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Novel Process Windows as Gate Opener Green Chemistry

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Abstract

Micro Process Technology has given strong push to continuous chemical manufacture via facilitating heat and mass transfer (transport intensification). The next big step is to develop tailored process chemistry in flow under highly intensified conditions: Flow Chemistry. This has been coined Novel Process Windows [1-3] and has two research pillars, – the exploration of unusual and typically harsh process conditions (chemical intensification) and, in a more holistic picture, a completely new and often simpler process design (process-design intensification).

The 1,3-Huisgen cycloaddition (Click Chemistry), the Claisen and Johnson-Claisen rearrangements, the Heck C-C coupling, the Hantzsch dihydropyridine synthesis, the H2O2-based direct adipic acid synthesis, and more were processed harshly and chemically intensified [3-7]. Emphasis will be given on homogeneous catalysis applications in flow [4]. Click Chemistries can be integrated in multi-step (tandem, cascade, …) synthesis which is done at the example of Rufinamide synthesis (Top200 5-ring drug) [3,4]. All reactions stand for generic approaches to boost reactivity via high-T, high-p, high-c (solvent-free; alternative solvent) concepts and more. The use of alternative energy for reaction activation will be exemplified at the Claisen rearrangement. A photo-route opens new synthetic possibilities which are further diversified by direct flow-to-flow coupling to the reaction forming the Claisen precursor [5]. Yet, regioisomers are formed via biradicalic intermediates. Then, the question to answer is – experimentally and theoretically (QM calculations) – if novel process windows can control the reaction course and in this way steer the product formation, i.e. the isomeric ratio. Recently, biotechnology and flow chemistry merged into enzymatic microreactors (alpha amino alcohols from Threonine Aldolase, transesterifications from Lipase) [6]. Main issue here is to achieve productivity, sufficient at least for pharma level. Starting from such new reaction designs, new process designs in flow are developed, such as the large-scale industrial direct adipic acid [7] and hydroformylation processes [4]; with major consequences on CAPEX/OPEX costs [6,8,9] sustainability [10], and energy consumption (heat integration, pinch analysis) [11].

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