**TOPIC: Machine-Assisted Organic Synthesis**

1. **Iterative synthesis**
   1. Iterative synthesis

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| Iterative synthesis is the stepwise synthesis of molecules consisting of repeated building blocks by using the repeated succession of similar reaction sequences (from Latin: *iterare, iterum -* again). |
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| [Vögtle *Top. Curr. Chem.* **1998**, *197*, 1](http://download.springer.com/static/pdf/154/bok%3A978-3-540-69779-4.pdf?auth66=1415544959_b2b0a43eb448844b119d81a995beaf10&ext=.pdf) |
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Iterative strategy plays an importance role in biosynthesis of complex molecules. For example, the assembly of acyl units by sequential Claisen condensation to form fatty acids. Polypeptides are built from the repetitive amidation of amino acids in ribosomes. In the same fashion, oligonucleotides are derived from nucleotide monomers; oligosaccharides from sugar units. Also, most of small-molecule natural products are the results of iterative synthesis from smaller building blocks: polyketides from malonyl-CoA or methylmalonyl-CoA, non-ribosomal peptides from aminoacids, polyterpens from isoprenes, …

Using nature as a model, chemists have studied and established iterative and automated synthesis not only for biopolymers (polypeptides, oligonucleotides, oligosaccharides), but also organic polymers, natural products, and *small molecules.*

* 1. Strategies
     1. Basic steps

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| Generally, there are two steps for iterative synthesis:  (1) coupling  (2) activation/deprotection  Iterative synthesis sequence:  In controlled iterative reactions, bi- and multifunctional building blocks are employed that contain **only one** reactive functional group (“ON”), while all other groups are unreactive (“OFF”) thereby suppressing uncontrolled polymerization. After the selective **coupling** of the reactive group, another, previously unreactive functional group is **activated/deprotected** (“ON”) and the coupling sequence repeated, thus allowing the efficient formation of defined oligomers from readily available building blocks. This enables even non-experts to synthesize complex molecules in a short time, and promotes the rapid investigation and application of these compounds in chemistry and biology. |
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| [Glorius *ACIE* **2009,** *48*, 5240](http://onlinelibrary.wiley.com/doi/10.1002/anie.200901680/pdf) |

* + 1. Ideal iterative synthesis

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| (1) Building blocks and their derivatives should be readily available and inexpensive  (2) All steps in iterative steps are high yielding, are tolerant of many different functional groups, and do not require nor produce toxic compounds  (3) Easy handling and facile separation or purification  (4) Iterative coupling sequences are reliable and predictable  (5) The sequence is suitable for solid phase synthesis and automation |
| [Glorius *ACIE* **2009,** *48*, 5240](http://onlinelibrary.wiley.com/doi/10.1002/anie.200901680/pdf) |

* + 1. Solid phase peptide synthesis (SPPS)

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| The development of SPPS by Merrifield revolutionized the field of peptide chemistry. Today, SPPS is acknowledged as the method of choice for creating peptides in a synthetic manner. In the most common strategy the C-terminus of an amino acid (with protected side chain and N-terminus) is immobilized on a solid support (e.g. cross-linked polystyrene resin). Then the amino protecting group is removed and coupled to a second fully protected amino acid with an activated carboxyl group. This process of deprotection and coupling is repeated until the desired sequence is achieved. Final side chain deprotection and cleavage from the resin yield the free peptide. |
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| [Merrifield *JACS* **1963**, *85*, 2149](http://pubs.acs.org/doi/pdf/10.1021/ja00897a025) |
| For SPPS it is important to choose the correct protecting group strategy. During the several deprotection steps of the N-termini the protecting groups of the amino acid side chains have to stay untouched (orthogonality of protecting groups) and the peptide must not be cleaved from the resin. Today, there are two major strategies: The Fmoc and the Boc-strategy. |
| |  |  |  | | --- | --- | --- | |  |  | | | Cleavage | Boc cleaved under acidic conditions (TFA in CH2Cl2). Cbz group of side chains and resin (e.g. Merrifield resin) stable to TFA, normally cleaved by treatment with very strong acids. | Fmoc cleaved under basic conditions (Piperidine in DMF). Boc deprotection and cleavage from resin (e.g. Wang resin) with TFA in CH2Cl2. | | Advantages | Boc-protected amino acids normally cheaper. Repetitive treatment with TFA prevents peptide aggregation (increased solubility) | Fmoc strategy allows for milder deprotection scheme and is considered truly orthogonal. No special equipment needed. | | Disadvantages | In Boc strategy the final deprotection of side chains and cleavage from resin require gaseous HF (very corrosive and dangerous, special equipment!). | Peptide aggregation can be a problem, especially when peptide sequence consists of several hydrophobic amino acid residues. | |
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| Since its introduction 40 years ago SPPS was substantially optimized. New linkers, side chain protecting groups and activating groups for the carboxylic acid have improved the overall method and SPPS can be considered as a fully automated process (peptide synthesizer). |
| Reviews: [Merrifield *Protein Science* **1996**, *5*, 1947](http://onlinelibrary.wiley.com/doi/10.1002/pro.5560050925/pdf)  [Seebach *J. Pept. Res.* **2005**, *65*, 229](https://www1.ethz.ch/loc/people/emerit/Seebach/775-J.Pept.Res_2005.pdf) |

1. **Polynucleotide (RNA/DNA) synthesis**
   1. Biosynthesis

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| - Polynucleotides are biopolymers composed of 13 or more nucleotides as monomers. DNA and RNA are examples of polynucleotides. Polynucleotides are biosynthesized via replication or transcription of DNA.  - A single nucleotide consists of a phosphorylated deoxyribose (for RNA: ribose) unit that is attached at the 1’-position to a nucleobase. For DNA/RNA synthesis all the building blocks (with different protecting groups) are commercially available. |
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[Todd *J. Chem. Soc.* **1955**, 2632](http://pubs.rsc.org/en/content/articlepdf/1955/jr/jr9550002632?page=search)

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| Caruthers and Köster introduced an approach that is nowadays considered as the state of the art for oligonucleotide synthesis. The advantage of their method is that they start from more reactive phosphor(III) triesters (nucleoside phoshporamidite building blocks, commercially available). The method can be performed on solid phase (control pore glass, CPG) and is fully automated. |
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| [Caruthers JACS 1981, 103, 3185](http://pubs.acs.org/doi/pdf/10.1021/ja00401a041)  [Köster *Nucleic Acids Res.* **1984**, *12*, 4539](http://nar.oxfordjournals.org/content/12/11/4539.full.pdf+html) |

1. **Carbohydrate synthesis**
   1. Biosynthesis

(1) Carbohydrates (saccharides) encompass four subgroups: **monosaccharides**, **disaccharides**, **oligosaccharide** and **polysaccharides**. They plays important roles in living things (energy storage, components of coenzymes, genetic molecules, immune system…)

(2) Monosaccharides are the smallest carbohydrates, which cannot be further metabolized. Disaccharides are formed via the condensation of two monosaccharides. Oligo- and polysaccharides are composed of longer chains of monosaccharides linked by glycosidic bonds*.*

(3) In contrast to the biosynthesis of polypeptides, which depends on genetic codes, the structures of oligo-, polysaccharides are determined by the action of enzymes.





**Solid-phase oligosaccharide synthesis (SPOS)**

The advantages of SPOS:

(1) only one chromatography step is needed in most cases at the end of the reaction

(2) unwanted reagents and side products can be removed simply by washing and filtering, and so a large amount of the glycosyl donor or acceptor can be applied to ensure a high production yield

Key issues in SPOS:

(1) selection of the polymer support, (2) linker design, (3) choice of the glycosyl donor or acceptor, (4) selection of a protecting group pattern for protection, (5) monitoring of the reaction course, and (6) product cleavage from the resin and product characterization.

[Seeberger *Chem. Soc. Rev.* **2008**, *37*, 19](http://pubs.rsc.org/en/content/articlepdf/2008/cs/b511197h?page=search)

Schmidt *Frontiers in Modern Carbohydrate Chemistry.* **March 13, 2007**, 209 (Chapter 3)

[Wong *ACIE* **2011**, *50*, 11872](http://onlinelibrary.wiley.com/doi/10.1002/anie.201100125/pdf)

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| **Automated SPOS**  An ideal automated SPOS:  (1) A set of monosaccharide building blocks with suitable protective groups should be utilized  (2) Coupling and deprotection conditions should be rapid, selective and quantitative  (3) Real-time monitoring of coupling efficiency is highly desirable  (4) Efficient cleavage of the linker at the end of the synthesis should render the oligosaccharide either as the free reducing terminus or in a form that allows for the creation of glycoconjugates  (5) Ready removal of all protective groups  (6) Purification and quality control of the final product  Synthetic strategy: **acceptor-bound approach**  Automated oligosaccharide synthesis relies on the attachment of the nucleophile to the solid support, the acceptor-bound approach.  Application:  The automated oligosaccharide synthesis has been used to synthesize several important carbohydrates, which include globo-H hexasaccharide, the core pentasaccharide of *N*-linked glycans, -mannoside, oligomannosides, oligorhamnosides, the phytoalexin elicitor family of glucans, and the parasitic vaccine candidates against malaria and leishmaniasis. |
| [Seeberger *Chem. Soc. Rev.* **2008**, *37*, 19](http://pubs.rsc.org/en/content/articlepdf/2008/cs/b511197h?page=search)  [Wong *ACIE* **2011**, *50*, 11872](http://onlinelibrary.wiley.com/doi/10.1002/anie.201100125/pdf) |
| The general applicability of automated SPOS is nicely demonstrated by the synthesis of a nonasaccharide of Ley-Lex (KH-1) antigen derivative. |
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| [Seeberger *ACIE* **2004**, *43*, 602](http://onlinelibrary.wiley.com/doi/10.1002/anie.200352539/pdf) |
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| Seeberger and co-workers first introduced an automated oligosaccharide synthesizer, which was modified from an original peptide synthesizer and optimized for automated SPOS. |
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| [Seeberger *Science* **2001**, *291*, 1523](http://diyhpl.us/~bryan/papers2/bio/Automated%20solid-phase%20synthesis%20of%20oligosaccharides%20-%202001.pdf) |
| Future challenges:  (1) Building blocks are used in **excess**  (2) Complete control over stereochemistry at each new anomeric carbon cannot be exercised  (3) Not every glycosidic linkage can presently be installed by automated synthesis  (4) **Thioglycoside building blocks cannot be used**  (5) Linker cleavage is slow  (6) Linker functionalization and protecting group removal require several steps  (7) The low temperature (below -20 oC) converted peptide synthesizer is not commercially available |
| [Seeberger *Carbohydr. Res.* **2008**, *343*, 1889](http://ac.els-cdn.com/S0008621508002917/1-s2.0-S0008621508002917-main.pdf?_tid=1e7f2ece-681c-11e4-a87c-00000aab0f02&acdnat=1415543250_88cee9b0d76cb61401b6898f0ccc290d) |

1. **Iterative cross-coupling reaction**
   1. Iterative cross-coupling reactions

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| A cross-coupling reaction is a reaction in which two fragments are coupled with the aid of catalyst. An ideal cross-coupling reaction for iterative synthesis should occur under mild conditions, be tolerant of a variety of functional groups, and allow for the assembly of a collection of building blocks pre-constructed with all required functional groups and correct stereochemical relationship. |
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| Amongst the cross-coupling reactions, metal-catalyzed cross-coupling reactions are the most popular ones. (Nobel Prize in Chemistry 2010)  Common metal-catalyzed cross-coupling reactions: |

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| An iterative cross coupling strategy has been used for a long time in the synthesis of organic polymers (oligothiophene, oligo(-phenylene ethynylenes, …). In those cases, the required building blocks (monomers) are easily activated or protected, allowing selective coupling (ex: halogenation of thiophene). Recently, the synthesis of more challenging oligoarenes with benzene or its derivatives as monomers, have been developed. |

* 1. π-Conjugated oligomers - Oligothiophene synthesis

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| - π-Conjugated oligomers (including oligoenes, oligoenynes, oligoenediynes, oligoynes, oligostyrenes, oligothiophene,…) are widely used in material science for electronic and photonic applications. The most elegant and efficient way to prepare them is through an iterative strategy.  - In this lecture note, we will focus on the synthesis of oligothiophenes, which received the most careful studies and applications in industry (transitors, diodes, electroluminescent devices). Amongst the methods for thiophene preparation, iterative cross-coupling reactions (Kumada, Suzuki-Miyara, Stille) have been widely used. |
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| [Diederich *ACIE* **1999**, *38*, 1350](http://onlinelibrary.wiley.com/doi/10.1002/%28SICI%291521-3773%2819990517%2938:10%3C1350::AID-ANIE1350%3E3.0.CO;2-6/pdf) |

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| Iterative oxidative cross-coupling. This method is restricted to symmetrical oligothiophenes and thiophene-based materials with no base-sensitive functional groups. |
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| [Lukevics *Heterocycles* **2003**, *60*, 663](http://www.heterocycles.jp/newlibrary/downloads/PDF/12162/60/3) |

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| Iterative Suzuki-Miyaura cross-coupling (solution / solid phase) |
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| [Suss-Fink et al. *Heteroatom Chemistry* **2004**, *15*, 121](http://onlinelibrary.wiley.com/doi/10.1002/hc.10224/pdf)  [Bauerle *Chem. Comm.* **2002**, 1015](http://pubs.rsc.org/en/content/articlepdf/2002/cc/b108846g?page=search) |

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| “Double coupling” oligothiophene synthesis.  Spivey et al. developed a new strategy for the synthesis of regioregular oligothiophene that allows for double-coupling after each iteration to minimize deletion sequences. |
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| [Spivey *OL* **2002**, *4*, 1899](http://pubs.acs.org/doi/abs/10.1021/ol025879x) |

* 1. Oligoarene synthesis

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| - Oligoarenes are oligomers of aromatic rings such as benzene and/or its derivatives through single bonds. They are widely used as backbones in molecular electronics, self-assembling molecules, bioactive compounds, catalysts, … |
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| The most reliable and efficient method to synthesize multifunctionalized oligoarenes is the repetitive addition of each building block - monomer - via cross-coupling reactions: iterative cross-coupling (esp. Suzuki-Miyaura cross-coupling reaction). In this type of iterative cross-coupling approach, building blocks having all the required functional groups, with required stereochemistry are connected using stereospecific, chemospecific cross-coupling reactions. |
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| [Manabe *Chem. Comm.* **2008**, 3829](http://pubs.rsc.org/en/content/articlepdf/2008/cc/b807779g?page=search) |

1. **Flow chemistry**

In term of equipment, anyone could start with an inexpensive HPLC or syringe pump connected to a reaction coil/cartridge made of chemically inert materials to carry out organic synthesis using flow chemistry.

The cartoon below illustrate the basic concept of flow chemistry:



The reagents are pumped through and being mixed up in the T-pieces or in-line mixer pior to the reactors coil. The length, inner diameter, and temperature of the reactor coil could be accurately determined to provide correct heat/mass transfer, which leads to high reproducibility for the reaction optimization. Depending on the application, the materials used for the reaction coil could be glass, PTFE, copper, or palladium alloys…etc. From the exhaust of the reaction stream, the reaction mixture could be further reacted, quenched, or purified by passing it through cartridges containing solid‑supported reagents. All of the flow lines could be monitored in real time by UV detectors, in-line flow IR, or mass spectrometry techniques.

[Jamison *Angew. Chem. Int. Ed.* **2015**, *54*, 983](http://onlinelibrary.wiley.com/doi/10.1002/anie.201409093/abstract)

[Ley *ACIE* **2015**, *127*, 10260](http://onlinelibrary.wiley.com/doi/10.1002/ange.201501618/abstract)

The advantages of flow chemistry:

(1) Increased process safety, harzardous substances are in the sealed system

(2) Reproducibility, all the parameters can be accurately controlled by software or manual methods

(3) Facilitate 24/7 working regimes, the chemical reaction can be monitored via internet remotely

(4) Integrated synthesis, work-up and analysis

(5) Easy scale-up, due to maintaining excellent mixing and heat transfer.

(6) Rreaction conditions not possible in batch

(7) Faster Reactions, flow reactors are easily pressurized, allowing reactions to be heated above their

normal boiling point

Some producer of flow chemistry systems:

[TalesNano](http://www.thalesnano.com)

[Vapourtec](https://www.vapourtec.com)

[Uniqsis](http://www.uniqsis.com)

[Syrris](http://syrris.com/applications/flow-chemistry)

1. **Synthesis of small molecules**

Flow chemistry has been successfully optimized for the iterative synthesis of peptides, oligonucleotides and oligosaccharides. However, when it comes to small molecules, the synthetic strategy and purification strongly depend on each particular structure, hence limiting the possibility of developing a common methodology to carry out flow synthesis.

To implement a method for the iterative synthesis of small molecules, several criteria should be fulfilled:

(1) Need for robust chemistry

(2) Effective protection of undesired reactive sites

(3) Straightforward in-line purification

Recently, as a milestone in the field, Burke and co-workers reported a remarkable flow synthesis of a wide series of natural product-like scaffolds, via Suzuki or Csp3 couplings using a boronic-acid MIDA-masking and deprotection strategy (D-C-P stands for Deprotection-Coupling-Purificaiton).

Firstly, a MIDA-protected boronic acid is deprotected using aqueous base, and then coupled with an ambivalent unit having a halide and another MIDA-protected boronic acid. Their success is largely relying on MIDA scaffold itself, since it allowed for a catch-and-release purification strategy in silica. By eluting the crude material with 1.5% MeOH in CH2Cl2, MIDA boronates remained stuck to the column and all excess reagents and byproducts are washed out. Then, the product is released by eluting with THF, and subjected to successive deprotection-coupling-purification steps until the final target material is obtained.



Many intricate structures can be prepared by employing the above strategy; one of them are shown below.



[Burke *Science* **2015**, *347*, 1221](http://www.sciencemag.org/content/347/6227/1221)

On the other hand, Ley and co-workers adapted the azide-alkyne click reaction for a flow-based synthesis of triazoles. The corresponding alkyne and azide partners are mixed together and syringed first through an immobilized cooper iodide cartridge to perform the transformation, and then through a solid‑supported thiourea to scavenge any leached copper. Since excess azide is required to drive the reaction to completion, the output is also flown through a phosphine-containing resin to trap the unreacted azide reagent via iminophosphorane formation.



The methodology shows several improvements when compared to the standard batch-mode synthesis. Firstly, it allows for the in-line preparation of both starting materials, thus avoiding potentially toxic and hazardous reagents. Moreover, by means of the flow process, reactants are exposed to a higher apparent catalyst concentration, which means it is possible to use a reduced loading of copper iodide. Finally, Glaser homocoupling and related side reactions can be more easily avoided in flow.

[Ley *OBC* **2007**, *5*, 1559](http://pubs.rsc.org/en/content/articlelanding/2007/ob/b702995k)

Here’s another example of using flow chemistry to handle hazardous chemicals, the same group developed an in-line generation of destabilized diazo compounds by flow oxidation of hydrazones, thus facilitating the use of these highly explosive materials for organic synthesis. Their protocol consists of column packed with activated MnO2 to generate a transient diazo compound that is quenched in flow with a variety of carboxylic acids to yield the corresponding ester products. A wide range of esters could be made in flow by using this protocol, where the most electro-poor hydrazones giving the best yields (due to a better stabilization of the corresponding diazo intermediates).



Furthermore, the protocol could also be applied to the Barluenga coupling of diazo compounds with boronic acids. This transformation typically requires high temperatures to take place, as the generation of the diazo compound is usually a bottleneck of the transformation. With the above flow conditions, diazo compound is efficiently generated, by just mixing with a boronic acid at rt, the corresponding coupled products were afforded in moderate to excellent yields.



Moreover, by means of flow techniques, the authors could prove the formation of a transient secondary boronic acid by oxidizing it in-line with H2O2, affording secondary alcohol as major product.



[Ley *Chem. Sci.* **2015**, *6*, 1120](http://pubs.rsc.org/en/Content/ArticleLanding/2015/SC/C4SC03072A)

1. **Synthesis of medicinal compounds**

Flow chemistry could be successfully applied to the synthesis of many active pharmaceutical ingredients (APIs) as well. Ley and co-workers have developed protocols for the flow synthesis of a variety of commercial drugs, showing its advantages when compared to batch methods.

The flow sequence for the synthesis of Imatinib, a tyrosine kinase inhibitor developed by Novartis AG, is shown below.

(1) Acyl chloride is firstly activated by trapped onto a solid-supported DMAP, then aniline is flown through to form the corresponding amide.

(2) Carboxylic acid from hydrolyzed acyl chloride is scavenged, followed by solvent switch to DMF, then nucleophilic substitution of the benzylic chloride with *N*-methylpiperazine takes place in flow.

(3) After scavenging the excess piperazine with a solid-supported isocyanate cartridge, the product is caught into a polymer-supported sulfonic acid to eliminate any unreacted material, and released by eluting with DBU and a 1:1 mixture of dioxane and *t-*BuOH.

(4) The product from the previous step is coupled with pyrimidin-2-amine via Buchwald-Hartwig protocol using XantPhos and palladium catalyst (used to minimize degradation to Pd black in-line). The reaction mixture is chromatographed in flow to afford the target material in 32% overall yield and more than 95% purity.



[Ley *Chem. Commun.* **2010**, *46*, 2450](http://pubs.rsc.org/en/content/articlelanding/2010/cc/c001550d)

Here is another example about the flow synthesis of medicinal compound, the *δ*-opioid receptor agonist (a medicine developed by AstraZeneca).

(1) Ester having is transamidated with Et2NH and deprotonated at the diarylmethyl position by using isopropylmagnesium chloride in conjunction with LiCl to avoid salt precipitation (The deprotonation can be monitored by the red coloration of the diarylmethyl anion).

(2) Then, the reaction mixture is mixed with *N*-Boc-4-oxopiperidine to afford the alcohol intermediate, whichis purified by chromatography by SiO2 cartridge (the excess Et2NH is quenched with sulfonic acid resin;and ketone quenched with hydrazine resin).

(3) Alcohol intermediate is then dehydrated by mixing with a stream of Burgess reagent at 60 °C. Excess dehydrating reagent was removed by flowing through a cartridge with a mixture of amine and sulfonic acid resins.

(4) Finally, N-Boc is deprotected by flowing through a sulfonic acid resin at 60 °C, where the deprotected secondary amine is therefore caught on the same cartridge. Subsequent release by eluting with NH3 in MeOH provides the final compound in 35% yield and high purity. The whole process can be monitored by in‑line IR spectroscopy to render the process more effective.



[Ley *Chem. Eur. J.* **2010**, *16*, 12342](http://onlinelibrary.wiley.com/doi/10.1002/chem.201002147/abstract)

Baxendaledescribed a general flow protocol for the preparation of a series of casein kinases, which was reported by Sanofi-Aventis in 2010. As shown below, the group developed a 2-loop injection system able to keep a continuous flow of organolithium reagents and at the same time keep them below ambient temperatures.

(1) By means of their device, ketone could be prepared by reacting ethyl 4-fluorobenzoate with 4-methylpyridine, using LiHMDS at 0 °C to deprotonate the latter.

(2) Ketone then undergoes *α*-halogenation using a solid-supported pyridinium tribromide.

(3) The next step involves a condensation with aminopyridazine to afford the imidazopyridazine bicyclic core, by heating in DMF at 120 °C.

(4) Finally, aromatic substitution of the bicyclic core with *N*-methylpiperazine using superheated ethanol affords the final product in high purity.



[Baxendale *OBC* **2010**, *8*, 1798](http://pubs.rsc.org/en/content/articlelanding/2010/ob/b925327k)

Finally, the synthesis of quinolone as a potent 5HT1B receptor inhibitor, developed by AstraZeneca, is also described.

(1) Aryl fluoride and *N*-methyl1,4-diazepine are reacted together via aromatic substitution in superheated ethanol, and then the output stream is flown through an amine-containing resin to quench the highly toxic HF byproduct.

(2) The Nitro group is hydrogenated in-line and passed by a solid-supported thiourea to trap any leached palladium catalyst from the cartridge from H-Cube.

(3) At this point, solvent is exchanged to toluene, and the flow is mixed and reacted via 1,4-addition with a stream of dimethyl acetylenedicarboxylate. The excess dicarboxylate is scavenged with a solid-supported primary amine, excess water from the hydrogenation step is removed with a K2CO3-packed column, and then heated to 245 °C to effect the cyclo-condensation reaction leading to the quinolone core.

(4) Then, the remaining methyl carboxylate group is hydrolyzed and trapped by flowing through a trimethylammonium hydroxide resin. The trapped carboxylate is both released and activated by eluting with a stream containing TBTU and HOBt in DMF, and subsequently coupled with aniline to form the amide bond.

(5) The flow is passed through a sulfonic acid resin to catch the product, which is released afterwards by eluting with NH3 in MeOH. The desired target material was obtained in 18% overall yield and excellent purity after recrystallization from methanol.



[Baxendale *Synlett* **2010**, *4*, 505](https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0029-1219358)

1. **Synthesis of natural products**

Natural products typically consist of a broad variety of structurally complicated molecules, whose synthesis usually implies many sequence steps. In this regards, flow chemistry processes provide a powerful tool to save time and money and render the overall process more environmental friendly. Many flow synthetic routes have been developed for a variety of natural products. Some of the most outstanding strategies are illustrated below.

The synthesis of the neolignan grossamide was implemented via amide formation and enzymatic oxidation in flow.

(1) First of all, starting material containg carboxylic acid are injected into a cartridge packed with polymer‑supported HOBt. The stream is recirculated several times, so that the activated carboxylic acid gets attached onto the polymer.

(2) After washing out the unreacted materials, the appropriate amine is flowed through the cartridge containing the active ester from the previous step to afford the corresponding amide product.

(3) The next step involving enzymatic oxidative dimerization of amide in the presence of H2O2-urea complex, by flowing through a silica gel-supported horseradish peroxidase to afford grossamide. The whole process is self-controlled by UV and LC-MS.



[Tranmer *Synlett* **2006**, *3*, 427](https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2006-926244)

The synthesis of oxomaritidine, a cytotoxic alkaloid from *Amaryllidaceae* plant family, is another example of the power of flow chemistry to efficiently achieve complex structures. In this example, most of the reagents can be immobilized on a solid support through which the substrates are flown.

(1) The synthesis starts with the formation of azide and aldehyde, which are pumped sequentially into a solid-supported phosphine reagent to afford the corresponding imine via tandem Staudinger and aza‑Wittig reaction.

(2) Imine is subsequently hydrogenated and trifluoroacetylated in flow. At this point, trifluoroacetic acid byproduct and the remaining trifluoroacetic anhydride are scavenged by using a silica-supported diamine.

(3) Amide is oxidized to the corresponding monoquinone by using immobilized PIFA (bis(trifluoroacetoxy)iodobenzene, a hypervalent iodine), and then passed by a trimethylammonium hydroxide-containing cartridge to deprotect and cyclize the amide via 1,4-addition, affording oxomaritidine in a 40% overall yield and in just several hours of continuous flow synthesis.



[Tranmer *Chem. Commun.* **2006**, 2566](http://pubs.rsc.org/en/content/articlehtml/2006/cc/b600382f)

Histrionicotoxins are a family of highly neurotoxic alkaloids isolated from poison-arrow frogs. In the following scheme, an integrated flow and batch protocol, for producing isoxazolidine intermediate for the synthesis of perhydrohistrionicotoxin (pHTX), is described.

(1) Starring material alkyne is lithiated in flow with a stream of LDA and then mixed with lactone. The generated lithium alkoxide is subsequentially quenched by flowing it through a dicarboxylic acid resin.

(2) Then, triple bond hydrogenation and mesylation in flow affords the intermediate, which could be used by batch conditions.

(3) In the batch condition, the isoxazolidine ring is obtained via nitrone formation and subsequent one-pot [3+2] cyclization in neat styrene using a microwave-assisted batch process (exo/endo 85:15).

(4) Finally, acetal group is deprotected by acid hydrolysis to afford bicyclic aldehyde.



[Ryan *Chem. Eur. J.* **2010**, *16*, 11471](http://onlinelibrary.wiley.com/doi/10.1002/chem.201001435/abstract)

The last example is the flow synthesis of an oxazole intermediate of the preparation of *O*-methylsiphonazole.

(1) The sequence starts with the coupling of carboxylic acid and threonine tert-butyl ester mediated by CDI (carbonyldiimidazole). Then, the corresponding oxazoline is formed by DAST (diethylaminosulfur trifluoride)-mediated deoxygenation, and purified in-line by flowing through sulfonic acid resin (to scavenge all amine byproducts), tertiary amine resin (to remove residual acids) and CaCO3 and silica (to quench and trap DAST and HF).

(2) Subsequently, the desired oxazole structure is prepared by oxidizing the oxazoline ring with BrCCl3 and DBU.

(3) Finally, tert-butyl ester group is cleaved by heating using a sulfonic acid resin.



[Nikbin *Synlett* **2011**, *10*, 1375](https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0030-1260573)