

Book Reviews*

Analysis of Drug Impurities. R. J. Smith and M. L. Webb, Eds. Blackwell Publishing: Oxford. 2007. 275 + ix pp. £99.50. ISBN 1-4051-3358-6.

This is a unique book; the editors are to be congratulated on persuading their industrial colleagues to write chapters, providing an industrial focus on analytical issues.

The book begins with a view from FDA authors on organic impurities in the drug substance—origin, control and measurement. This is a rather superficial overview of the subject with constant references to ICH guidelines. I feel it would have been helpful to readers who are new to the subject to highlight and quote some of the key sections from these; as it is, there is only 1 quote from Q3A.

The second chapter looks at impurities in drug product and was a much more in-depth study with good examples. This was followed by a chapter on stereochemical impurities. In fact this was almost entirely to do with enantiomers, separation of enantiomers and measurement of enantiomeric purity, which were examined in detail. The subject of diastereoisomers and geometric isomers was not covered.

The most interesting chapter, in my view, was the one by Peter Skett of GSK on “low level measurement of potential toxins”. In this chapter he discusses the classes of genotoxic impurities (alkylating agents, reactive amines, fused tricyclics, substituted purines and pyrimidines, and hydroperoxides) and the analytical challenge of looking at ppb levels. GC, HPLC, TLC and other methods are discussed in detail, as is the validation of trace analytical methods.

A chapter on “Systematic Approach to Impurity Identification” is valuable for the case studies at the end. The following chapter on the “Use of Chromatography and On-Line Structure Elucidation using Spectroscopy” was an excellent detailed review of coupled methods (LC–MS and LC–NMR), with lots of examples to aid the discussion. This was followed by a useful chapter on preparative isolation of impurities including scale up.

The final chapter, while interesting, seemed out of place in this book. “The Impact of Continuous Processing” was probably included to incorporate some discussion of Process Analytical Technology and included brief sections on process analysis using IR, UV, Raman, NIR, NMR, MS and other techniques. With 168 references, this was an informative guide.

In conclusion, this is a useful volume which fills a gap in the literature. However, references in the chapters are only to early 2005, so this multi-author work has been a long time reaching the market. The publishers should have had ample time to spot an awful error—that the spelling of chromatography (not chromatography) is incorrect on the headings of every other page in the chromatography chapter

(25 occasions). Other than this annoying error, I would recommend the book to all process and analytical chemists.

OP7001529

10.1021/op7001529

Fine Chemicals—The Industry and the Business. By Peter Pollak. Wiley Interscience: Hoboken, NJ. 2007. 234 + xiii pp. £55.95. ISBN 978-0-470-05075-0.

The fine chemicals industry, according to the author, is worth \$75 billion production value, some of which is for captive use, leaving an estimated \$45–50 billion worth of potential business for the fine chemical industry. Despite the importance of the industry, there have been hardly any books that have tried to describe what the industry is and how it functions. It is an industry currently going through many changes.

The author spent over 30 years with Lonza in Switzerland and the U.S.A. and provides a unique perspective on the industry from both a technological and a commercial viewpoint. His view is very much a Lonza approach, and others may disagree with his emphasis. Nevertheless it is the first book to delve into the depths of the industry and look at the critical success factors.

It is divided into three parts. In part one, *The Industry*, Peter Pollak looks at the technologies underlying the fine chemicals industry and the range of products it offers and includes chapters such as *What Fine Chemicals Are*, which he defines as complex single pure chemical substances produced in limited quantities (<1000 t/a) in multipurpose plants by multistep batch chemical or biochemical processes. They are sold for >\$10/kg (distinguishing them from commodities), usually for further processing within the chemical, pharmaceutical, agrochemical, and other industries. It includes building blocks, active intermediates, and active ingredients, particularly APIs.

In later chapters he covers the structure of the industry and its products and its technologies. In the *Technologies* chapter, traditional chemical syntheses are covered with mention of new technologies such as microreactors and solid phase synthesis in peptides. The latter part of the chapter focuses on biotechnology, including cell cultures, a theme he comes back to later in the *Outlook* section.

Chapter 5 covers facilities and plants, including design and plant operation. This is very much a Lonza approach that other companies may not operate, particularly in India and China. At the end of the chapter there is an interesting and valuable discussion on capacity utilisation.

A short chapter on *Research and Development* follows. This does not do justice to the importance of R&D, particularly process R&D in producing novel processes and in producing

*Unsigned book reviews are by the Editor.

cost-effective processes for manufacture. Thus the following brief chapter (4 pp) on cost calculations, whilst valuable in examining manufacturing costs, does not emphasise how choice of raw materials, synthetic route, reagents, work-up, etc. can influence a process. The first section concludes with a short chapter on management aspects, including performance metrics and benchmarking, and organisation.

The book's strength is in the section on the business, with chapters on *Market Size and Structure*, the *Business Condition* (including outsourcing), the *Customer Base*, particularly the pharmaceutical and agrochemical industries, and other speciality chemicals such as aroma chemicals. A long and important chapter on *Marketing*, one of the author's strengths, covers business development, target products and services, custom manufacturing, APIs for generics, target markets distribution channels, pricing, IPR supply contracts, promotion, and network and contract development (i.e., the tricks of the trade). In this section of the book the chapters are packed with useful tables and contain information not readily available elsewhere (except perhaps in Pollak's chapter in *Kirk-Othmer on Fine Chemicals* (2004).

The final section in *Outlook* contains only 35 pages but 8 chapters, some of which are only 2 pages long. It covers general trends and growth drivers, globalisation, biotechnology, custom manufacturing in pharma, both ethical and generics, agro fine chemicals, contract research organisations, and a final chapter on *Who is the Fittest for the Future*. Eight short but useful Appendices are followed by an 11 page index.

From a list of subjects covered, it is clear that the author has undertaken a mammoth task to describe a complex industry in under 250 pages. Inevitably some areas have received minimal discussion, one of them being the importance of emerging pharma companies and virtual pharmaceuticals and the different strategies needed in working with them compared to big multinational pharma companies.

The author has made a brave and largely successful attempt to cover such a broad topic in a unique approach and in a style that is readable yet often full of useful numerical data. However, the text is littered with typos—I found one on almost every page—so that I wondered whether the numbers on the tables were always accurate. The text would have benefited not only from better proof reading but also from removing some strange expressions that look as they have become “lost in translation”, for example, “the variation in the voice ‘piping’ is given by, among other things, the piping concept” and “whereas controlling determines the cost of a product or service, marketing sets the price”. It makes one wonder whether anyone at the publishers actually reads the text!

The book could also have more references; each of the three sections has a list of references but these are often general. The author, for example, mentions that Roche's Fuzeon uses initially solid phase synthesis to make the fragments followed by liquid-phase synthesis to stitch them together. But no reference. Similarly, “More recently GlaxoSmithKline patented an efficient fermentation route...”, but this is not referenced. For the scientific reader, these omissions are annoying.

Despite these drawbacks, the book can be recommended to all those working in the fine chemicals industry, whether in management, process R&D, or business development, and to those in other industries, particularly pharmaceuticals, who are involved in processes, manufacturing, and particularly in outsourcing. For newcomers to the fine chemical industry, it should be compulsory reading.

OP7001936

10.1021/op7001936

Methods and Reagents for Green Chemistry—An Introduction. P. Tundo, A. Perosa, F. Zecchini, Eds. Wiley Interscience: New York. 2007. 314 pp. £55.95. ISBN 978-0-471-75400-8.

The Summer School on Green Chemistry, founded in 1998, has an excellent reputation, and a collection of lectures from these summer schools was produced in 2001 and later updated. The present volume has also arisen from the Italian Summer School, and it is essentially a collection of lectures including those from famous names in Green Chemistry.

The book is divided into three sections, beginning with *Green Reagents*. In this section “Multicomponent Reactions of Isocyanides”, “Carbohydrates as Renewable Raw Materials”, “Photochemistry”, and “Dimethyl Carbonate” are discussed. Whilst each chapter is written by an expert in the area, the subject of green reagents would have benefited from an initial overview. The chapter on multicomponent reactions had references only to 2002 and so is considerably out of date, whereas other chapters had references to 2004 and occasionally 2005. There are some statements made in the chapter on dimethyl carbonate that need challenging. Methylation using this reagent requires high temperatures (> 160 °C) and increased pressure, but the statement “such conditions are not prohibitive, however, especially according to industrial practice, where pressures up to 20–30 bar and temperatures up to 250 °C are not a concern” needs some amendment. Whilst such conditions are fine for dedicated continuous processes for bulk chemicals, the fine chemicals industry, which urgently needs a green “methylating agent” has general purpose equipment that cannot operate under these conditions. As a result, dimethylcarbonate will not be widely used in the fine chemicals industry until less harsh conditions or better catalysts are discovered. This should be the focus of future research in this area.

The second section on *Alternative Reaction Conditions* begins with an entertaining chapter from Ken Seddon on “Ionic Liquids”. He reminds researchers that work is not green just because you call it green and publish it in *Green Chemistry* journal; it has to be applied to a total process, not an individual step, and involves commercialisation. With ionic liquids, commercialisation has been slow, but the reasons behind this are not explored in the chapter. Other chapters in this section are on “Supported Liquid-Phase Systems in Transition Metal Catalysis”, “Organic Chemistry in Water”, and “Formation, Mechanisms, and Minimization

of Chlorinated Micropollutants (Dioxins) Formed in Technical Incineration Processes”.

The final section, *Green Catalysis and Biocatalysis*, has 7 chapters beginning with a brief overview from Roger Sheldon. An industrial approach to seamless chemistry for sustainability provides a valuable industrial viewpoint, though from a bulk chemical industry standpoint. A chapter on “Enantioselective Metal Catalysed Oxidation Processes” fails to focus on the greenness of such processes. Other chapters on “Zeolites” and “Acid and Superacid Catalysts” provide a more practical overview of how these materials are and continue to be used in designing cleaner processes in the petrochemicals and bulk chemical industries. A focussed chapter on “Oxidation of Isobutene to Methacrylic Acid” makes excellent reading for process chemists and engineers and shows how difficult it is to bring green oxidation processes to commercial viability.

The final chapter, “Biocatalysis for Industrial Green Chemistry”, is an overview of some attractive transformations, particularly selective hydroxylations, which show promise for the fine chemicals industry of the future. However, the latest references are only to 2002!

Overall, the book, as with any volume that derives from a conference or a summer school, provides snippets of useful information. However, many of the chapters lack depth, and some are now out-of-date. Can the book be recommended? Most of the information provided here is probably available elsewhere in more comprehensive reviews by the same chapter authors, and therefore the book adds little to the current literature on Green Chemistry.

OP700192W

10.1021/op700192w

Boronic Acids. Hall, D. G., Ed. Wiley-VCH: Weinheim. 2005. 549 + xxv pages. EUR159. ISBN 978-3-527-30991-8.

For some reason, this excellent book did not get reviewed as soon as it was published, but we would like to remedy this now. Dennis Hall has produced a remarkable book; a few years ago it would be inconceivable that someone could write nearly 550 pages on boronic acids. But the synthetic utility of these intermediates, which developed after 1979, and the occasional use as medicinal agents has ensured that this volume has lots to interest the process chemist. Scale-up of methods to produce boronic acids and their subsequent reactions are now commonplace in industry, and there have been several examples in OPRD.

The year 1979 was a turning point in boronic acid chemistry with the publication of Miyaura and Suzuki’s famous cross-coupling reaction, which has been embraced by academia and medicinal and process chemists as one of the most versatile chemical reactions in a chemist’s armoury. This volume has chapters by both Suzuki (cross-coupling with aromatics) and Miyaura (metal-catalysed borylation of alkanes and alkenes) to update on latest thoughts on mechanism and scope of reactions.

The multiauthor work begins with an outstanding 99-page overview of “Structure, Properties and Preparation of Boronic Acid Derivatives” including their reactions and applications, by the editor, who also contributes another chapter (with J. W. J. Kennedy) on “Recent Advances on the Preparation of Allyl Boronates and Their Use in Tandem Reactions with Carbonyl Compounds”. The only chapter solely by industrial authors is by D. M. T. Chan (DuPont) and P. Y. S. Lam (BMS) on “Copper-Promoted C-Heteroatom Bond Cross-Coupling Reactions”, useful for diaryl ether synthesis and for making phenols and arylamines. In the latter process, which should be of interest to process chemists, a comparison with Buchwald–Hartwig palladium chemistry is inevitable, and the authors provide at the end of this chapter a useful list of pros and cons of the Chan–Lam copper chemistry versus Buchwald–Hartwig’s. In addition, a 1-page summary of reactions carried out at DuPont and BMS (unfortunately without references) is provided.

Another chapter which process chemists will enjoy is B. T. Cho’s “Oxazaborolidines as Asymmetric Inducers for the Reduction of Ketones and Ketimines”, whereas discovery chemists may prefer the last two chapters devoted to “Boronic-Acid Based Receptors and Sensors for Saccharides” and “Biological and Medicinal Applications of Boronic Acids”.

The other chapters not mentioned earlier are devoted to other uses in synthesis (e.g., the Petasis reaction). The comprehensive index (36 pages) makes it easy to find what you want.

In conclusion, this excellent book deserves to be on the bookshelf of all synthetic chemists, whether in discovery or process chemistry.

OP700204N

10.1021/op700204n

Encyclopedic Dictionary of Named Processes in Chemical Technology, 3rd ed. By Alan E. Comyns. CRC Press/Taylor and Francis: Boca Raton. 2007. £85. ISBN 978-0-8493-9163-7.

Although this dictionary contains over 3000 named processes (450 new to this edition), I had heard of less than 10%. The reason is that most of the processes relate to the bulk chemical industry, rather than the fine chemicals industry. So you will find information on the COREX process rather than Corey’s reactions, COPE modification (Claus Oxidation-base Process Expansion) rather than Cope rearrangement, and a continuous process for soap making (Sharples process) rather than Sharpless oxidation.

Nevertheless, process chemists can learn a lot from some areas, particularly the different ways of removing and detoxifying waste products. I also learned that Wilkinson’s catalyst, $(\text{Ph}_3\text{P})_3\text{RhCl}$, was simultaneously invented by two ICI chemists (R. S. Coffee and B. J. Smith) as well as Wilkinson, which I did not know before. (Wilkinson’s Nobel Prize was for ferrocene, not for the catalyst!)

On the subject of Nobel Laureates, I was surprised that Noyori was not mentioned in the context of asymmetric isomerisation. However, according to the author, this process is correctly called the Takasago process. I also learned that diethyl zinc vapour was once used for preserving books and documents using the DEZ process, developed by Texas Alkyls and the U.S. Library of Congress.

The recent edition is up-to-date with processes such as BASIL and VARICOL included.

So if you wish to know what the acronyms/names BLISS, RIP, SHOP, ARS, ROSE, POX, RAM, SCORE, SMART, VERA, EVA-ADAM, ELSE, SHARON, Pidgeon or Mohawk mean, and if you prefer HARP to Sam Adams, Miller-Kühne to Muller-Thurgau, Merrill-Crowe to Sheryl Crowe, Ryan-Holmes to Sherlock Holmes or SEPA CLAUS to Santa Claus, then this is the book for you. Acronymphomaniacs will love it.

OP700205Y

10.1021/op700205y

Chirality in Drug Research, Volume 33. E. Francotte and W. Lindner, Eds. Wiley-VCH: Weinheim. 2006. 351 + xix pp. EUR139. ISBN 3-527-31076-2.

Process chemists should not be misled by the title of this book, which is volume 33 in the series “Methods and Principles in Medicinal Chemistry”. The multiauthor work is an excellent read for all chemists involved in process R&D. There is a comprehensive chapter on “Stereoselective Synthesis of Drugs—An Industrial Perspective” from H.-J. Federsel of AstraZeneca, which focuses on methods used in process chemistry and manufacture rather than medicinal chemistry. Similarly, the chapter on “Biotransformation Methods for Preparing Chiral Drugs and Drug Intermediates” by M. Müller and M. Wubbolts is also very industry-orientated.

There is an interesting chapter both from a theoretical and practical view, by K. Saigo and K. Sakai (the latter name being unfortunately omitted on the contents page) on “Resolution of Chiral Drugs and Drug Intermediates by Crystallisation”. In contrast to the chapters mentioned previously, the authors concentrate on their own work rather than giving an overview of the whole topic. However, since much of their work is not so well-known in the industrial community—and deserves to be more widely used—this is an opportunity to explore a different approach to resolution, using a more fundamental understanding rather than simply screening resolving agents.

One of the editors (E. Francotte) provides a chapter on “Isolation and Production of Optically Pure Drugs by Enantioselective Chromatography”, which overlaps somewhat with the following chapter, “Selective Chromatography Methods for Drug Analysis”, which focuses very much on stationary phases. The earlier chapter also briefly mentions process, pilot scale and production separations but could have discussed the advantages and disadvantages of SMB approaches for kilogram and tonne manufacture.

Other chapters cover topics such as capillary electrophoresis coupled to MS, chiral molecular tools for determining absolute configuration, and molecular modelling, which are of less interest to the process chemistry community.

Overall this is a useful book for process chemists working with chiral compounds in industry, and the chapters highlighted in this review are recommended reading.

OP700206Q

10.1021/op700206q

Kirk-Othmer Concise Encyclopedia of Chemical Technology (2 Volumes), 5th ed. Wiley-Interscience: West Sussex, U.K. 2007. 2711 + xxv pages. £208. ISBN 978-0-470-04748-4.

The encyclopedia contains an abridged version of every article in the fifth edition of the full 27-volume Kirk-Othmer Encyclopedia of Chemical Technology. However, the abridged versions are often too short to be really useful (e.g., catalysis is covered in five pages, though there are other headings which cover related topics). I have always been a fan of Kirk-Othmer and find it a useful encyclopedia which complements Ullmann. However, the abbreviated version lacks the authority of the “Full Monty”—it could have been made more useful by more extensive referencing.

My advice—save up and buy the full version!

OP700209Z

10.1021/op700209z

Organic Reactions in Water: Principles, Strategies and Applications. U. Marcus Lindström, Ed. Blackwell: London. 2007. 405 + xv pages. £99.50. ISBN 978-1-4051-3890-1.

Most, if not all, of the top researchers in the area of organic reactions in water have contributed chapters to this excellent volume, which is the best and most up-to-date book on this subject. The book begins with a “50-year Perspective on Chemistry in Water” from Ron Breslow, followed by a thoughtful chapter from Jan Engberts on “Structure and Properties of Water”. Thereafter the chapters are more specific, and most are excellent reviews of the individual researcher’s speciality. Thus, there are contributions from the groups of Kobayashi, Li, Rajanbabu, Sheldon, Sinou, Liotta, and Fokin/Sharpless.

An excellent chapter from Nakamura and Matsuda covers “Biocatalysis in Water”, whereas an industry perspective on “Water as a Reaction Solvent” is given by Wiebus and Cornils. This last chapter is more focused toward the bulk chemical industry rather than the fine chemical/pharmaceutical industry.

A minor criticism is the assumption that water as an organic solvent is always environmentally good but there is no discussion on workup and product isolation, where the organic solvents used for workup will contaminate the water

and may make it unsuitable for reuse. Many of the reactions described are not in pure water; they are in aqueous–organic solvents and may not have environmental advantages over reactions on organic solvents alone. It would have been valuable if these issues had been addressed in a concluding chapter, which would have pointed the way forward for both academic and industrial researchers.

In summary, this excellent collection of reviews deserves to be read by all process chemists and should be in all chemistry libraries.

OP700214Z

10.1021/op700214z

Systematic Nomenclature of Organic, Organometallic and Coordination Chemistry. Ursula Bünzli-Trepp, Ed. CRC Press, Taylor and Francis Group: London, 2007. 636 + ix pages. £99. ISBN 978-1-4200-4615-1.

This comprehensive volume is a practical nomenclature manual for those chemists needing to name a compound or derive a formula from a name. It is based on the nomenclature guidelines used by Chemical Abstracts Service (CAS) but also contains most IUPAC-accepted trivial names and IUPAC recommendations.

This is a beautifully produced book which contains lots of examples to assist the reader, with multicoloured drawings of structures. It should be in every reference library.

For those interested in nomenclature, updates to the book are available at www.chemical-nomenclature.ch. The latest CAS guidelines are at www.cas.org/CASFILES/updates.html.

OP700215W

10.1021/op700215w

Catalysts for Fine Chemical Synthesis, Volume 5: Regio- and Stereo-Controlled Oxidations and Reductions. Stanley M. Roberts and John Whittall, Eds. Wiley: West Sussex, U.K. 2007. 312 + xxii pages. £100. ISBN 978-0-470-09022-0.

This series is designed to provide, in one volume, practical procedures for preparation and use of a variety of catalysts. The recipes included are often more extensive than those found in the experimental sections of journals; thus, they are extremely valuable to process chemists.

The first chapter by one of the editors, John Whittall, gives a useful overview on “Industrial Catalysts for Regio- and Stereo-selective Oxidations and Reductions; A Review of Key Technologies and Targets”. This 33-page summary with 83 references (including some patents) covers the literature

to 2006 and provides a process chemist’s view of what is valuable in this important area and where academic discoveries have been taken up by industry. Of course, much of the discussion is to do with asymmetric oxidation and reduction.

The subsequent eight chapters then describe practical procedures under the general titles “Asymmetric Hydrogenation of Alkenes, Enones, Ene-Esters and Ene-Acids”, “Asymmetric Reduction of Ketones; Imine Reduction and Reductive Amination”, “Oxidation of Primary and Secondary Alcohols”, “Hydroxylation, Epoxidation and Related Reactions”, “Oxidation of Ketones to Lactones or Enones”, “Oxidative C-C Coupling”, and “Oxidation of Sulphides and Sulphoxides”. These procedures have been submitted by more than 100 authors, most of them from academic institutions rather than industry. The procedures describe equipment as well as raw materials but in most cases do not comment on the source or quality of the materials, which may be important in catalysis. The products are often analysed by NMR but rarely by HPLC; thus, one is never clear about the absolute purity. Solids are rarely recrystallised, and melting points are not provided. Workups are often via evaporation to dryness followed by chromatography.

As a result, these procedures are interesting to the process chemist but not particularly more useful than the original literature. The over-reliance on optical rotation as a measure of purity is particularly old-fashioned.

Some of the procedures even use carbon tetrachloride and, in one case, benzene is used as eluent for a chromatography. These are unacceptable procedures in a modern-day laboratory. One of the procedures is the preparation of the oxidising agent IBX (p 264), but no safety procedures are provided for handling this material. The process calls for drying the solid, but no temperature is given. Earlier on, however, a procedure which uses IBX (p 189) has a footnote “IBX, like other hypervalent iodine oxidants, can explode on impact or heating”.

Inevitably, most of the pages are concerned with the procedures for the synthesis of ligands which are not commercially available, and to have so many procedures available in one small volume is particularly valuable. Some quality control data would have made these procedures even more valuable, particularly to industrial chemists. It is a pity there are not more industrial submissions.

A 10-page index allows the reader to find where particular ligands, catalysts, and reagents have been used, though not all common abbreviations (e.g., IBX) are included in the listings.

Overall, this is a useful, practical book of procedures, with the limitations discussed earlier.

OP700213V

10.1021/op700213v