

Preface

Combinatorial chemistry marks the biggest revolution in synthetic organic chemistry within the past 150 years, a break with classical strategies. Around 1985, in the early beginning, the new approach was oversold, as so many drug discovery technologies are in their very beginning. The production of huge libraries of mixtures of poorly defined analogs was in the foreground. Much hope (and hype) existed at this time. It was anticipated that a vast number of new chemical compounds would more or less automatically produce an unprecedented number of new drug candidates; these early expectations failed completely, due to the lack of druglikeness of most libraries, in properties and in structures. Compounds were too lipophilic and, due to over-decoration, too large in their molecular weight.

After this failure, combinatorial chemistry matured in the mid-90's and underwent significant changes. It was the merit of Chris Lipinski at Pfizer, with his rule of five, to make the chemists of his company and the whole scientific community aware of the physicochemical properties that are typical for successful drug candidates. Nowadays, library production is not any longer driven by chemical accessibility (this, of course, still being a necessity) but by design, be it for pharma, agro, or materials. Instead of undefined mixtures, single purified compounds are produced by automated parallel synthesis, followed by solid phase extraction (SPE), high performance liquid chromatography (HPLC) or parallel column chromatography purification. The most important application of combinatorial chemistry resides in drug discovery but it is no exaggeration to say that the need for effectiveness in parallel synthesis stimulated the development of new techniques for classical synthesis. Just one example is the use of solid-phase reagents and scavengers in multi-step natural product syntheses.

Only a few years ago, in 2000, Willi Bannwarth and Eduard Felder edited the book "Combinatorial Chemistry – A Practical Approach" (Volume 9 of "Methods and Principles in Medicinal Chemistry"), which immediately became a standard text in this area. However, a few years are almost an eternity in this discipline: new techniques, new reagents, and new, exemplary applications demanded a new edition. Because of the significant updates and additions, this edition is published as a new Volume in our series.

The updated and, in part, completely new chapters of this book cover all important aspects of combinatorial chemistry, with special emphasis on solid-phase

organic synthesis, linkers and their cleavage, C–C bond formation, syntheses of heterocycles, polymer-supported reagents, encoding strategies, purification in high-speed solution phase synthesis, automation and devices, and computer-assisted library design. An Appendix provides information on cheminformatics and Web resources for combinatorial chemistry.

We are very grateful to the Editors Willi Bannwarth and Berthold Hinzen, and all chapters authors, for having undertaken this task. Last, but not least we thank the publisher Wiley-VCH, especially Renate Dötzer and Dr. Frank Weinreich, for the ongoing support of our series “Methods and Principles in Medicinal Chemistry”.

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