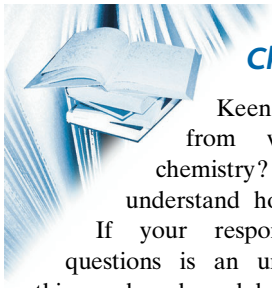
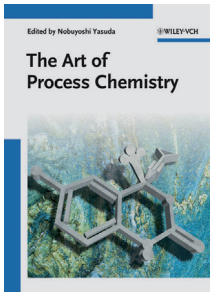


The Art of Process Chemistry

Keen on some excitement from within the world of chemistry? Are you curious to understand how "they" are doing it? If your response to these straight questions is an unambiguous "yes", then this newly released book really is a must for you. The Process Research Group of Merck Research Laboratories in Rahway, New Jersey, has for many years been regarded by most of its peers in the industry as the world-leading institution engaged in the design and development of chemical processes for the large-scale manufacture of pharmaceutically active ingredients, and it probably still is. How else could you explain the fact that a whole book of 282 pages is entirely devoted to case histories that emanate from work carried out in the Merck facilities (from the 1990s and onwards), now compiled in the form of nine chapters (each consisting of between 20 and 40 pages) for the benefit of all of us "outsiders"? In fact, the title of the book should leave nobody in any doubt—this exemplarily short title shows this to be a piece of work that makes clear its fascination with the subject of process chemistry. The esteem goes so far as to put the discipline on a level where it is seen to be on a par with art in general—a viewpoint developed by the editor in some detail in the preface. Some people outside the core area of process chemistry might not entirely agree, but this excellent book will definitely contribute to raising the profile of what must be regarded as a fascinating topic, which is largely pursued in an industrial environment outside academic institutions. The fact that the work of designing and developing safe, robust, and viable processes has been carried out with the ultimate aim of transferring them to commercial production has traditionally led to a reluctance to present the achievements to an external audience. However, much of that belongs to the past, and over the recent two or three decades a tremendous change has taken place that encourages wider dissemination, albeit this openness to communicate is not embraced by everyone. In this development, Merck has played a seminal role by taking a leading position in the transformation of process research from a low-profile subject ("it's just about the scaling up of laboratory procedures, so what's the big deal?") to an area that has gained the reputation of operating at the highest scientific level, second to none. We owe Merck a lot for what they have contributed and shared with all of us, and therefore they should be entitled to our admiration and esteem. Aspects of all this, based on what has become a long tradition within Merck, are treated thoroughly in the book. If you want to gain a deeper insight into the Merck world of chemical processes in order to find out what they are doing so well, and how, then you must read this book!

I will now consider the contents in more detail and discuss some particular strengths and weaknesses. Looking at the specific drug projects that are covered, it becomes evident that they span a broad range in terms of molecular diversity, coupled with a wide variation in the associated chemistry-related challenges. Many of the compounds for which large-scale synthetic processes have been developed, as described in the book, have actually ended up in commercially launched medicines, and a few of these are enjoying a worldwide reputation as the basis of breakthrough therapies offering significant benefit to patients. Thus, branded drugs such as the HIV antiviral Efavirenz, finasteride/Proscar for the treatment of prostatic hypertrophy, the anti-migraine agent rizatriptan/Maxalt, and raltegravir/Isentress as the first HIV/AIDS integrase inhibitor are thoroughly documented in the book, and in these examples its value becomes especially clear by virtue of our insight that they "made it all the way". Every project offers some learning, but this is especially pronounced for successful products for two reasons: firstly, the processes developed have been shown to be suitable for commercial production, not just for pilot scale production, and secondly, because of the extremely high rate of project attrition in the pharmaceutical industry, we rarely get to know the intrinsic details that underlie full-scale manufacturing methods. As the book fulfills the role of conveying a deep understanding of the harsh realities in process research and of the different degrees of success in solving problems—often coupled with a high level of smartness, innovation, and creativity—the work is worthy of attracting a large readership, ranging from professionals in the pharmaceutical business to graduate students who hope to find a position in an industrial development department, and to academics with the ambition to gain invaluable information about "what they are doing in industry and what problems they are grappling with".

Nowadays, reporting on the design and development of chemical processes is by no means unique, as shown by recently published books on topics such as asymmetric catalysis and green chemistry. However, what differentiates this work is that it homes in on the endeavors and achievements of just one group, providing a learning experience about how a world-leading team goes about performing its tasks. Each of the chapters follows a generic structure divided into two sections: "Project Development" and "Chemistry Development". In the former



The Art of Process Chemistry
Edited by Nobuyoshi Yasuda. Wiley-VCH, Weinheim 2010. 282 pp., hardcover € 119.00.—ISBN 978-3527324705

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section, the reader will learn about the original synthetic route designed by the medicinal chemistry team, followed by a deeper dive into the details of the process development that has been undertaken, including topics such as the selection of routes to various building blocks or intermediates, and optimization studies, before focusing on the manufacturing process. The second section describes mechanistic details, explaining the observations made and further process development to address weaknesses and bottlenecks of the first-generation manufacturing method. Each chapter ends with a conclusions paragraph and a list of references.

This book is a real treasure-trove, which informs readers about the secrets behind the development of validated methods for the production of small-molecule drugs, applying a process understanding rationale as a key driver and principle to ensure success. Although the general impression is that "Merck will solve every problem", there is the occasional moment when you realize that this is not the case, for example in the statement " … *zinc addition … was so complex that these issues could not be resolved*" (p. 41). But these are really the exceptions, as you will be able to enjoy a wealth of useful information on various synthetic procedures, covering not only the "usual suspects" but also some quite "exotic" transformations, such as the Sugasawa (pp. 10–15), Bodroux (pp. 93–95), and Kursanov–Parne (pp. 144–145) reactions (ever heard of these before?—I hadn't!). As in all multi-authored texts, there are individual variations from chapter to chapter, which can be simply summarized as: some are better than others from a linguistic point of view, but none is really a disaster. Careful reading reveals surprisingly few errors, flaws, typos, etc., so it is not really worthwhile spending time to list them comprehensively, with two exceptions: 1) already on pages 2–3, in the very first step of the first reaction (!), "dimethoxycarbonate" is introduced as a reactant, instead of dimethyl carbonate; 2) compound 81b on page 137 is not an acetal as written, but a ketal.

A word of warning is necessary when the text mentions the cost of the chemicals used (e.g., pp. 3, 22), inasmuch as the projects they are involved in were carried out back in the 1990s. How relevant is this information today, and what significance does it have today, 15 or 20 years later? Another concern is the structural layout of the chapters, where in my view the fine-tuning has gone too far. In Chapter 2, for example, this takes the reader from the overarching separation into two discrete paragraphs (2.1 and 2.2) down to a stunning level of detail—2.1.2.1.1 and 2.1.2.2.2 just as examples—and one might wonder for what purpose? I find it disturbing. The coverage of the literature is very good, and extends up to 2009. However, providing a reliable list of relevant and correct literature references is one of the cornerstones in all publishing, and the format should be consistent and uniform throughout. Therefore, I am amazed that the basic rules are not adhered to in this case, which is even more surprising as all the authors belong to a single entity (Merck). Some of the authors prefer inclusive pagination (e.g., in Chapters 1 and 3), whereas others just document the first page in a paper (Chapters 4, 8, and 9). There is even an example where the two practices are mixed (Chapter 4). Using the correct abbreviations for journals is not always easy, but the use of different formats (e.g., "*Tetrahedron Asym.*" [incorrect] on page 164, refs. [11f,g], and on page 238, ref. [3b], compared with "*Tetrahedron: Asymmetry*" [correct] on page 42, ref. [6d]) in this "in-house" publication is annoying and quite unnecessary. It is pleasing to see that most, if not all, of the original research and results discussed in the book has previously been published in high-profile peer-reviewed journals (an exemplary policy that is strongly recommended as best practice for all companies to follow), which obviously makes it easy for anyone seeking more information to know where to look. However, one must question the inclusion of what appears to be too long a list of sub-references under a single reference number. A somewhat frightful example of this is found on pages 113–114, where reference [3] lists altogether 24 (!) entries, just to emphasize the wide use that has been made of a Merck modification of the protocol for making Weinreb amides. What is the purpose? As a curiosity, the only case that I spotted where an author's name is spelled out in full is that of a close colleague of mine in AstraZeneca, Thomas Elebring (p. 164, ref. [11f]). The illustrations in general and the synthetic and structural schemes in particular are mostly of very high quality, a feature of immense importance in a field such as organic chemistry. My only criticisms here are that there is too much variation in the size of molecules and in the font of the atoms inserted in the schemes, and that space limitations sometimes force the authors to compress the formulas so that they almost coalesce with the text below and above the associated arrows (p. 48, Scheme 2.4; p. 125, Scheme 4.9).

All in all, the united team of Merck authors have to be congratulated for succeeding in the preparation of such a classy book that brings so much of high interest to so many, in such a concerted manner. The clear recommendation is that as many as possible should read this account of successful process chemistry, and I can guarantee you a very joyful and engaging couple of hours when diving into this piece of "art".

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DOI: 10.1002/anie.201103165

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