Automated Synthesis

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Iterative Syntheses—The Gateway to New Automation Protocols

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More than five decades ago Bruce Merrifield introduced the idea of automation to organic chemistry through the use of solid supports as an enabling technology that facilitates synthesis as well as work-up.[1] The age of combinatorial chemistry popularized solid-phase-assisted synthesis, but also paved the way for new enabling technologies and technical devices such as liquid-handling systems, radiofrequency tags, as well as microwave and inductive heating (Scheme 1).[2] Nonconventional solvents such as ionic liquids, perfluorinated solvents, as well as supercritical fluidic conditions are other options to simplify organic synthesis and work-up procedures. Multistep continuous synthesis and microreactor design coupled with online monitoring are the latest trends in automation.[3]

In addition to enabling technologies and technical devices, the automation of multistep processes is closely linked with certain methods and chemical concepts such as multicatalysis, multicomponent and domino reactions, and iterative processes (Scheme 1).[4] Modularity and iteration are also common structural as well as processing concepts found in nature, as manifested in polypeptides, oligonucleotides, and oligosaccharides as well as in secondary metabolites such as terpenes and polyketides.[4] Iterative multistep processes are known in organic synthesis because it provides complexity in a modular fashion from simple precursors. Peptide and nucleic acid syntheses are the most prominent examples, but in other synthetic arenas iteration is still in its infancy. The research groups of Aggarwal[5] and Burke[6] both disclosed impressive new iterative processes in which C–C coupling reactions play a key role.

Aggarwal's iterative approach is based on the homologation of boronic esters **5** in the reaction with lithiated benzoates **6**. After a Matteson-type rearrangement, boronate **7** is formed, which is used in the next iterative process. This iterative homologation can provide complex methyl-branched alkyl chains in high yield after nine iterative loops with minimal purification (Scheme 2).

Burke's concept utilizes bifunctional MIDA boronates (MIDA = *N*-methyliminodiacetic acid) **1**, and importantly the automation of this chemistry was demonstrated for the first time using liquid-handling systems as technical devices.[7] Boronates **1** lack the necessary reactivity under common transition-metal cross-coupling conditions. However, their hidden reactivity can be unleashed under basic hydrolytic conditions, which forms the more reactive boronic acids **3**. The cross-coupling reaction with bifunctional MIDA boronates yields new extended adducts $n+1$ **2**, again containing the MIDA boronate moiety, and the iterative loop is closed after the new MIDA boronate is submitted to the initial hydrolytic conditions (Scheme 1).[6]

To automate this iterative process, a technically simple set up based on liquid-handling concepts was developed that relates to solid-phase peptide synthesis. It comprises deprotection (**D**), coupling (**C**), and purification (**P**) units (Figure 1). Three syringe pumps deliver solvents, solutions, and reaction mixtures. The deprotection unit **D** is responsible for activation of the MIDA boronate terminus of the starting building block as well as the products obtained after each iterative cycle. The coupling module **C** is a cartridge that contains all the reagents necessary for the cross-coupling reactions such as the extender building block that contains halide and MIDA boronate termini, the catalysts, and other agents if required. The purification module **D** consists of a precipitation cartridge for the separation of salts from the reaction mixture and a silica gel plug for purification through a "catch and release" mechanism. The "primary" syringe pump plays a key role in that it controls operations in all three modules **D**, **C**, and **P** by injecting and withdrawing reaction mixtures or washing solvents in and out of the cartridges at different stages of the process. A second pump, called the "wet" pump is only responsible for hydrolysis of the MIDA boronates, and a third pump, called the "auxiliary" pump, is involved in the purification of the cross-coupling product **2**.

In the following, the whole process, the role of the pumps, and the function of the modules are described in detail. First, hydrolytic cleavage of the MIDA boronate **1** (lacking the halide terminus) is achieved by the action of two pumps. The "primary" pump adds THF and the "wet" pump adds water to the deprotection vessel, which is charged with the starting MIDA boronate and NaOH. The hydrolysis is terminated by the addition of phosphate buffer (pH 6) or a saturated solution of ammonium chloride using the "wet" pump. The "primary" pump adds diethyl ether, and mixing is achieved by pulses of nitrogen gas bubbles. The aqueous phase now

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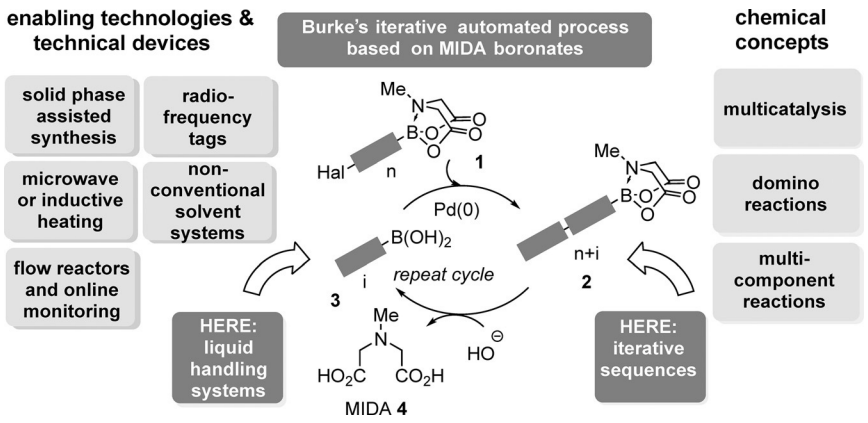
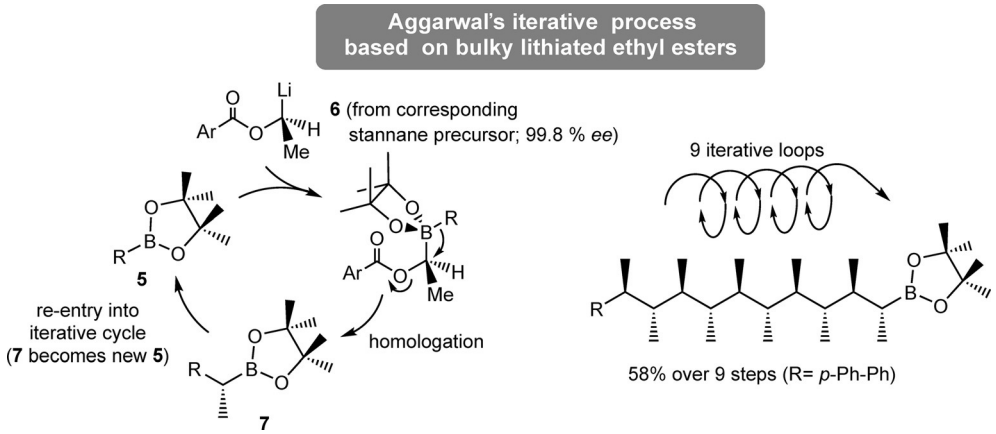


Scheme 1. Selected chemical concepts, technologies, as well as tools useful for automated synthesis; Burke's iterative process.



Scheme 2. Aggarwal's iterative process (Ar = 2,4,6-triisopropylphenyl).

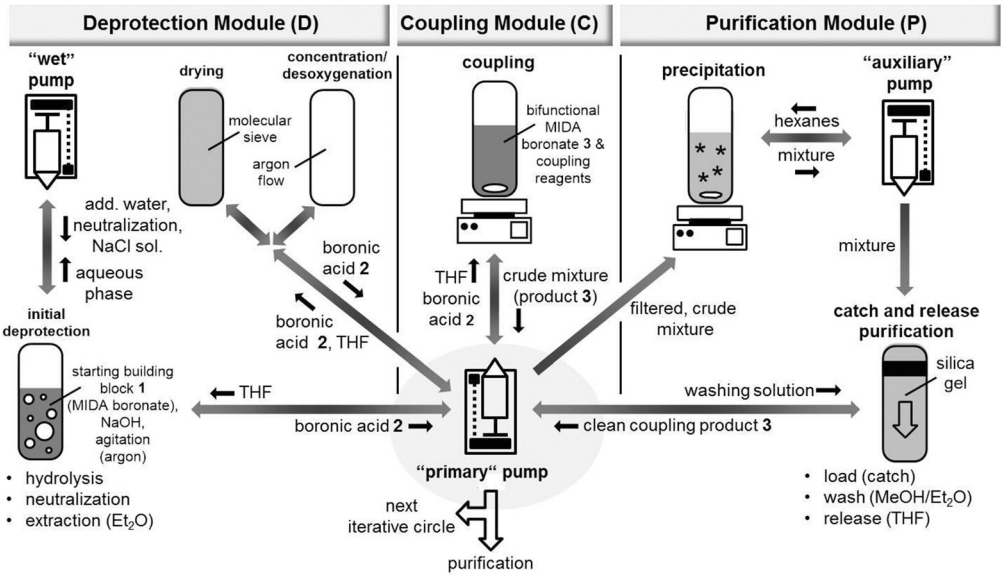
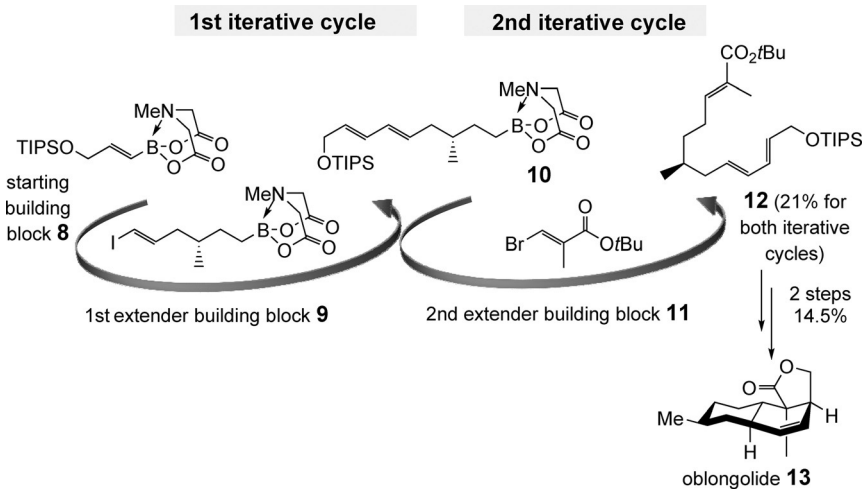


Figure 1. The automated process of one iterative cycle.

contains MIDA **4** and is removed for disposal by the "wet" pump. The organic layer contains the boronic acid **3**, which is washed by the addition of brine. The "wet" pump removes the aqueous phase for disposal. The "primary" pump now comes into play again. It repeatedly injects and withdraws the wet organic phase into a drying cartridge. Finally, the dry solution is passed to the concentration/deoxygenation cartridge, where the drying cartridge is washed with THF using the "primary"



Scheme 3. Selected examples of automated iterative syntheses (**8** resembles **1** without a halide terminus; **9** resembles **1**; **10** resembles **2**; **11** resembles **1** without an MIDA boronate terminus). TIPS = triisopropylsilyl.

pump. The washings are added to the reaction mixture stored in the concentration/deoxygenation cartridge. By passing a stream of argon through this cartridge, the volume of the combined organic phases is reduced to such a degree that the coupling module **C** can accommodate the solution.

Next, the "primary" pump picks up the boronic acid **3** from the concentration/deoxygenation cartridge and slowly injects the solution into the coupling module **C**, a cartridge charged with the bifunctional MIDA boronate **1** in THF, the metal catalyst, and additives such as the ligand and a base. After completion, the "primary" pump removes the reaction mixture from the coupling module **C** through a filter, thereby leaving solids in the reaction chamber. For purification of coupling product **2**, hexane is added to a precipitation cartridge using the "auxiliary" pump. A portion of the crude reaction mixture containing coupling product **2** is added to the precipitation chamber. Then, the mixture is withdrawn through a plug of silica gel and removed by the "auxiliary" pump for trapping. The process is repeated until the coupling vessel **C** is emptied. Finally, **C** is washed with THF and the washing is also transferred to the purification module **P**. Then, the "primary" pump adds diethyl ether containing 1.5% methanol to the precipitation chamber and the "auxiliary" pump withdraws the solution through the silica. MIDA boronate **2** is now trapped and the silica is washed with additional diethyl ether before **2** is dissolved and released from the silica by the addition of THF. After this "catch and release" procedure, the "primary" pump withdraws **2** through the silica plug to transfer the purified product to the deprotection module **D**, which again is charged with sodium hydroxide, thereby closing the iterative cycle.

A representative example reported in Ref. [7] is the preparation of oblongolide **13**, whose preparation started from MIDA boronate **8** (Scheme 3). Coupling with bifunctional MIDA boronate **9** provided **10** at the end of the first cycle, while vinyl bromide **11** was utilized in the second cycle for extension, and the resulting linear precursor **12** was elaborated to oblongolide **13** after deprotection through an intramolecular Diels–Alder reaction and lactonization.

The take-home message from the days of combinatorial chemistry remains valid, namely the quest for automated procedures in organic synthesis. Technically, one line of research is multistep flow chemistry, while another approach relies on liquid-handling systems successfully proven in the iterative syntheses of peptides and oligonucleic acids. The Burke group has introduced a very challenging topic (C–C coupling) to automated iterative syntheses. Clearly, this system is still in its infancy, for example, as online monitoring and feedback for the computer-assisted processing is still missing and some "manual handwork" is required. Nevertheless, it is a promising starting point and automation as well the search for iterative processes, which includes Aggarwal's method[7] too, are back on top of the agenda in organic synthesis.

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