Flow Chemistry

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Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients**

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Abstract: *While continuous chemical processes have attracted both academic and industrial interest, virtually all active pharmaceutical ingredients (APIs) are still produced by using multiple distinct batch processes. To date, methods for the divergent multistep continuous production of customizable small molecules are not available. A chemical assembly system was developed, in which flow-reaction modules are linked together in an interchangeable fashion to give access to a wide breadth of chemical space. Control at three different levels—choice of starting material, reagent, or order of reaction modules—enables the synthesis of five APIs that represent three different structural classes (γ-amino acids, γ-lactams, β-amino acids), including the blockbuster drugs Lyrica and Gabapentin, in good overall yields (49–75 %).*

Chemical synthesis traditionally takes a linear approach, developing both chemistries and technologies to achieve novel and more efficient routes towards specific targets.[1–4] In recent years, flow chemistry has emerged as a useful tool,[5–7] allowing access to advanced structures and active pharmaceutical ingredients (APIs) in both stepwise and multistep processes.[8–11] Conceptually, however, the field has not advanced, since multistep synthetic processes remain target oriented. Chemical assembly systems represent a novel paradigm in non-iterative[12] chemical synthesis, in which modular synthesis platforms are developed[13–15] that are capable of being applied in an interchangeable fashion, thereby allowing access to a wide breadth of chemical space. This allows a multiply divergent approach to multistep chemical synthesis, in which different targets, within one or several structural classes, can be quickly accessed through manipulation of the system, for example, by changing the order of the reaction modules or the reagents/compounds introduced. This conceptual advance represents the first step towards the chemical and pharmaceutical industries enjoying similar benefits to the automobile industry and other industries involving mass production, where assembly line manufacturing has made products significantly more available to the world-wide community.

Establishing a synthetic system requires careful development at the level of the individual transformations. While each of three consecutive reactions can be optimized individually in a rather straightforward manner, the general reaction conditions such as solvent, pH, and byproduct tolerance often differ from one step to another. When approaching a synthesis on a systems level, conditions must be chosen for each transformation that are compatible with all subsequent reaction units. For example, the choice of solvent for the first reaction module dictates the solvent for all subsequent reactions.

An assembly system provides control on three different levels and can be used to synthesize series of molecules with similar structural cores (Figure 1). The first level of control relates to the starting materials, which when exchanged, yield different molecules that share the same core functionalities. Control over the order of reaction modules provides access to different families of compounds.Using a certain set of starting materials and a given sequence of reaction modules, different structural classes of molecules can be synthesized by exercising control over the reagents within specific modules. The chemical space that can be accessed through an assembly system based on different modules is determined by these three levels of control (Figure 1). Herein, we describe the first non-iterative[12] chemical assembly system in which control at all three levels was exercised to prepare three classes of useful molecules: β-amino acids, γ-amino acids, and γ-lactams. Five APIs, including those present in the blockbuster drugs Pregabalin (Lyrica) and Gabapentin, were prepared in good yields with the presented system.

In taking on the conceptual challenge, flow reaction modules should be developed that cover commonly used transformations and can serve as proofs-of-principle for coupling to additional modules. A series of fundamental considerations were kept in mind while developing both the modules and the system as a whole. In addition to solvent compatibility throughout, the flow rate has to be maintained throughout the system. Byproduct formation should be minimized, although water-soluble byproducts that can be removed by in-line workup are acceptable. When multiple reagents are utilized for a particular transformation, they should be compatible to allow for mixing prior to addition to the system. Finally, the early reaction modules in the system should ideally be robust and flexible enough to accommodate a range of conditions. This flexibility is particularly important

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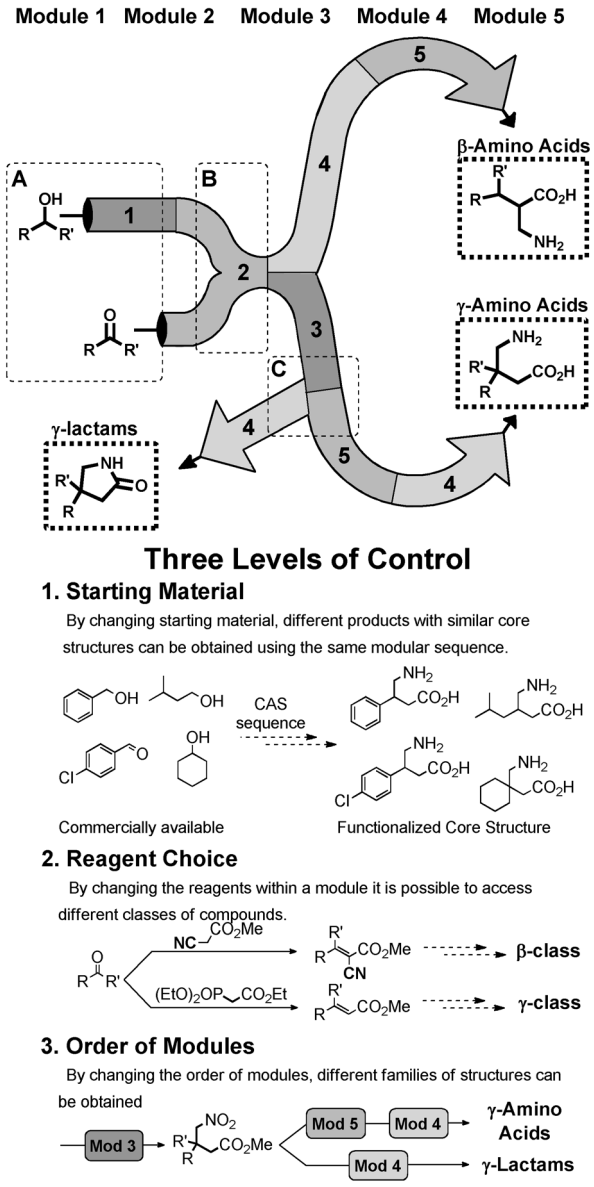

Figure 1. Chemical assembly systems operate with three levels of control—choice of pendent functionalities, choice of reagents, and choice of modular order—to selectively obtain different compounds with identical core functionalities, as well as compounds from different structural families and classes.

when adjustments to conditions are mandated by the sensitivities of downstream modules.

Mindful of the perspective to create a chemical assembly system for accessing several classes of pharmaceutically important molecules representing different molecular scaffolds, five interchangeable modules representing heavily utilized transformations[16] were developed for oxidation (module 1), olefination (module 2), Michael addition (module 3), hydrogenation (module 4), and saponification (module 5) reactions (Figure 2). Each reaction module, including in-line workup when necessary, was optimized individually within the context of the entire system, starting from benzyl alcohol (**1**), before being linked together to generate the full assembly system (see below).

Module 1 allows the biphasic oxidation of primary and secondary alcohols with TEMPO (0.03 equiv) and bleach (1.5 M $NaClO_4$ in water, 2.5 equiv).[17] Near quantitative conversion was obtained in dichloromethane and toluene at 0 °C after a 25 min residence time. The aqueous layer was efficiently removed in a continuous fashion by using a modified Jensen separator.[18]

The olefination module (module 2) relies on reagent control to access different structural classes of molecules, specifically either β- or γ-amino acid derivatives. Knoevenagel condensation of an aldehyde and methyl cyanoacetate in the presence of piperidine yields the corresponding α-nitrile ester as a first step towards β-amino acids. Aldehyde **2** was mixed with methyl cyanoacetate (0.5 M in toluene, 1.0 equiv) through a T-mixer at 50 °C. After a 60 min residence time, (*E*)-methyl 2-cyano-3-phenylacrylate (**4**) was obtained in 88 % yield (Figure 2). An in-line acidic workup allows the organic phase to be directly transfered to the next module without purification. When employing a phosphonate carbanion instead of a coupling reagent, a Horner–Wadsworth–Emmons homologation yields α,β-unsaturated esters as precursors of γ-amino acids.[19] Here, at least 10 % methanol was necessary to prevent phosphate salt precipitation. Methyl cinnamate (**3**) was obtained in 84 % yield with a 9:1 mixture of toluene/methanol in 10 min at ambient temperature, while the phosphate salts and methanol were completely removed during the in-line acidic workup.

The Michael addition of nitromethane to α,β-unsaturated esters to yield γ-nitro esters was developed by using tetrabutylammonium fluoride (TBAF) as a base (module 3). Methyl cinnamate (**3**) was mixed with a TBAF solution in nitromethane (1.3 equiv) at 50 °C and the desired product (**7**) was obtained in 97 % yield after a 60 min residence time (Figure 2). Toluene as the solvent facilitated the acidic in-line workup to remove excess TBAF, as well as nitromethane and related byproducts.

Module 4 is a metal-catalyzed hydrogenation with the commercially available H-Cube. When preparing β-amino acids, the unsaturated α-nitrile ester **4** enters the hydrogenation device, where it is mixed with hydrogen at 90 bar before entering a Raney-Ni-packed cartridge heated at 100 °C.[20] Complete reduction of both olefin and nitrile is achieved in two minutes and provides β-amino methyl ester **5** in 92 % yield (Figure 2). In the γ-path, module 4 is utilized to access different structural families of molecules. While both the Raney Ni and Pd/C cartridges can be used for the complete reduction of the nitro group with excellent yields, the product obtained is dependent on the pendant functionality. When nitroester **7** is transformed by using module 4, the corresponding γ-lactam **8** is obtained in 92 %. However, when **7** is hydrolyzed prior to module 4, the acyclic γ-amino acid **10** is obtained in 98 % yield (Figure 3).

Module 5 accomplishes a biphasic hydrolysis with aqueous lithium hydroxide. Following hydrolysis, the lithium carboxylate product remains in the basic aqueous layer, while all byproducts/unreacted material from the previous steps remain in the organic phase. Module 5 terminates the β-pathway and yields β-amino acids upon removal of the solvent and washing of the resultant solid with hot isopropanol. For

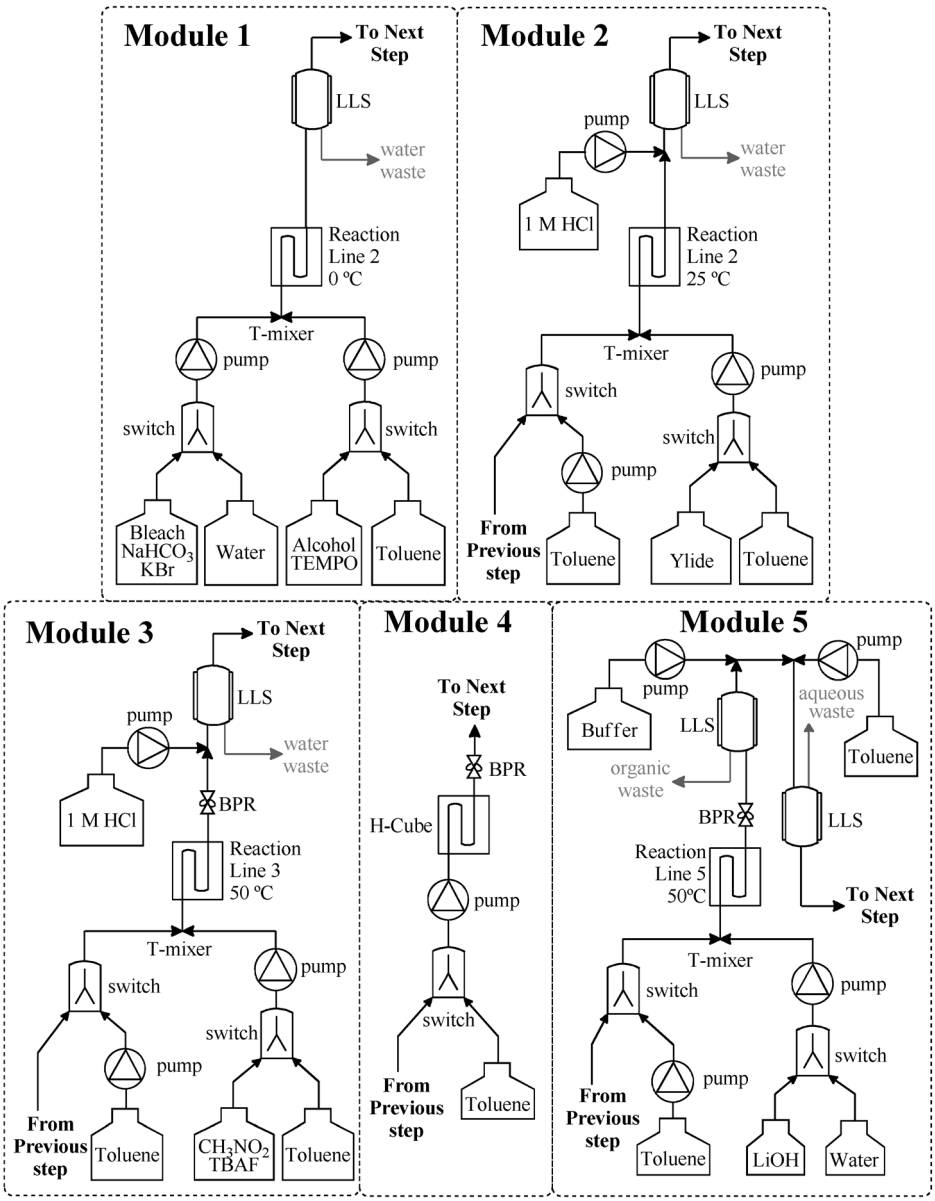

Figure 2. The individual modules making up the current chemical assembly system. Module 1: bleach 2.5 equiv, TEMPO 0.05 equiv, $NaHCO_3$ 0.3 equiv, KBr 0.2 equiv, 0 °C. Module 2: R = H Triethyl phosphonoacetate 1.1 equiv, *t*BuOK 1.1 equiv; R = CN Methyl cyanoacetate 1 equiv, piperidine 0.1 equiv, 50 °C. Module 3: CH_3NO_2 11 equiv, TBAF 1.3 equiv, 50 °C. Module 4: R = H 10% Pd/C, 60 °C, 60 bar; R = CN Raney Ni 100 °C, 90 bar. Module 5: R = H LiOH 3 equiv, 50 °C; R = CN LiOH 1.2 equiv, 50 °C. LLS = Liquid-Liquid Separator, BPR = Back Pressure Regulator.

the γ-pathway, upon separation of the basic aqueous layer (containing the product) from the organic phase, the solution is neutralized with phosphate buffer (1 M, pH 6) and the product is extracted into the organic phase with toluene. This solution can be used without modification in the subsequent module or dried to give near quantitative yield of γ-nitro carboxylic acid **9** (Figure 2).

With each individual module optimized, the five modules were combined in three different orders to create continuous-flow processes for the synthesis of β-amino acids, γ-amino acids, and γ-lactams (Figure 3). The biphasic oxidation (module 1) works equally well in a variety of organic solvents. Module 2 is also relatively solvent tolerant, whereas module 3 is not tolerant of methanol. Therefore, the methanol needed in module 2 has to be removed prior to module 3. Acidic in-line workup following module 2 was the most efficient when toluene was used as the solvent and thus became the choice for the entire synthetic system.

First, benzyl and isoamyl alcohols were processed via the β-pathway, utilizing modules 1, 2, 4, and 5 with aqueous in-line work-ups following modules 2 and 5. The total residence time through the four linked modules is 122 min and the corresponding β-amino acids were obtained as 50 mM aqueous solutions. No chromatography was utilized either during or following the synthesis, with in-line work-ups allowing the corresponding lithium salts to be easily purified through washing with hot isopropanol to yield 68% (9.1 g day^{-1}, 49.2 mmol day^{-1}), and 75% (8.9 g day^{-1}, 54.0 mmol day^{-1}) of the desired compounds (Figure 3).

The order of the modules determines whether γ-amino acids or γ-lactams are produced. Appropriate starting materials were selected to obtain key pharmaceutical ingredients, and in-line work-ups enabled production without the need for purification between modules. The γ-lactam Rolipram (**18**), an anti-inflammatory API,[21] was prepared in 58% overall yield from **17**[22] when modules 1, 2, 3, and 4 were combined, which allowed 11.8 g (42.8 mmol) Rolipram to be produced per day (Figure 3).

γ-Amino acids are produced when module 5 is inserted before module 4 to furnish the sequence 1→2→3→5→4. Four APIs were produced with this setup, simply by changing the commercially available starting material and without making any additional adjustments to the reaction system.[23] Each API was purified by simple crystallization after exiting the system (Figure 3). Pregabalin (**14**) is the active pharmaceutical substance in the blockbuster drug Lyrica, which is used both as an anticonvulsant[24] and to treat general anxiety disorder,[25] and was obtained in 68% yield[26] (8.0 g day^{-1}, 50.3 mmol day^{-1}). Gabapentin (**12**) was obtained in 49% yield

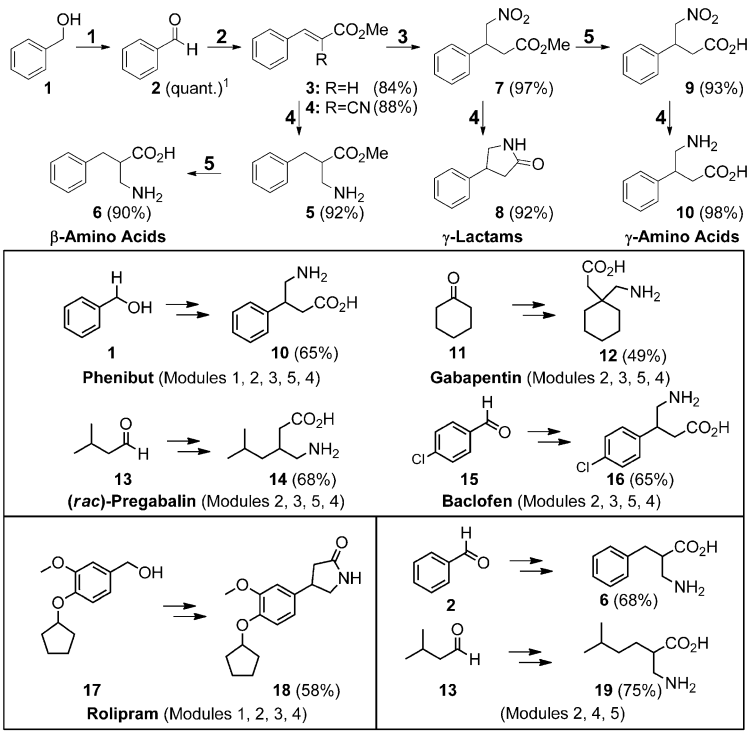

Figure 3. Top: Yields for individual modules determined upon isolation. Bottom: Yields for full processes without intermediate purification over the 3–5 steps. [a] Calculated based on ^{1}H NMR internal standard (1,2,4,5 tetramethylbenzene) upon partial removal of the solvent.

(6.2 g day^{-1}, 36.2 mmol day^{-1}) and is used to treat epilepsy.[27,28] Baclofen (**16**), used to treat spasticity,[29] was obtained in 65% yield (10.3 g day^{-1}, 48.1 mmol day^{-1}), and Phenibut (**10**), utilized for its anxiolytic effects,[30] was obtained in 65% yield (8.6 g day^{-1}, 48.1 mmol day^{-1}).

In summary, we have developed the first non-iterative chemical assembly system. The system is based on five individual reaction modules with tolerant and robust reactions capable of being interchangeably linked together. By following different paths within the system, a wide range of customizable small molecules can be accessed in a continuous fashion without the need for intermediary purification. Three classes of molecules, β-amino acids, γ-amino acids, and γ-lactams, were produced. Five active pharmaceutical ingredients present in generic or patented medications (Rolipram, Lyrica, Phenibut, Baclofen, and Gabapentin) were produced in good overall yields (49–75%). This first proof-of-principle for the chemical assembly system approach demonstrates how the production of small molecule drugs may be customized in the future and how generally applicable flow modules will help to construct a wide variety of molecular frameworks.

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