Highlights from the Flow Chemistry Literature 2016 (Part 4)

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In this Section of the journal, the literature on continuous flow synthesis (primarily organic synthesis and functional materials) from the period of October – December 2016 is presented. All the publications are listed ordered by journal name, with two Review articles appearing at the end. In this quarter the number of papers on continuous flow organic synthesis is relatively less as a few special issues are planned in the coming months. Two contributions on machine learning for optimization in flow synthesis and the scale-up of continuous flow reactors from Eli Lilly are the real highlights of this quarter!

Highlighted Articles

Synthesis of α-Nitro Carbonyls via Nitrations in Flow
Chentsova, A.; Ushakov, D. B.; Seeberger, P. H.; Gilmore, K.

The Journal of Organic Chemistry **2016**, *81,* 9415–9421

Authors have reported a neat method for the synthesis of α-nitro esters where nitronium ions (generated from the mixture of sulfuric acid and fuming nitric acid) attach to an aromatic ring through electrophilic substitution. Subsequent deacetylation of the nitro derivatives of 1,3-dicarbonyl compounds is reported via a semicontinuous approach that gives excellent yield of α-nitro esters and amides. This example indicates that sometime chemistry and rates of reactions demand a semi-continuous process too.

Optimizing the Heck–Matsuda Reaction in Flow with a Constraint-Adapted Direct Search Algorithm
Cortés-Borda, D.; Kutonova, K. V.; Jamet, C.; Trusova, M. E.; Zammattio, F.; Truchet, C.; Rodriguez-Zubiri, M.; Felpin, F. X.

Organic Process Research & Development **2016**, *20*, 1979–1987

Authors have integrated decision making through artificial intelligence for optimization of a palladium-catalyzed Heck–Matsuda reaction. This is a new trend in the synthetic chemistry and indeed useful to reduce the overall time required in the assessment of certain synthetic routes. It also helps to enhance reproducibility of the methods significantly. A logic based approach also helps to quickly analyze the multidimensional optimization space for fixed objective functions like maximum yield, highest throughput, and lowest production cost.

Development and Manufacturing GMP Scale-up of a Continuous Ir-Catalyzed Homogeneous Reductive Amination Reaction
May, S. A.; Johnson, M. D.; Buser, J. Y.; et al.

Organic Process Research & Development **2016**, *20*, 1870–1898

This is an excellent work reported by the Eli Lilly team on the design, development, and scale-up of a continuous iridium-catalyzed homogeneous high pressure reductive amination reaction for the production of an intermediate in Evacetrapib. This work shows cases of the approach for transforming initial batch chemistry at milligram scale to a full-scale continuous production under GMP conditions. While the paper brings out several thumb rules while implementing such transformations it also gives details on how to characterize such large systems. This is a must read for process chemists and process engineers to get to know about some new factors that can affect the performance of a reaction during scale-up of a continuous process.

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Suzuki–Miyaura Cross-Coupling Optimization Enabled by Automated Feedback
Reizman, B. J.; Wang, Y.-M.; Buchwald, S. L.; Jensen, K. F.

Reaction Chemistry & Engineering **2016**, *1*, 658–666

Another milestone in integrating logic and machine learning through automated synthesis platforms is demonstrated by Reizman et al. for Pd-catalyzed Suzuki–Miyaura cross-coupling reactions. An optimal DoE-based algorithm is implemented to increase the turnover number and yield of the catalytic system considering both discrete as well as continuous variables simultaneously. Feedback loops in the system helped to have only 96 experiments to reach optimal set of conditions. Importantly, exhaustive information that results from the response surfaces can be used to have better understanding of discrete variables in the reaction mechanism.

Organic Synthesis

"Toward the Synthesis of Noroxymorphone via Aerobic Palladium-Catalyzed Continuous Flow *N*-Demethylation Strategies"
Gutmann, B.; Elsner, P.; Cox, D. P.; Weigl, U.; Roberge, D. M.; Kappe, C. O.
ACS Sustainable Chemistry & Engineering **2016**, *4*, 6048–6061

"Selective Direct Synthesis of Trialkoxysilanes in a Packed Bed Flow Tubular Reactor"
Chigondo, F.; Zeelie, B.; Watts, P.
ACS Sustainable Chemistry & Engineering **2016**, *4*, 6237–6243

"Countercurrent Droplet-Flow-Based Mini Extraction with Pulsed Feeding and without Moving Parts"
Xu, C.; Jing, S.; Chu, Y.
AIChE Journal **2016**, *62*, 3685–3698

"Continuous Consecutive Reactions with Inter-Reaction Solvent Exchange by Membrane Separation"
Peeva, L.; Da Silva Burgal, J.; Heckenast, Z.; Brazy, F.; Cazenave, F.; Livingston, A.
Angewandte Chemie **2016**, *128*, 13774–13777

"Development of a Continuous Process for α-Thio-β-Chloroacrylamide Synthesis with Enhanced Control of a Cascade Transformation"
Dennehy, O. C.; Cacheux, V. M.; Deadman, B. J.; et al.
Beilstein Journal of Organic Chemistry **2016**, *12*, 2511–2522

"Continuous-Flow Synthesis of Primary Amines: Metal-Free Reduction of Aliphatic and Aromatic Nitro Derivatives with Trichlorosilane"
Porta, R.; Puglisi, A.; Colombo, G.; Rossi, S.; Benaglia, M.
Beilstein Journal of Organic Chemistry **2016**, *12*, 2614–2619

"Towards the Development of Continuous, Organocatalytic, and Stereoselective Reactions in Deep Eutectic Solvents"
Brenna, D.; Massolo, E.; Puglisi, A.; et al.
Beilstein Journal of Organic Chemistry **2016**, *12*, 2620–2626

"Let the Substrate Flow, not the Enzyme: Practical Immobilization of D-Amino Acid Oxidase in a Glass Microreactor for Effective Biocatalytic Conversions"
Bolivar, J. M.; Tribulato, M. A.; Petrasek, Z.; Nidetzky, B.
Biotechnology and Bioengineering **2016**, *113*, 2342–2349

"Continuous Precipitation of Process Related Impurities from Clarified Cell Culture Supernatant Using a Novel Coiled Flow Inversion Reactor (CFIR)"
Kateja, N.; Agarwal, H.; Saraswat, A.; Bhat, M.; Rathore, A. S.
Biotechnology Journal **2016**, *11*, 1320–1331

"Review: Microstructured Reactors as Efficient Tool for the Operation of Selective Oxidation Reactions"
Pennemann, H.; Kolb, G.
Catalysis Today **2016**, *278*, 3–21

"Selectivity and Lifetime Effects in Zeolite-Catalysed Baeyer–Villiger Oxidation Investigated in Batch and Continuous Flow"
Yakabi, K.; Milne, K.; Buchard, A.; Hammond, C.
ChemCatChem **2016**, *8*, 3490–3498

"Gas–Liquid Mass Transfer in a Falling Film Microreactor: Effect of Reactor Orientation on Liquid-Side Mass Transfer Coefficient"
Lokhat, D.; Domah, A. K.; Padayachee, K.; Baboolal, A.; Ramjugernath, D.
Chemical Engineering Science **2016**, *155*, 38–44

"The Plug & Play Reactor: A Highly Flexible Device for Heterogeneous Reactions in Continuous Flow"
Lichtenegger, G. J.; Tursic, V.; Kitzler, H.; Obermaier, K.; Khinast, J. G.; Gruber-Wölfler, H.
Chemie Ingenieur Technik **2016**, *88*, 1518–1523

"Using Anilines as Masked Cross-Coupling Partners: Design of a Telescoped Three-Step Flow Diazotization, Iododediazotization, Cross-Coupling Process"
Teci, M.; Tilley, M.; McGuire, M. A.; Organ, M. G.
Chemistry-A European Journal **2016**, *22*, 17407–17415

"Design of a Heterogeneous Catalytic Process for the Continuous and Direct Synthesis of Lactide from Lactic Acid"
Upare, P. P.; Yoon, J. W.; Hwang, D. W.; et al.
Green Chemistry **2016**, *18*, 5978–5983

"A Combination of Natural Deep Eutectic Solvents and Microflow Technology: A Sustainable Innovation for the Tandem Synthesis of 3-Aminohexahydrocoumarins"
Zamani, P.; Khosropour, A. R.
Green Chemistry **2016**, *18*, 6450–6455

"Reduction of Catalyst Deactivation Effects on Styrene Monomer Production in Multistage Radial Fixed Bed Reactor"
Bahadori, F.; Azizi, A.; Ghasemzadeh, K.
Journal of Flow Chemistry **2016**, *6*, 315–322

"In Situ Generation and Diels—Alder Reaction of Benzynes Derivatives with 5-Membered Ring Heterocycles Using a Microcapillary Flow Reactor"
Khadra, A.; Organ, M. G.
Journal of Flow Chemistry **2016**, *6*, 293–296

"Application of Flow Chemistry to Macrocyclization of Crown Ethers"
Fődi, T.; Kupai, J.; Túrós, G.; et al.
Journal of Flow Chemistry **2016**, *6*, 297–301

"Microfluidic Implementation of Ru-Catalyzed Methylation of Amines Using CO_2 as Carbon Source"
Perkins, G.; Khatib, O.; Peterson, M.; et al.
Journal of Flow Chemistry **2016**, *6*, 302–308

"Kinetic Study and Intensification of Acetyl Guaiacol Nitration with Nitric Acid—Acetic Acid System in a Microreactor"
Zhang, C.; Zhang, J.; Luo, G.
Journal of Flow Chemistry **2016**, *6*, 309–314

"Dispersion Photopolymerization of Acrylated Oligomers Using a Flexible Continuous Reactor"
Roose, P.; Berlier, M.; Lazzaroni, R.; Leclère, P.
Macromolecular Reaction Engineering **2016**, *10*, 502–509

"A Single-Stage, Continuous High-Efficiency Extraction Device (HEED) for Flow Synthesis"
Day, C.; Saldarriaga, A.; Tilley, M.; Hunter, H.; Organ, M. G.; Wilson, D. J.
Organic Process Research & Development **2016**, *20*, 1738–1743

"A Small-Footprint, High-Capacity Flow Reactor for UV Photochemical Synthesis on the Kilogram Scale"
Elliott, L. D.; Berry, M.; Harji, B.; Klauber, D.; Leonard, J.; Booker-Milburn, K. I.
Organic Process Research & Development **2016**, *20*, 1806–1811

"Development and Manufacturing GMP Scale-up of a Continuous Ir-Catalyzed Homogeneous Reductive Amination Reaction"
May, S. A.; Johnson, M. D.; Buser, J. Y.; et al.
Organic Process Research & Development **2016**, *20*, 1870–1898

"Life Cyle Assessment Based Environmental Performance Comparison of Batch and Continuous Processing: A Case of 4-D-Erythronolactone Synthesis"
Lee, C. K.; Khoo, H. H.; Tan, R. B.
Organic Process Research & Development **2016**, *20*, 1937–1948

"Handling Hazards Using Continuous Flow Chemistry: Synthesis of N 1-Aryl-[1, 2, 3]-Triazoles from Anilines via Telescoped Three-Step Diazotization, Azidodediazotization, and [3+2] Dipolar Cycloaddition Processes"
Teci, M.; Tilley, M.; McGuire, M. A.; Organ, M. G.
Organic Process Research & Development **2016**, *20*, 1967–1973

"Optimizing the Heck–Matsuda Reaction in Flow with a Constraint-Adapted Direct Search Algorithm"
Cortés-Borda, D.; Kutonova, K. V.; Jamet, C.; Trusova, M. E.; Zammattio, F.; Truchet, C.; Rodriguez-Zubiri, M.; Felpin, F. X.
Organic Process Research & Development **2016**, *20*, 1979–1987

"Using Flow to Outpace Fast Proton Transfer in an Organometallic Reaction for the Manufacture of Verubecestat (MK-8931)"
Thaisrivongs, D. A.; Naber, J. R.; McMullen, J. P.
Organic Process Research & Development **2016**, *20*, 1997–2004

"Microwave Heated Continuous Flow Palladium (II)-Catalyzed Desulfitative Synthesis of Aryl Ketones"
Skillinghaug, B.; Rydfjord, J.; Savmarker, J.; Larhed, M.
Organic Process Research & Development **2016**, *20*, 2005–2011

"A Mild and Selective Method for the Catalytic Hydrodeoxygenation of Cyanurate Activated Phenols in Multiphasic Continuous Flow"
Zhao, Y.; King, G.; Kwan, M. H.; Blacker, A. J.
Organic Process Research & Development **2016**, *20*, 2012–2018

"Continuous-Flow Diazotization for Efficient Synthesis of Methyl 2-(Chlorosulfonyl) Benzoate: An Example of Inhibiting Parallel Side Reactions"
Yu, Z.; Dong, H.; Xie, X.; Liu, J.; Su, W.
Organic Process Research & Development **2016**, *20*, 2116–2123

"Microfluidic Synthesis of Size-Controlled and Morphologically Homogeneous Lead Trinitroresorcinate Produced by Segmented Flow"
Zhou, N.; Zhu, P.; Rong, Y.; et al.
Propellants, Explosives, Pyrotechnics **2016**, *41*, 899–905

"A Laboratory-Scale Continuous Flow Chlorine Generator for Organic Synthesis"
Strauss, F. J.; Cantillo, D.; Guerra, J.; Kappe, C. O.
Reaction Chemistry & Engineering **2016**, *1*, 472–476

"Decay Kinetics of Sensitive Bioinorganic Species in a SuperFocus Mixer at Ambient Conditions"
Schurr, D.; Strassl, F.; Liebhäuser, P.; Rinke, G.; Dittmeyer, R.; Herres-Pawlis, S.
Reaction Chemistry & Engineering **2016**, *1*, 485–493

"A Miniature CSTR Cascade for Continuous Flow of Reactions Containing Solids"
Mo, Y.; Jensen, K. F.
Reaction Chemistry & Engineering **2016**, *1*, 501–507

"Combining Microfluidics and FT-IR Spectroscopy: Towards Spatially Resolved Information on Chemical Processes"
Perro, A.; Lebourdon, G.; Henry, S.; Lecomte, S.; Servant, L.; Marre, S.
Reaction Chemistry & Engineering **2016**, *1*, 577–594

"A Greener Process for Flow C–H Chlorination of Cyclic Alkanes Using in Situ Generation and on-Site Consumption of Chlorine Gas"
Fukuyama, T.; Tokizane, M.; Matsui, A.; Ryu, I.
Reaction Chemistry & Engineering **2016**, *1*, 613–615

"Photonic Contacting of Gas–Liquid Phases in a Falling Film Microreactor for Continuous-Flow Photochemical Catalysis with Visible Light"
Rehm, T. H.; Gros, S.; Löb, P.; Renken, A.
Reaction Chemistry & Engineering **2016**, *1*, 636–648

"Continuous Flow Gas Phase Photoreforming of Methanol at Elevated Reaction Temperatures Sensitised by Pt/TiO_2"
Caravaca, A.; Daly, H.; Smith, M.; Mills, A.; Chansai, S.; Hardacre, C.
Reaction Chemistry & Engineering **2016**, *1*, 649–657

"Suzuki–Miyaura Cross-Coupling Optimization Enabled by Automated Feedback"
Reizman, B. J.; Wang, Y.-M.; Buchwald, S. L.; Jensen, K. F.
Reaction Chemistry & Engineering **2016**, *1*, 658–666

"Direct Amide Synthesis over Core–Shell TiO_2@ $NiFe_2O_4$ Catalysts in a Continuous Flow Radiofrequency-Heated Reactor"
Liu, Y.; Gao, P.; Cherkasov, N.; Rebrov, E. V.
RSC Advances **2016**, *6*, 100997–101007

"A Benchtop NMR Spectrometer as a Tool for Monitoring Mesoscale Continuous-Flow Organic Synthesis: Equipment Interface and Assessment in Four Organic Transformations"
Archambault, C. M.; Leadbeater, N. E.
RSC Advances **2016**, *6*, 101171–101177

"The Continuous-Flow Synthesis of Carbazate Hydrazones Using a Simplified Computer-Vision Controlled Liquid–Liquid Extraction System"
O'Brien, M.; Cooper, D. A.; Mhembere, P.
Tetrahedron Letters **2016**, *57*, 5188–5191

"Isopropyl 2-Ethoxyacetate—An Efficient Acylating Agent for Lipase-Catalyzed Kinetic Resolution of Amines in Batch and Continuous-Flow Modes"
Oláh, M.; Boros, Z.; Hornyánszky, G.; Poppe, L.
Tetrahedron **2016**, *72*, 7249–7255

"Applying Green Processes and Techniques to Simplify Reaction Work-ups"
Andrade, C. K. Z.; Dar, A. R.
Tetrahedron **2016**, *72*, 7375–7391

"Continuous-Flow Electrophilic Amination of Arenes and Schmidt Reaction of Carboxylic Acids Utilizing the Superacidic Trimethylsilyl Azide/Triflic Acid Reagent System"
Chen, Y.; Gutmann, B.; Kappe, C. O.
The Journal of Organic Chemistry **2016**, *81*, 9372–9380

"Synthesis of α-Nitro Carbonyls via Nitrations in Flow"
Chentsova, A.; Ushakov, D. B.; Seeberger, P. H.; Gilmore, K.
The Journal of Organic Chemistry **2016**, *81*, 9415–9421

"Selective Pinacol-Coupling Reaction Using a Continuous Flow System"
Sotto, N.; Cazorla, C.; Villette, C.; Billamboz, M.; Len, C.
The Journal of Organic Chemistry **2016**, *81*, 11065–11071

"Application of the Photoredox Coupling of Trifluoroborates and Aryl Bromides to Analog Generation Using Continuous Flow"
DeLano, T. J.; Bandarage, U. K.; Palaychuk, N.; Green, J.; Boyd, M. J.
The Journal of Organic Chemistry **2016**, *81*, 12525–12531

Nanomaterials

"Bifunctional Ruthenium Nanoparticle-SILP Catalysts (RuNPs@ SILP) for the Hydrodeoxygenation of Eucalyptol under Batch and Continuous Flow Conditions"
Luska, K. L.; Migowski, P.; El Sayed, S.; Leitner, W.
ACS Sustainable Chemistry & Engineering **2016**, *4*, 6186–6192

"Controllable Synthesis of Gold Nanoparticles in Aqueous Solution by Microwave Assisted Flow Chemistry"
Bayazit, M. K.; Yue, J.; Cao, E.; Gavriilidis, A.; Tang, J.
ACS Sustainable Chemistry & Engineering **2016**, *4*, 6435–6442

"Continuous Formation of a Seed Layer and Vertical ZnO Nanowire Arrays Enabled by Tailored Reaction Kinetics in a Microreactor"
Choi, C.-H.; Levin, J. B.; Chang, C.-h.
CrystEngComm **2016**, *18*, 8645–8652

"A Spray-Drying Continuous-Flow Method for Simultaneous Synthesis and Shaping of Microspherical High Nuclearity MOF Beads"
Garzón-Tovar, L.; Cano-Sarabia, M.; Carné-Sánchez, A.; Carbonell, C.; Imaz, I.; Maspoch, D.
Reaction Chemistry & Engineering **2016**, *1*, 533–539

Reviews

"Aerobic Oxidations in Flow: Opportunities for the Fine Chemicals and Pharmaceuticals Industries"
Gavriilidis, A.; Constantinou, A.; Hellgardt, K.; et al.
Reaction Chemistry & Engineering **2016**, *1*, 595–612

"Engineering Chemistry: Integrating Batch and Flow Reactions on a Single, Automated Reactor Platform"
Fitzpatrick, D; Ley, S.
Reaction Chemistry & Engineering **2016**, *1*, 629–635