 149–158. https://doi.org/10.1039/C6RE00184J.

(73) Rossi, E.; Woehl, P.; Maggini, M. Scalable in Situ Diazomethane Generation in Continuous-Flow Reactors. *Org. Process*

Res. Dev. **2012**, *16* (5), 1146–1149. https://doi.org/10.1021/op200110a.

(74) Klöpfer, V.; Eckl, R.; Floß, J.; Roth, P.; Reiser, O.; Barham, J. P. Catalyst-Free, Scalable Heterocyclic Flow Photocyclopropanation. *Green Chem.* **2021**, 10.1039.D1GC01624E. https://doi.org/10.1039/D1GC01624E.

(75) Penverne, C.; Hazard, B.; Rolando, C.; Penhoat, M. Scale-up Study of Benzoic Acid Alkylation in Flow: From Microflow Capillary Reactor to a Milliflow Reactor. *Org. Process Res. Dev.* **2017**, *21* (11), 1864–1868. https://doi.org/10.1021/acs.oprd.7b00246.

(76) Maralla, Y.; Sonawane, S.; Kashinath, D.; Pimplapure, M.; Paplal, B. Process Intensification of Tetrazole Reaction through Tritylation of 5-[4’-(Methyl) Biphenyl-2-Yl] Using Microreactors. *Chemical Engineering and Processing: Process Intensification* **2017**, *112*, 9–17. https://doi.org/10.1016/j.cep.2016.12.003.

(77) Gaikwad, S. M.; Jolhe, P. D.; Bhanvase, B. A.; Kulkarni, A.; Patil, V. S.; Pimplapure, M. S.; Suranani, S.; Potoroko, I.; Sonawane, S. H.; Sonawane, S. S. Process Intensification for Continuous Synthesis of Performic Acid Using Corning® Advanced-Flow™ Reactors. *Green Processing and Synthesis* **2017**, *6* (2). https://doi.org/10.1515/gps-2016-0147.

(78) Silva-Brenes, D. V.; Emmanuel, N.; López Mejías, V.; Duconge, J.; Vlaar, C.; Stelzer, T.; Monbaliu, J.-C. M. Out-Smarting Smart Drug Modafinil through Flow Chemistry. *Green Chem.* **2022**, *24* (5), 2094–2103. https://doi.org/10.1039/D1GC04666G.

(79) Yun, L.; Zhao, J.; Tang, X.; Ma, C.; Yu, Z.; Meng, Q. Selective Oxidation of Benzylic Sp ^{3} C–H Bonds Using Molecular Oxygen in a Continuous-Flow Microreactor. *Org. Process Res. Dev.* **2021**, acs.oprd.1c00080. https://doi.org/10.1021/acs.oprd.1c00080.

(80) Kassin, V.-E. H.; Gérardy, R.; Toupy, T.; Collin, D.; Salvadeo, E.; Toussaint, F.; Van Hecke, K.; Monbaliu, J.-C. M. Expedient Preparation of Active Pharmaceutical Ingredient Ketamine under Sustainable Continuous Flow Conditions. *Green Chem.* **2019**, *21* (11), 2952–2966. https://doi.org/10.1039/C9GC00336C.

(81) Lee, K.; Lin, H.; Jensen, K. F. Ozonolysis of Quinoline and Quinoline Derivatives in a Corning Low Flow Reactor. *React. Chem. Eng.* **2017**, *2* (5), 696–702. https://doi.org/10.1039/C7RE00084G.

(82) Vaz, M.; Courboin, D.; Winter, M.; Roth, P. M. C. Scale-Up of Ozonolysis Using Inherently Safer Technology in Continuous Flow under Pressure: Case Study on β-Pinene. *Org. Process Res. Dev.* **2021**, acs.oprd.1c00008. https://doi.org/10.1021/acs.oprd.1c00008.

(83) Buisson, B.; Donegan, S.; Wray, D.; Parracho, A.; Gamble, J.; Caze, P.; Jorda, J.; Guermeur, C. Slurry Hydrogenation in a Continuous Flow Reactor for Pharmaceutical Application. *Chemistry Today* **2009**, *27* (6), 12–16.

(84) Salique, F.; Musina, A.; Winter, M.; Yann, N.; Roth, P. M. C. Continuous Hydrogenation: Triphasic System Optimization at Kilo Lab Scale Using a Slurry Solution. *Front. Chem. Eng.* **2021**, *3*, 701910. https://doi.org/10.3389/fceng.2021.701910.

(85) Horn, C. R.; Cerato-Noyerie, C. A PdCl2 -Based Hydrogenation Catalyst for Glass Microreactors. *Journal of Flow Chemistry* **2014**, *4* (3), 110–112. https://doi.org/10.1556/JFC-D-13-00036.

(86) Moniri, A.; Wang, H.; Wu, X. (Eric). Application of Corrosion-Resistant Corning Advanced-Flow Reactors for

Multiphase Bunsen Reaction Part One: Investigation on SO2 Absorption. *International Journal of Petrochemical Science & Engineering* **2019**, *4* (4), 122–136.

(87) Moniri, A.; Wang, H.; Wu, X. (Eric). Application of Corrosion-Resistant Corning Advanced-Flow Reactors for Multiphase Bunsen Reaction Part Two: Investigation on Multiphase Reaction. *International Journal of Petrochemical Science & Engineering* **2019**, *4* (4), 153–160.

(88) Kassin, V.-E. H.; Morodo, R.; Toupy, T.; Jacquemin, I.; Van Hecke, K.; Robiette, R.; Monbaliu, J.-C. M. A Modular, Low Footprint and Scalable Flow Platform for the Expedient α-Aminohydroxylation of Enolizable Ketones. *Green Chem.* **2021**, 10.1039.D0GC04395H. https://doi.org/10.1039/D0GC04395H.

(89) Morodo, R.; Gérardy, R.; Petit, G.; Monbaliu, J.-C. M. Continuous Flow Upgrading of Glycerol toward Oxiranes and Active Pharmaceutical Ingredients Thereof. *Green Chem.* **2019**, *21* (16), 4422–4433. https://doi.org/10.1039/C9GC01819K.

(90) Marus, G. A. The Application of Green Chemistry and Engineering to Novel Sustainable Solvents and Processes. PhD Thesis Georgia Institute of Technology 2012.

(91) Kassin, V.-E. H.; Toupy, T.; Petit, G.; Bianchi, P.; Salvadeo, E.; Monbaliu, J.-C. M. Metal-Free Hydroxylation of Tertiary Ketones under Intensified and Scalable Continuous Flow Conditions. *J Flow Chem* **2020**, *10* (1), 167–179. https://doi.org/10.1007/s41981-019-00073-6.

(92) Gérardy, R.; Estager, J.; Luis, P.; Debecker, D. P.; Monbaliu, J.-C. M. Versatile and Scalable Synthesis of Cyclic Organic Carbonates under Organocatalytic Continuous Flow Conditions. *Catal. Sci. Technol.* **2019**, *9* (24), 6841–6851. https://doi.org/10.1039/C9CY01659G.

(93) Wang, Z.; Gérardy, R.; Gauron, G.; Damblon, C.; Monbaliu, J.-C. M. Solvent-Free Organocatalytic Preparation of Cyclic Organic Carbonates under Scalable Continuous Flow Conditions. *React. Chem. Eng.* **2019**, *4* (1), 17–26. https://doi.org/10.1039/C8RE00209F.

(94) Peer, M.; Weeranoppanant, N.; Adamo, A.; Zhang, Y.; Jensen, K. F. Biphasic Catalytic Hydrogen Peroxide Oxidation of Alcohols in Flow: Scale-up and Extraction. *Org. Process Res. Dev.* **2016**, *20* (9), 1677–1685. https://doi.org/10.1021/acs.oprd.6b00234.

(95) Zhang, Y.; Born, S. C.; Jensen, K. F. Scale-Up Investigation of the Continuous Phase-Transfer-Catalyzed Hypochlorite Oxidation of Alcohols and Aldehydes. *Org. Process Res. Dev.* **2014**, *18* (11), 1476–1481. https://doi.org/10.1021/op500158h.

(96) Ducry, L.; Roberge, D. M. Dibal-H Reduction of Methyl Butyrate into Butyraldehyde Using Microreactors. *Org. Process Res. Dev.* **2008**, *12* (2), 163–167. https://doi.org/10.1021/op7002002.

(97) Lim, J. J.; Arrington, K.; Dunn, A. L.; Leitch, D. C.; Andrews, I.; Curtis, N. R.; Hughes, M. J.; Tray, D. R.; Wade, C. E.; Whiting, M. P.; Goss, C.; Liu, Y. C.; Roesch, B. M. A Flow Process Built upon a Batch Foundation—Preparation of a Key Amino Alcohol Intermediate via Multistage Continuous Synthesis. *Org. Process Res. Dev.* **2020**, *24* (10), 1927–1937. https://doi.org/10.1021/acs.oprd.9b00478.

(98) Suranani, S.; Maralla, Y.; Gaikwad, S. M.; Sonawane, S. H. Process Intensification Using Corning® Advanced-Flow™ Reactor for Continuous Flow Synthesis of

Biodiesel from Fresh Oil and Used Cooking Oil. *Chemical Engineering and Processing - Process Intensification* **2018**, *126*, 62–73. https://doi.org/10.1016/j.cep.2018.02.013.

(99) Monbaliu, J.-C. M.; Winter, M.; Chevalier, B.; Schmidt, F.; Jiang, Y.; Hoogendoorn, R.; Kousemaker, M. A.; Stevens, C. V. Effective Production of the Biodiesel Additive STBE by a Continuous Flow Process. *Bioresource Technology* **2011**, *102* (19), 9304–9307. https://doi.org/10.1016/j.biortech.2011.07.007.

(100) Monbaliu, J.-C. M.; Winter, M.; Chevalier, B.; Schmidt, F.; Jiang, Y.; Hoogendoorn, R.; Kousemaker, M. A.; Stevens, C. V. Feasibility Study for Industrial Production of Fuel Additives from Glycerol. *Chemistry Today* **2010**, *28* (4), 8–11.

(101) Novak, U.; Lavric, D.; Žnidaršič-Plazl, P. Continuous Lipase B-Catalyzed Isoamyl Acetate Synthesis in a Two-Liquid Phase System Using Corning® AFR™ Module Coupled with a Membrane Separator Enabling Biocatalyst Recycle. *Journal of Flow Chemistry* **2016**, *6* (1), 33–38. https://doi.org/10.1556/1846.2015.00038.

(102) Suryawanshi, P. L.; Sonawane, S. H.; Bhanvase, B. A.; Ashokkumar, M.; Pimplapure, M. S.; Gogate, P. R. Synthesis of Iron Oxide Nanoparticles in a Continuous Flow Spiral Microreactor and Corning® Advanced Flow™ Reactor. *Green Processing and Synthesis* **2018**, *7* (1), 1–11. https://doi.org/10.1515/gps-2016-0138.

(103) Qin, Y.; Lu, X.; Que, H.; Wang, D.; He, T.; Liang, D.; Liu, X.; Chen, J.; Ding, C.; Xiu, P.; Xu, C.; Gu, X. Preparation and Characterization of Pendimethalin Microcapsules Based on Microfluidic Technology. *ACS Omega* **2021**, *6* (49), 34160–34172. https://doi.org/10.1021/acsomega.1c05903.

(104) Hessel, V.; Sarafraz, M. M.; Tran, N. N. The Resource Gateway: Microfluidics and Requirements Engineering for Sustainable Space Systems. *Chemical Engineering Science* **2020**, *225*, 115774. https://doi.org/10.1016/j.ces.2020.115774.