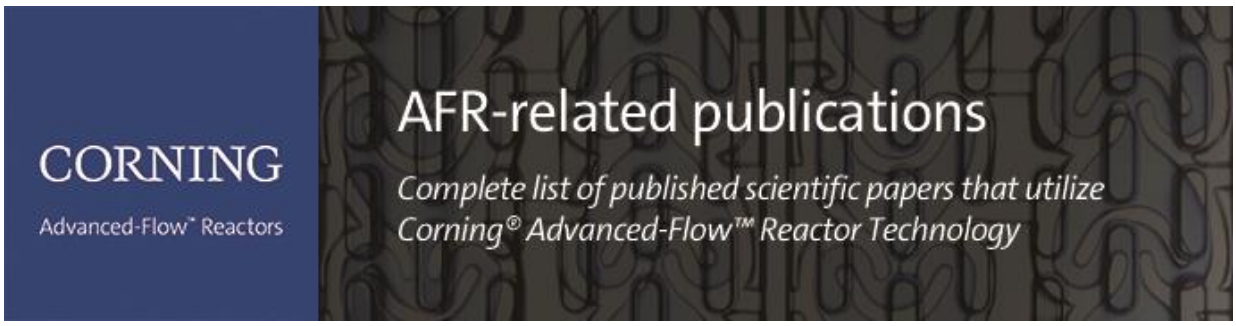

Publication Date: January 2024

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] Behavior of gas bubbles was also studied.[28]

To help with industrialization, the design of Corning's reactors ensured a scalable system such as liquid/liquid systems from Low-Flow to G1[29], and up to production.[30,31] The concept behind flow reactors and scale-up has been summarized.[32]

3. Published applications in Corning AFR

3.1. Photochemistry

Photochemistry is possible due to an LED system, used from laboratory to industrial scale.[33–35] While each individual wavelength was characterized,[27] the behavior of a multiphasic system with photochemistry was also characterized.[36]

3.1.1. Gas photochemistry: Oxygen oxidation.

For alpha-terpinene oxidation, optimizing photochemistry guidelines were published.[37] β-

dicarbonyl compounds were enantioselectively oxidated.[38] Sulfured Methionine amino acid was oxidisized[39] and the protocol was extended so that mustard gas can be neutralized by air.[40] The generation of hypochlorite for this work can be performed continuously.[41] Use of sensitizer on nanoparticles was compared to batch for an oxygen oxidation.[42] Function of terminal N-Methyl groups into aldehydes could also be performed without metals.[43] Use of Naphthoquinones as catalysts allowed effective transformation of naphtols into naphtoquinones under visible light.[44] Solvent Free oxidation of Citronellol using subpart-per-million Heavy Metal-Free Red-Light Photocatalyst was achieved.[45]

3.1.2. Materials

Gold nanoparticles can be synthesized, showing the multi-purpose possibility of the reactor.[46] 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.[47] Benzylic bromination reaction was also successfully performed[48]. Another example on G1 scale using NBS was successful.[49] An atom-economical selective chlorination was also performed.[50] Synthesis of Thiomorpholine at 4 M via a Telescoped Photochemical Thiol–Ene/ Cyclization Sequence was performed.[51]

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[52] and industrial scales.[53,54] Similarly, nitrosyl chloride can perform photonitrisation.[55] N-Chloroamines were synthesized metal-free by radical addition reactions in continuous flow.[56,57] Hypochlorites were also synthesized *in situ*.[41]

3.1.5. Cycloaddition

Selective photoredox transformation can be performed.[58] [2+2] Cycloaddition reaction, supported *in silico*, were performed in G1 reactors .[59] Cerium also catalyzed Cycloalkanols Cycloaddition[60] and functionalize alkanes.[61]

Using renewable source chemicals, γ-butyrolactone were synthesized.[62]

3.1.6. Organometallics

Using Nickel as a catalyst, arylhydrazines were synthesized.[63] Using inline NMR monitoring, Nickel Negishi coupling reactions were also carried out.[64] An API intermediate was synthesized this way.[65]

3.1.7. Green Chemistry

Direct metal free organocatalytic arylation coupling to aryl bromide was performed.[66] Enantioselective α-Alkylation of Aldehydes was achieved in scalable conditions, whereas it is not that common.[67]

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.[68] The use of the appropriate analytical tools (such as

Raman spectroscopy) is an asset to ensure a full optimization of process in flow.[69]

Collecting internal data, a Moffat-Swern oxidation was translated from Batch to Flow Chemistry.[70] 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.[71] Cyclic phosphate could be accessed through flow chemistry.[72]

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.[73] Similar nitration reactions can be performed effectively.[74] Synthesis of energetic material can also be synthesized in a more controlled environment.[75] Nitration of aromatic compounds was also performed in G1 Reactors.[76]

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.[77] Despite the risks associated with hydrazoic acid, there is a synthesis of Diphenylphosphoryl azide.[78] Using azides, Ritalin was synthesized.[79] Similarly, *in situ*, generated diazomethane was used in a synthetic way.[80] Cyclopropanation was successfully implemented through Design of Experiment strategy.[81]

Benzoic acid alkylation reaction, generating and consuming *in situ* dangerous intermediate species, was performed in flow.[82] Tetrazole coupling reaction was performed, keeping in check all parameters in typically unstable condition.[83]

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.[84] Synthesis of Modafinil was performed smoothly with Hydrogen Peroxide as an oxidant.[85]

3.2.2.4. Use of Gas.

Using oxygen, benzylic oxidation was carried out in metal free and reagent recyclable conditions.[86] Oxygen was also helped with the hydroxylation of ketones and ketamine synthesis.[87]

Ozonolysis, which is potentially hazardous even at a trace level, was performed in a Low Flow Reactor.[88] A successful case was published at kilo lab scale.[89] Ozone thiol selective oxidation into sulfoxide was also performed effectively.[90]

On the other hand, reduction via hydrogenation could be performed, too.[91,92] For a hydrogenation reaction, a system with Pd allowed a temporary Pd deposit in situ.[93]

Challenging Bunsen reaction (Gas SO_2/liquid) requiring precise mixing was industrially implemented. [94,95]

Synthesis of an anti-bacterial agent performic peracid was successfully carried out.[84]

The electrophilic α-aminohydroxylation of ketones was carried out by preparing *in situ* the 1-chloro-1-nitrosocyclopentane reagent.[96]

CO_2 was used in the green reagent for Scalable Production of Bio-Based Glycerol Carbonate.[97]

3.2.3. Green Process

Using flow chemistry, a strong emphasis on Green Chemistry is pushed.[98,99]

3.2.3.1. Greener conditions

First, existing applications are optimized in a more ecofriendly way. Tertiary Ketone were hydroxylated without need for metal.[100]

Cyclic organic carbonates were synthesized[101] and solvent-free options were also developed.[102] CO_2 was used in the green reagent for Scalable Production of Bio-Based Glycerol Carbonate.[97] Solvent free biphasic alcohol oxidation was carried out and scaled up in a Low Flow Reactor .[103] Using bleach, alcohol was oxidized and scale up in a biphasic mixture in a metal free process.[104] LAH reduction of esters into aldehyde was performed in mild conditions.[105] Epoxide nucleophilic opening was used for a coupling reaction en route to the synthesis of an API, telescoping steps and removing DCM as a solvent.[106]

A Wittig reaction alongside an enzymatic hydrolysis reaction were both performed in AFR, using Semi-supervised machine learning to study their kinetics.[107]

3.2.3.2. Sustainable Material

Synthesis from green glycerol towards oxiranes was performed. Biodiesel could be synthesized from cooking oil.[108] Similarly, biodiesel additive STBE was synthesized from bio-sourced glycerol.[109,110] Total synthesis of Modafinil was entirely performed in flow in 3 steps.[85]

3.2.3.3. Biosynthesis

The bioprocess of lipase β-catalyzed isoamyl acetate synthesis was carried out in flow.[111]

A Wittig reaction alongside an enzymatic hydrolysis reaction were both performed in AFR, using Semi-supervised machine learning to study their kinetics.[107]

3.2.4. Material Chemistry/Nanoparticles

Iron oxide nanoparticles were synthesized.[112] Further characterization of the equipment and synthesis of iron nanoparticles was successfully carried out.[19] Micro-encapsulation led to smooth, monodisperse and stable components.[113] Nanoemulsion in water/oil system allowed particles size down to 62 nm.[114] ZnMgO nanoparticles were synthesized as well.[115]

Working on asteroids, valuable metals were extracted.[116]

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