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Book Reviews *

Pharmaceutical Substances; Synthesis, Patents and Applications, 3rd ed. (in English). By A. Kleemann, J. Engel, and B. Kutscher. Reichert D. Thieme: Stuttgart. 1999. 2286 pp. $375. ISBN 0-86577-817-5 (CD-ROM ISBN 0 86577-818, #749) ISBN 3-13-558403-8 (CD-ROM ISBN 3-13-115133-1)

The previous edition of Kleemann and Engel (in German) has long been out of print so the authors, all from Asta Medica in Frankfurt, are to be congratulated on putting together a much-expanded third edition of this most valuable compendium. For those younger readers, who may not have come across this work before, it describes, for each drug substance (over 2000) on the market (up to approximately 1998), the synthetic routes used, use, dosage forms, alternative names (including trade names), with references to the patent literature (and occasionally to journal references). In addition, the CAS registry number, the Chemical Abstracts name, the molecular formula, the ATC code number, the EINECS number (where available), the molecular weight, and acute toxicity are given. The patent literature gives the priority dates, patent information on alternative routes, new formulations, crystalline forms, etc. Of great value are the indices of trade names, intermediates, enzymes and microorganisms etc., and substance classes. Perhaps an index of companies would also be useful, although that is probably easy to search for on the CD-ROM version.

The synthetic schemes are presented without any commentary on which is the best route, although it is usually clear from the dates of patents which is the original medicinal chemistry synthesis and which are subsequent process patents. The volume thus provides quick access to the patent literature on synthetic routes to new and existing drugs and includes routes used by generic manufacturers (where patented).

I checked a number of recently introduced compounds (e.g., Viagra) and found the data comprehensive. Whilst the patent literature is comprehensively covered, the academic literature occasionally lacks an up-to-date reference (e.g., on Saquinavir) which could add useful information for the process chemist. Data presented in lectures at process chemistry meetings is not referred to—again, this would be a useful source of information concerning the current manufacturing route. But these are very minor criticisms of an outstandingly useful volume, which should be in **every** industrial library. The book will be useful to synthetic chemists, analytical chemists, pharmacists, business development managers seeking markets for their intermediates, and many others. Order it for your library without delay!

I hope that there will be future editions of this reference text; if so the compilers could reduce the space occupied by the structural formula by abbreviating benzene rings to Ph, $C(CH_3)_3$ to *t*-Bu and particularly cumbersome $(CH_3)_3C-Si(CH_3)_2-$ to TBDMS; I am sure there are many more examples where the important structural elements in the drug substance or intermediate are made difficult to see, owing to the preponderance of benzene rings or CH_3 groups. Other than this, it is hard to see how future editions could improve on the third edition.

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Applications of Hydrogen Peroxide and Derivatives. By C. W. Jones. Royal Society of Chemistry: Cambridge, UK. 1999. 264 pp. £59.50. ISBN 0-85404-536-8.

The second book in a series of monographs on Clean Technology is a useful volume for process chemists. The author, formerly with Solvay Interox at Widnes UK, has spent many years working in the area, and his choice of chapter topics reflects his industrial bias. Academics may be disappointed with this choice, but industrial chemists will welcome the applied chemistry details and the extensive references to the patent literature—in some chapters more than half the references are to patents. Chapter 1 covers the main manufacturing methods for hydrogen peroxide and its derivatives, explaining the advantages and disadvantages of each. It also includes a detailed section on the safe use of hydrogen peroxide which should be compulsory for all chemists—whether in academia or industry—to read. Those involved in safety evaluation of processes would also learn much from this section, particularly regarding decomposition of excess peroxides or peroxygen compounds after reaction has been completed. For example, addition of sulphite to peracids may give rise to explosive diacyl peroxides which are not further reduced, whereas addition of peracid to excess sulphite (particularly at higher temperature) does not and is thus the safest procedure. A very useful chart on p 30 illustrates the options for residual peroxide removal and destruction. Chapter 2 examines activation of H_2O_2 and the basic chemistry of peroxy reagents and is followed by the main chapter on "Application of H_2O_2 for the Synthesis of Fine Chemicals" (98 pages). This is a comprehensive account of where peroxygen compounds have been used or have the potential to be used in industrial processes. The 493 references testify to its breadth of coverage, but of course the details on each topic are necessarily reduced—for example, enantioselective oxidations are covered briefly. The literature coverage is only to 1997 so that up-to-date references to Jacobsen−Katsuki epoxidation and to the Yang method for asymmetric epoxidation using dioxiranes are missing. Nevertheless, the extensive coverage of the patent literature makes up for this deficiency. The remainder of the book is focused towards clean technology issues including heterogeneous activation of H_2O_2, environmental applications

*Unsigned book reviews are by the Editor.

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(mostly related to effluent treatment and remediation), and miscellaneous uses (e.g., in chemical purification). A minor criticism of the environmental chapter is the lack of comparison with other treatment options.

The book is recommended to industrial organic chemists and chemical engineers seeking environmentally friendly synthetic routes, and processes, and for those looking for treatment options for difficult waste streams. The monograph should be in every industrial library.

OP000003W

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Pilot Plants and Scale-Up of Chemical Processes II. Edited by W. Hoyle. Royal Society of Chemistry: UK. 1999. 110 pp. £49.50. ISBN 0-8540-4719-0.

This is the second volume in the series which arises from the proceedings of a conference of the same name held on October 14−15, 1998. The opening chapter, entitled "Speciality Chemical Manufacturing in the UK—has it a future?" describes the BRITEST project—BRITEST stands for batch route innovative technology, evaluation and selection techniques—which has been funded by the UK government with industrial sponsorship from 12 companies and by involvement with three university groups. The aim is to open the way to major savings in time and cost in batch manufacturing by reducing the time processes spend in development and in plant and reducing the cost of new plants and of modifying existing plants. For further details the website, http://www.britest.co.uk, can be consulted, since the chapter only gives brief details concerning how the objectives are to be achieved.

The second chapter on "Chemical Aspects of Scale-up" by J. Atherton of Zeneca (now Avecia) has essentially been published elsewhere (see "Highlights from the Literature" in *Org. Process Res. Devel.* **2000**, *4*, 2−9) but is nevertheless a very readable account of what goes wrong on large scale. The following chapter on "Phase Transfer Catalysis" from M. Halpern (PTC Technology) and R. Grinstein (Henkel) looks at the choice of PTC not only for reaction optimisation but also for ease of separation. The chapter contains much useful data on the distribution of quaternary ammonium salts between organic and aqueous phases. This data will be useful to chemists and engineers who are concerned about effluent management.

The group of K. Roberts (Heriot-Watt, Edinburgh) is working in collaboration with a number of companies to develop an on-line batch process engineering facility for examining the crystallisation of organic speciality chemical products, and this chapter focuses on analytical measurements including UV turbidometry, ATR-FTIR, ultrasonic spectroscopy, and laser-doppler anemometry to examine onset of crystallisation, reactant supersaturation, particle size distribution in solution, and turbulence/particle velocities in the crystalliser. It is expected that such on-line techniques will assist in the improvement in performance of scale-up of crystallisation processes.

The chapter on "Safe Scale-up of Grignard Processes" covers much of the ground already published in *Org. Process Res. Devel.* from D. am Ende at Pfizer. The following chapter, "Process Development and Scale-up of Organolithium Reactions" (T. Rathman and F. Reed, FMC Lithium Division) provides insight into choice of reagent and solvent, safety and handling procedures on scale, decomposition in storage, handling of byproducts (e.g., butane) and process optimisation. Practical examples are given which show how to avoid insoluble anions and how to avoid quench impurities.

Table 1.

	lab 100 mL	plant 2.5 m^3
heat loss	3.68 W/kg/K	0.054 W/kg/K
reaction temp. 80 °C		
reaction time 1 h		
rate of heat loss	210 °C/hr	2.8 °C/hr
rate of heat production	100 °C/hr	100 °C/hr
	needs HEATING	**needs COOLING**

The final chapter, intriguingly entitled "Oft Forgotten Physical Chemical Laws on Fire, Explosion and Chemical Reaction Hazards during Scale-up" by R. L. Rogers and N. Maddison (Inburex) briefly summarises the hazards of scale-up but says little that is new to those who have read Roger's book on *Chemical Reaction Hazards*. It does, however, provide a neat example to illustrate that exothermic processes are often not detected in laboratory equipment because of high heat loss. Thus, a simple batch-fed process with a heat of reaction of 34 kJ/mol (MW $\approx$ 200) for which the reagent has been added over 1 h will need heating in the lab and cooling in the plant (see Table 1).

Overall this slim volume has some useful information of value to the process chemist/engineer but is an expensive book when one considers that some of the material is available elsewhere in more or less the same format.

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Transition Metals for Organic Synthesis. Vols. I, II. Edited by M. Beller and C. Bolm.Wiley-VCH: Weinheim. 1998. 1030 pp. $595.00. ISBN 3-521-29501-1.

Conducting organic synthesis without transition metals is rather like driving on a German autobahn in a 1940s VW Beetle: you would be restricted to the slow lane and constantly overtaken. Even though it is widely known that transition metals can offer tremendous advantages in improvements in yield, chemo-, regio-, and enantioselectivity together with milder reaction conditions, there is still resistance, in some quarters, to their use. This avoidance presumably comes from a combination of ignorance concerning their value together with uncertainty as to which combination of metal/metal salt and ligand to use and fear of handling potentially air-sensitive catalysts. This two-volume set on *Transition Metals for Organic Synthesis* should go a long way in addressing all of these concerns. Indeed, the editors should be congratulated in bringing together the leaders in transition metal mediated organic synthesis who, together, have contributed 60 chapters brimming with a wealth of interesting

and useful chemistry. It is a pity that the high price of this two-volume set will limit individuals acquiring it, as I believe it is an invaluable resource for both academic and industrial chemists.

In general, each chapter gives a brief historical review of the pioneers in the area, the optimum catalysts, recent developments, applications in academia as well as in industry, together with conclusions and potential future developments. Thus, the book serves not only to update practitioners in transition metal catalysis (most references go up to 1996) but also to provide newcomers with an overview of the field.

Standard reactions employing transition metals (e.g., oxidation, reduction) are covered comprehensively. For example chapters on reduction include homogeneous and heterogeneous C═C, C═O, C═N hydrogenation and transfer hydrogenation, hydrosilylation, metal-catalysed hydroboration, and reductions using metal hydrides. Where appropriate, asymmetric versions are also described. Palladium-mediated transformations are also comprehensively covered and include carbonylations, cross-coupling reactions (Suzuki, Stille, Negishi), C−N and C−O couplings, Heck reactions, allylic substitution reactions, allylic oxidations, and the Wacker oxidation. In addition to standard transition metal mediated transformations, the book also covers important, emerging new developments and includes rhenium-mediated epoxidations, and the use of lanthanides and bimetallic catalysts (heterometallic lanthanoids) in organic synthesis. However, in these rapidly moving areas further developments have occurred since 1996, and these chapters in particular already feel rather dated. I was disappointed not to read a chapter on aziridination processes, and although carbometalation of alkenes is covered well, it was disappointing that the important area of carbometalation of alkynes received only one page of coverage.

These minor criticisms should not detract from what is otherwise an outstanding contribution. Anyone willing to take the time to read part or all of this work will undoubtedly come away with new ideas, as I have, and be able to trade the old VW Beetle for a brand new series 7 BMW and race along the autobahn. Go for it!

Varinder Aggarwal

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Handbook of Chiral Chemicals. Edited by D. J. Ager. Marcel Dekker: New York. 1999. 382 pp. $165. ISBN 0-8247-1058-4.

As stated in the preface, the purpose of this work is to highlight the problems with the production of chiral compounds on a commercial scale, and thus the book will be of great interest to the modern process chemist. The chapter authors are mostly process chemists and biochemists from NSC Technologies, U.S.A. with one or two chapters from experts from other companies [for example Burk, (Chiroscience) on asymmetric hydrogenation; Bulliard (PPG-Sipsy) on oxazaborolidines]. Surprisingly, there are no academics involved, although several authors are former university professors. After an introductory chapter on the principles and processes for the synthesis of chiral compounds at scale and a second useful chapter on sourcing (Tucker, Kenley Chemicals), the synthesis of the top selling chiral compounds—pharmaceuticals, agrochemicals, food ingredients—is briefly summarised. The rest of chapters refer to the synthesis of particular compounds or classes of compounds (including phenylalanine, carbohydrates, terpenes, unnatural amino acids, aspartic acid) or to particular technologies or methodologies (substitution reactions, resolutions at large scale, transition metal-catalysed processes, pericyclic reactions, asymmetric reductions, asymmetric oxidations, biotransformations, industrial applications of chiral auxiliaries, and asymmetric catalysis). The final chapter on synthesis of homochiral compounds—small company's role (Wakefield, UFC Pharma, UK) gives a few examples of custom synthesis of small-volume products such as leukotrienes.

The book provides a useful summary, from an industrial point of view and with examples from kg or tonne scale, of the current state of play in chiral chemistry. Scale up is not really discussed as such—the problems of scale up of some processes are hinted at but not covered in depth. The approach is similar to that of an earlier book from the same publisher on a similar topic (*Chirotechnology* by R. Sheldon), and it will inevitably be compared to that volume. There are some omissions: the section on Jacobsen−Katsuki epoxidation is very brief and fails to mention work done at SmithKline Beecham and Merck on kg-scale oxidations, where the use of promoters such as isoquinoline-*N*-oxide or 3-phenylpropylpyridine-*N*-oxide is so crucial to the efficient use of catalyst. In the chapter on resolution, the "Dutch" resolution method is not mentioned, although perhaps this is too recent for the cut-off date for publication (most references are up to 1997 with a few from 1998). In the sections which cover menthol manufacture, the Harmann and Reimer processes using resolutions (chemical and enzymatic), which account for a considerable percentage of world production of menthol, are not referred to.

In summary, the coverage of the literature could be described as selective—critics may call it "patchy" (e.g., asymmetric phase-transfer catalysis is not covered). There are also one or two frustrating sentences such as "a good example...has been reported in the preparation of BMS 181100", but no reference is given to allow follow up of this statement.

One or two glaring errors were noticed. I do not think the chemists at Parke Davis will be pleased to see a section heading entitled "Lilly route to CI-1008" with a reference to the excellent 1997 Parke Davis publication in OPRD.

The volume brings together the essence of a very large amount of academic and industrial chemistry of the 1990s in a single work and provides a useful summary for the industrial process chemist and the specialist in chiral chemical methods. I hope the authors will produce a second edition in 4−5 years time.

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