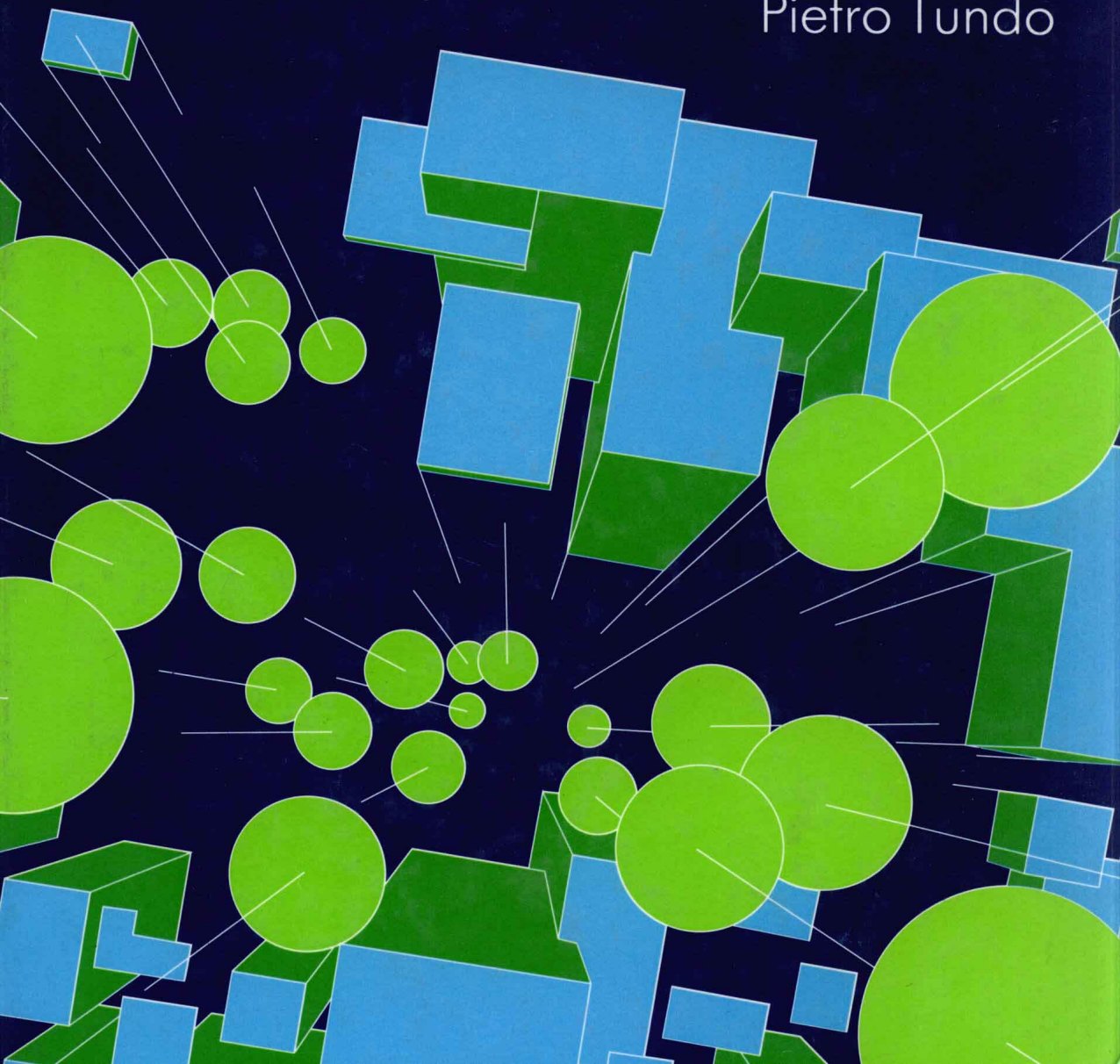
ELLIS HORWOOD SERIES IN ORGANIC CHEMISTRY

CONTINUOUS FLOW METHODS IN ORGANIC SYNTHESIS

Pietro Tundo



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ORGANIC CHEMISTRY
Series Editor: Dr JOHN MELLOR, Department of Chemistry, University of Southampton

CONTINUOUS FLOW METHODS IN ORGANIC SYNTHESIS

PIETRO TUNDO, Professor of Organic Chemistry, Faculty of Sciences, University of Venice, Italy
With a foreword by Professor P. HODGE, Department of Chemistry, University of Lancaster

Organic syntheses carried out under continuous-flow conditions have been widely employed in industry because they can economically supply large quantities of a wide variety of chemicals.

The world output of fine chemicals has continued, and will continue to increase significantly. The book shows how improved new processes under flow conditions can be achieved as a result of new organic reaction methods and by the introduction of new resistant supports. Incorporating the knowledge we have of macromolecular chemistry, it addresses industrial problems via modern organic chemical methods. The author also shows that flow processes have the advantage that operational difficulties can be easily controlled, demonstrating how chemical research can take care of both environmental protection and work safety.

Continuous flow methods have been divided into:

(i) Reactions carried out in gas-phase, by means of solid catalysts.
(ii) Reactions carried out in gas-phase by means of liquid catalysts supported on solid matrices.
(iii) Reactions carried out in liquid phase by means of catalysts supported on solid matrices.

There is discussion on numerous differing varieties of support catalysts, and how they can be combined in manufacture, introduced according to the classifications i, ii, and iii listed above. The applications include:

— gas-liquid phase-transfer analysis
— solid-phase peptide synthesis
— hydroformylation and other reactions under supported liquid-phase catalysis conditions
— recent synthetic applications of zeolites in fine chemistry
— reactions of Nafion-catalysts and other acidic exchange resins
— decontamination of mineral oils containing polychlorinated biphenyls
— immobilized enzymes in organic synthesis
— continuous-flow synthesis in phase-transfer catalysis.

An appendix provides more hints on reactors and included are lengthy accounts of recent supports for catalysts such as membranes and monoliths. There are 3000 references to the literature which should pave the way for further investigative research.

Readership: Researchers and graduate students of organic chemistry and industrial chemistry. Also of interest to researchers and graduate students of macromolecular and polymer chemistry. Plastics, pharmaceutical, and fine chemical industries will also find the book valuable.

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CONTINUOUS FLOW METHODS IN ORGANIC SYNTHESIS

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to my much loved parents
and my brother Paolo

Foreword

Students of organic chemistry will be well aware that when a compound needs to be synthesized there are often two ways in which it can be achieved: the laboratory way and the industrial way. Usually the former involves batch processes whereas the latter involves continuous flow processes. Continuous flow methods have the advantages that the reaction conditions are normally easily controlled and reproduced and that a relatively small reactor can be used to produce large amounts of product. It is perhaps inevitable that with the passage of time the differences between the two approaches would decrease and, indeed, this is now the case. Thus, whilst many industrial continuous flow reactions involve gases, continuous flow liquid phase reactions are also common and the latter are beginning to appear in the research laboratory. For example, Merrifield's original method of solid phase peptide synthesis has been developed into a laboratory flow process. Immobilized enzymes can also be used in flow reactors. I believe the method can be applied with benefit to many other areas of organic synthesis and that one day small computer-controlled bench-top flow reactors will be a common feature of many research laboratories. Studies involving flow reactors are, however, interdisciplinary and there is little doubt that this has hampered developments. Accordingly, when the opportunity arose I encouraged Pietro Tundo, an organic chemist who has pioneered novel developments in laboratory flow reactors, to make available to others the benefits of his experience and to draw together into a book the various interdisciplinary aspects. The result is the present book. Whilst it considers industrial continuous flow processes, the emphasis is on principles and innovative developments, especially in small-scale and laboratory-scale processes. I am confident the book will become a reference point for future work and am proud to have been involved in the project. I look forward to future developments in the field.

Philip Hodge
Manchester

Preface

The future of industrial chemistry is bound up with how closely both environmental needs and increasing automation are coupled with the development of new ideas in basic research. In this respect, the optimization of the raw materials used, of energy consumption, of product yields and of the efficiency of reactors, together with the reduction of waste, are a constant challenge. Improvements in the individual steps of a production process may often be more important than the development of a new process.

The successful solution of the problems thus raised will require a team of experts drawn from a variety of disciplines who will be able to combine new materials and new catalysts with new reaction conditions. Particularly significant will be the design and preparation of selective catalysts for new processes in which continuous-flow conditions are of primary importance. It is the continuous-flow process, moreover, that utilizes such innovative supports as membranes and monoliths.

The aim of this book is to link the different pursuits of pure research and industrial development. While I cannot hope to do full justice to such an enormously wide field, I do hope that I succeed in making a contribution in the problem area that is at the heart of the evolution of the chemical industry.

P. Tundo

Abbreviations

CF	Continuous-flow
GL-PTC	Gas–liquid phase-transfer catalysis
PTC	Phase-transfer catalysis
SA-PC	Supported aqueous-phase catalysis
SL-PC	Supported liquid-phase catalysis
PFR	Plug-flow reactor
CSTR	Continuously stirred tank reactor
SPPS	Solid-phase peptide synthesis
SPS	Solid-phase synthesis
AIBN	Azobis*iso*butyronitrile
Py	Pyridine
DMF	*N*,*N*′-Dimethylformamide
THF	Tetrahydrofuran
HMPA	Hexamethylphosphoramide
DDC	*N*,*N*′-Dicyclohexylcarbodiimide
DVB	Divinylbenzene
PEGs	Polyethylene glycols
PCBs	Polychlobiphenyls
Boc	*t*-butoxycarbonyl
Fmoc	9-Fluorenylmethoxycarbonyl
DMC	Dimethyl carbonate
PTFE	Polytrifluoroethylene
DMTr	4,4′-Dimethoxytrityl
TFA	Trifluoroacetic acid
Ts	Tosyl
Ms	Mesyl
mEq	10^{-3} equivalents
mmol	10^{-3} moles
μmol	10^{-6} moles

molEq	Molar equivalents
MPa	10^6 pascals
ee	Enantiomeric excess
τ	Contact time, space time
GHSV	Gas hourly space velocity
LHSV	Liquid hourly space velocity
WHSV	Weight hourly space velocity
i.r.	Infrared spectroscopy
n.m.r.	Nuclear magnetic resonance
u.v.	Ultraviolet spectroscopy
TGA	Thermal gravimetric analysis
BET	Brunauer–Emmett–Teller's method for surface area determination