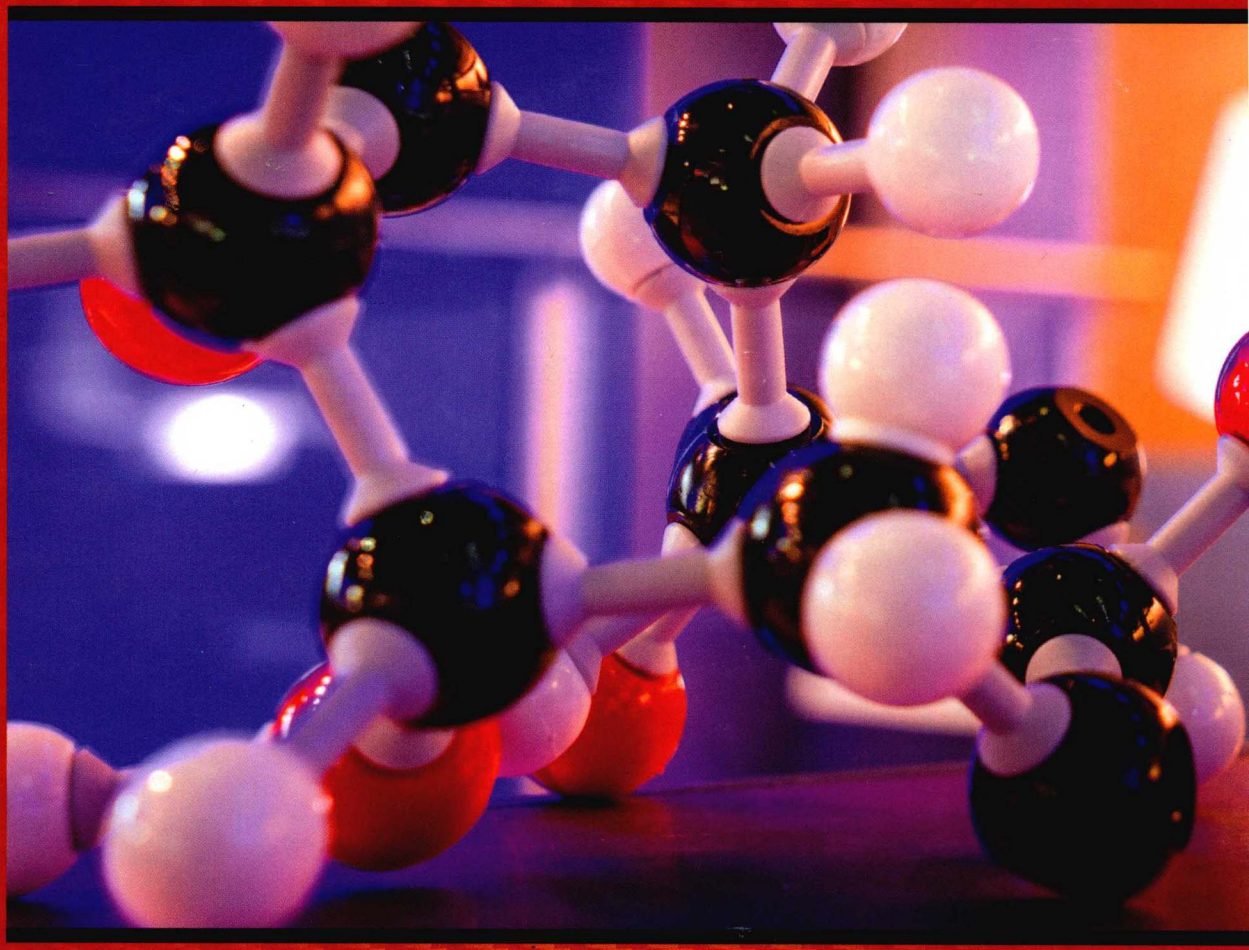
Handbook for Chemical Process Research and Development



CRC Press
Taylor & Francis Group

Wenyi Zhao

Handbook for Chemical Process Research and Development

Wenyi Zhao

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed at CPI on sustainably sourced paper
Version Date: 20160819

International Standard Book Number-13: 978-1-4987-6799-6 (Hardback)

Library of Congress Cataloging-in-Publication Data

Names: Zhao, Wenyi (Chemist)
Title: Handbook for chemical process research and development / Wenyi Zhao.
Description: Boca Raton : CRC Press, 2017. | Includes bibliographical references and index.
Identifiers: LCCN 2016032433 | ISBN 9781498767996 (hardcover : alk. paper)
Subjects: LCSH: Drugs--Research. | Drugs--Research--Methodology. | Pharmaceutical industry.
Classification: LCC RM301.25 .Z44 2017 | DDC 615.1/9--dc23
LC record available at https://lccn.loc.gov/2016032433

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Preface

Forty years ago, there was little process research and development (R&D) activities in the pharmaceutical industry partially due to the simplicity of the drug molecules. Over the past decades, however, considerable attention has been paid to the process R&D of chemical synthesis for large-scale production. With increasing structural complexity, especially the introduction of chiral centers into drug molecules and in order to comply with the regulations set by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), process R&D has become one of the critical departments for pharmaceutical companies.

The scale-up of synthetic organic chemistry from laboratory glassware to large reaction vessels is by no means a simple linear process. Large-scale operations are expected to lead to expanded time scale, poor heat transfer, insufficient mixing, and loss of temperature control, which may potentially result in runaway reactions.

Therefore, the process R&D in pharmaceutical industry requires integration of a broad range of disciplines, including, but not limited to, synthetic organic chemistry, physical organic chemistry, analytical chemistry, chemical engineering, regulatory compliance, and plant operation. The key responsibility of process chemists is to develop chemical processes that are feasible for manufacturing pharmaceutical intermediates and final drug substances (active pharmaceutical ingredients [APIs]) for support of clinical studies and, eventually, for commercial production. A good chemical process shall meet all key elements: low cost, available raw materials and reagents, simple workup, robustness, high throughput (fast reaction with high concentration), good product purity, and minimum environmental impact.

P.1 EVALUATION OF PROCESS

Generally, the medicinal chemistry route serves as the starting point for most process development programs, though it is normally designed to be divergent and to allow access to a variety of targets in small quantities. The first activity in developing a chemical process is to evaluate the existing medicinal process. The initial evaluation of the route will be based on the following criteria: safety, economics, environmental impact (green chemistry), and legal issues.

P.1.1 Process Safety

Among various factors that need to be addressed appropriately during process R&D in laboratories, process safety is the most important aspect in the chemical process development. "If a route cannot be scaled up safely, then it should not be scaled up at all."[1]

Process safety refers to (a) thermal and reactive hazards and (b) health hazards. The thermal or reactive hazards associated with process and operator safety include reactions with gas evolution and the possibility of thermal runaway and explosion and reactions that involve shock or heat-sensitive and pyrophoric, flammable, or corrosive materials. It is important to have a hazard assessment for a given process, particularly when using materials or intermediates without an available material safety data sheet (MSDS). Early thermal decomposition data such as differential scanning calorimetry (DSC) can give an indication of operating limits for a particular process. For commercially available materials, MSDS is a valuable safety data. MSDS also provides important information of chemicals with health hazards.

P.1.2 Process Cost

Process costs depend largely on the following aspects: materials, labor, equipment, and waste disposal. In general, raw materials, intermediates, reagents, and solvents are comprised of 20%–80% of the total cost of a given process. An economic process will use less expensive, commercially available materials as much as possible. Quite often the cost and availability of raw materials can be one of the major considerations in the synthetic route selection (see Chapter 14). Fortunately, due to the development of new synthetic methodologies and catalysis systems, more chemical compounds are available in bulk quantity at affordable prices. Therefore, the limitation of raw materials has diminished, which gives process chemists more freedom in devising chemical processes. Some reagents can be generated in situ, and hydrogen chloride, for example, is frequently prepared especially when HCl is needed in requisite amount and under dry-reaction conditions.[2]

Obviously, less labor intense processes are preferred, for example, chromatographic purification is not an ideal process on a large scale due to the burden of intensive labor. As per reduction of process cost, the one-pot process is frequently employed to minimize process wastes, time-consuming isolations, and handling losses.

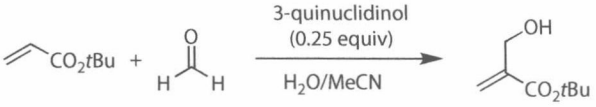
In addition, cryogenic reactions or reactions that require high temperature or pressure should be avoided as much as possible. These reaction conditions usually need special equipment and large amounts of energy, which, in turn, will increase process costs.

P.1.3 Environmental Impact

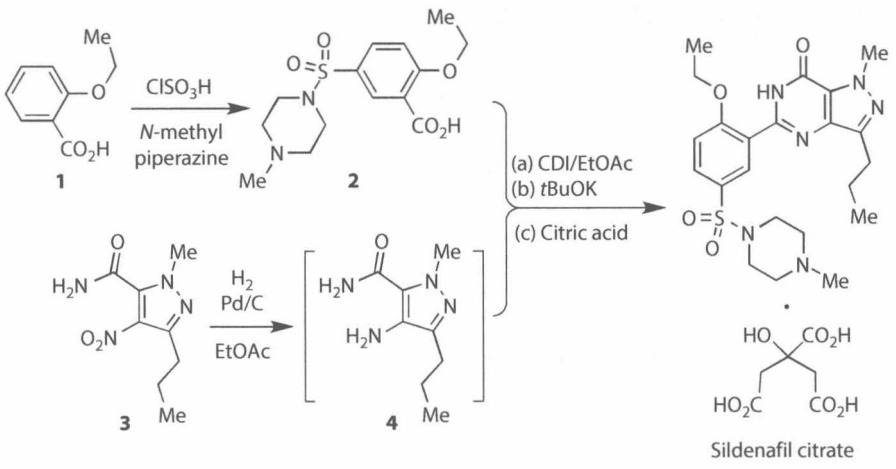
Green chemistry addresses environmentally benign chemical synthesis, encouraging the design of chemical processes that minimize the use and generation of hazardous substances. Paul Anastas and John Warner developed the 12 green chemistry principles.[3] The concept of atom economy[4] for organic reactions proposed by Trost addresses that a maximum number of atoms of reactants should end up in products. Thus, an ideal reaction would incorporate all of the atoms of the reactants with limited wastes, which, in turn, effectively reduces environmental pollution and improves efficiency.

Most chemical processes, however, produce products and wastes at the same time. These chemical wastes will, to a certain extent, have negative environmental impacts. Roger Sheldon, Professor Emeritus of Biocatalysis and Organic Chemistry at Delft University of Technology, the Netherlands, developed the concept of environmental factors (E-factors)[5] to assess the environmental footprint of chemical processes. The E-factor is defined as "kg of total waste"/"kg of product." Due to the complexity of the drug substance and tight quality regulations, pharmaceutical companies are more focused on the manufacture of molecules and the quality of the products.

Therefore, the pharmaceutical industry faces a great challenge as well as an opportunity to reduce environmental impact. Green chemistry encourages the use of more sustainable chemistry and provides some benchmarking data. Accordingly, significant improvement has been made. For instance, the process (shown in Equation P.1)[6] developed by Pfizer uses the Baylis–Hillman reaction in the synthesis of allyl alcohol, an intermediate for sampatrilat (an inhibitor of zinc metalloprotease). The inherently environmentally friendly, atom-efficient Baylis–Hillman reaction not only incorporates all the atoms of the two starting materials into the product, but it also adds environmental benefit since it allows the simple reuse of the 3-quinuclidinol and generated much less waste stream.



(P.1)



SCHEME P.1

Scheme P.1[7] demonstrates a highly convergent synthesis of sildenafil citrate, the active ingredient in Viagra, which was launched in early 1998. In this commercial manufacture route, the molecules, **2** and **3**, were put together by a hydrogenation, activation, and acylation sequence in one pot using ethyl acetate (Class 3 solvent) as solvent. The single solvent for the three telescoped steps allows easy solvent recovery.

This environmentally benign synthesis of sildenafil citrate has an E-factor of 6, which is significantly less than the industry standard (25–100). Consequently, the amount of waste produced per year is extremely low (just 6 kg of waste per kilogram of the product).[8]

P.1.4 Controlled Substances and Legal Issues

Any chemicals that can be used for illicit drug refinement are controlled by governments and constantly monitored by the International Narcotics Control Board (INCB). Licenses are often required for the possession, supply, and manufacture of these chemicals. For example, (+)-pseudoephedrine (Figure P.1) has many applications; it is used as a resolving agent, ligand, and intermediate in organic synthesis. (+)-Pseudoephedrine is, however, a regulated chemical in the UK and the United States.

International governments also tightly control chemicals that can be used in the production of chemical weapons. Notable examples include phosgene and cyanogen chloride.

In the development stage, intellectual property (IP) issues should be avoided or resolved as early as possible.

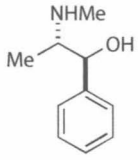


FIGURE P.1 The chemical structure of (+)-pseudoephedrine.

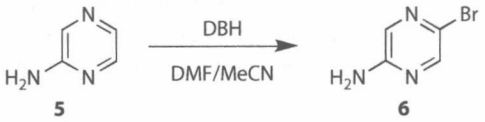
P.2 DESIGN OF NEW SYNTHETIC ROUTES

At the end of a process evaluation, a decision has to be made whether the existing process needs to be redesigned. When designing new synthetic routes, a rule of thumb should be followed:

- Use commercially available and less expensive materials.
- Use catalytic systems.
- Limit protecting group manipulations.
- Use convergent routes over linear ones.
- Use addition reactions.
- Use multicomponent reactions (MCRs).
- Use tandem or cascade processes, etc.

P.2.1 Materials and Reagents

The selection of starting materials and reagents is primarily based on process safety, cost, and commercial availability. Introducing atom-economical reagents into a process can potentially reduce costs and downstream wastes. For instance, similar reaction profiles were obtained when bromination of aminopyrazole **5** with either *N*-bromosuccinimide (NBS), 1,3-dibromo-5,5-dimethylhydantoin (DBH), or *N*-bromoacetamide (Equation P.2).[9]



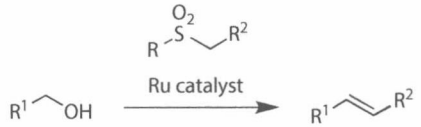
5 **6** (P.2)

Compared with NBS and DBH, *N*-bromoacetamide was more expensive and not readily available on scale. DBH was selected as the bromination reagent due to its robust solution stability in dimethyl formamide (DMF)/MeCN. It should be noted that both bromine atoms in DBH were utilized in this bromination reaction, making the process atom economical.

P.2.2 Catalytic Systems

A catalytic reaction proceeds through a transition state with lower activation energy, resulting in a higher reaction rate than an uncatalyzed reaction under otherwise the same reaction conditions. Thereby a catalytic reaction can be performed at relatively mild conditions, which is desired in large-scale production in terms of process costs and safety. Catalytic reactions are considered environmentally friendly due to the reduced amount of waste generated, as opposed to stoichiometric reactions.

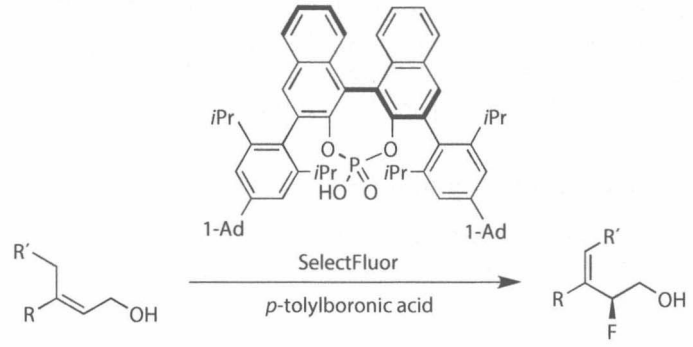
Classical olefinations, such as the Wittig reaction and Julia olefination, employ ketones or aldehydes as starting materials that are typically prepared by oxidation of the corresponding alcohols. A direct catalytic olefination of alcohols was realized using the thermally stable Ru-pincer catalyst (Equation P.3).[10] This approach represents a step-economical synthesis, which avoids the alcohol oxidation step.



(P.3)

Phase-transfer catalysis is a process in which a reaction proceeds in heterogeneous media. Enantioselective fluorination of allylic alcohols was effected using chiral anion phase–transfer

catalyst (Equation P.4).[11] This new method allows the fluorination reaction to be conducted in non-polar media (*p*-xylene/ethylcyclohexane) at room temperature using insoluble Selectfluor as the fluorine reagent and tolylboronic acid as the in situ directing group.



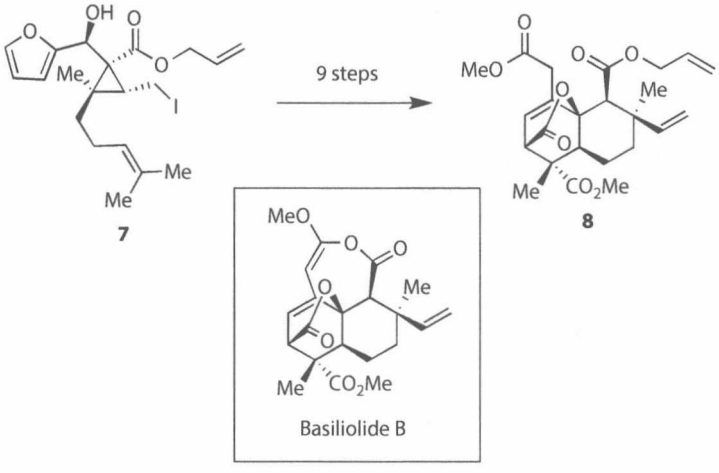
(P.4)

P.2.3 Protecting Groups

Chemoselective transformation via protection of functional groups is one of the standard tools in the total synthesis of natural products, and a large number of protecting groups[12] have been developed to fulfill the chemoselective construction of complex molecules. The protecting group has to be stable enough under certain reaction conditions and, at the end, the deprotection has to be selective. For instance, the synthesis of natural products, (±)-basiliolide B, involved transformation of **7** → **8** that contains nine synthetic steps, including cyclopropane ring opening, oxidation, olefination, Achmatowicz ring expansion, methylation, another olefination, oxidation of ketal to lactone, base-promoted double-bond migration to form 2-pyrone, and Diels–Alder cycloaddition (Scheme P.2).[13]

While the allylic protecting group in **7** survived in all nine chemical transformations, the removal of the allylic group in **8** had to be selective without damaging other existing ester functionalities. To that end, a palladium-catalyzed deprotection protocol was adopted.

However, these protecting/deprotecting manipulations render processes less efficient. Efforts in limiting protection/deprotection operations or protecting group-free synthesis[14] led to the development of various strategies (see Chapter 7).



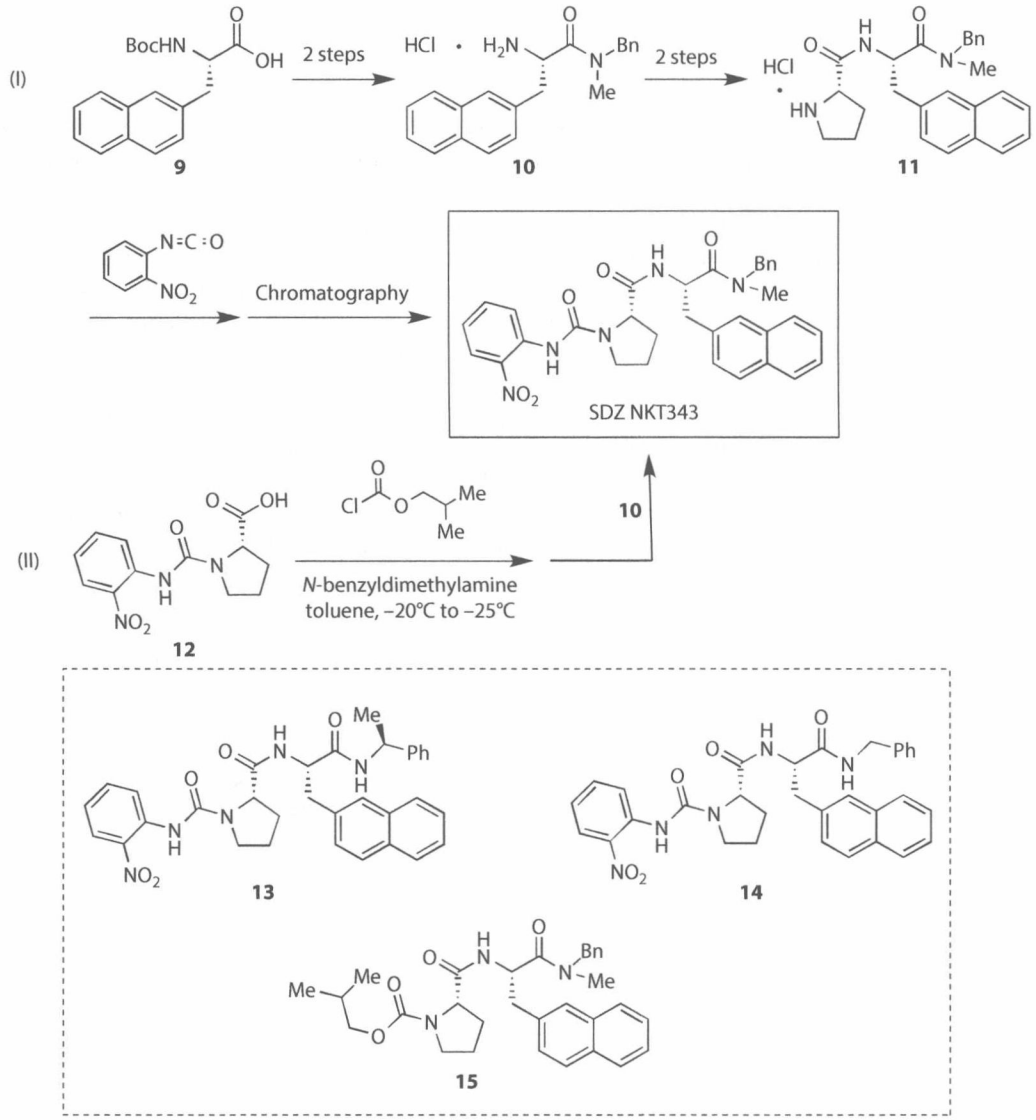
SCHEME P.2

P.2.4 Convergent Synthesis

Convergent synthesis allows the coupling of advanced intermediates at the later stage of synthesis, which not only shortens processing times but also provides a better opportunity to remove impurities. For example, a convergent synthesis (Route II, Scheme P.3) of SDZ NKT343, a human NK-1 tachykinin receptor antagonist developed by Novartis, avoided the formation of three impurities (**13–15**) generated from the linear synthesis (Route I, Scheme P.3).[15] Consequently, this convergent process allowed chromatography-free preparation of the drug substance on a large scale.

P.2.5 Addition and Substitution Reactions

In general, addition reactions are preferred over elimination reactions, as additions will build up molecular skeletons while eliminations will lose fragments of molecules that, in most cases, become



SCHEME P.3

wastes. Addition reactions are limited to compounds that have unsaturated bonds, such as carbon–carbon double bonds, triple bonds, or carbonyl groups.

Most organic transformations can be regarded as substitution reactions, in which X in the reactants RX is replaced by Y to form products RY (Equation P.5). Depending on reactants, these substitution reactions can generally be classified into nucleophilic substitution, electrophilic substitution, and free-radical substitution. Substitution reactions are inherently more balanced transformations, given that the replacement occurs between two compatible pieces in terms of mass.

$$\text{R–X} + \text{Y} \longrightarrow \text{R–Y} + \text{X} \tag{P.5}$$

Besides traditional aromatic substitution reactions, transition metal–catalyzed cross-coupling reactions (Equation P.6) are extensively applied in the pharmaceutical industry owing to the recent development on organometallic chemistry.

$$\text{R–X} \xrightarrow[\text{R′–Y}]{\text{Pd}} \left[\text{R–Pd–R′}\right] \longrightarrow \text{R–R′} \tag{P.6}$$

P.2.6 One-Pot Synthesis

The one-pot process is an economically favorable method by performing a series of bond-formation steps in a single reaction vessel without isolation of intermediates. The use of one-pot synthesis can greatly improve the process efficiency by minimizing isolation and purification steps. The current development of one-pot synthesis is summarized in a review article[16] that highlights various telescoping techniques, such as MCR,[17] cascade (or domino)[18] reaction, and tandem[19] reaction. Chapter 12 provides useful information regarding these telescoping strategies and their application in the chemical process development.

P.3 PROCESS OPERATION

Although the advent of flow chemistry has brought much attention recently, most chemical processes in the pharmaceutical industry are developed based on batchwise operation. The way of mixing starting materials, reagents, catalysts, etc., in the presence of a solvent (in most cases) has a direct impact on the outcome of a given reaction. As a consequence, it affects not only the product yield and purity but also the thermodynamic behavior and process safety.

There are several motivations for developing semibatch processes, such as control of reactant concentration to improve the selectivity of a reaction, avoidance of accumulation of reactants, and control of heat production of reactions (exothermic reactions). Most exothermic reactions are conducted in a semibatch fashion in order to mitigate the exothermic event and prevent a runaway reaction from occurring.

Chapter 1 discusses the details of addition-related processing issues and various methods that are frequently used in the pharmaceutical industry.

P.4 PROCESS OPTIMIZATION

Prior to scaling up, a number of process parameters need to be identified so that reactions can be carried out under optimal conditions. These parameters include the mode of addition of starting materials/reagents/solvents, temperature, solvent/concentration, pressure (for some cases), agitation rate, etc.

P.4.1 Reaction Temperature

A reaction temperature is established based primarily on the reaction rate and impurity profile. Ideally, the reaction temperature should be within the –20°C to 100°C range, too low or too high will

require additional energy and time at scale and sometimes special equipment is needed. Generally, a high reaction temperature will lead to poor selectivity, thereby forming impurities. Large jumps in temperature should be avoided.

P.4.2 Solvent and Concentration

Several solvent evaluation tools[20] are developed as solvent selection guides. Solvents shall be selected and assessed based on three general aspects: (a) toxicity (including carcinogenicity, mutagenicity, reprotoxicity, skin absorption/sensitization), (b) process safety (including flammability, emission, static charge, and potential for peroxide formation), and (c) environmental and regulatory considerations (including ecotoxicity, ground water contamination, and ozone depletion potential). Class 3 solvents, as proposed in the International Conference on Harmonization (ICH) guidelines, are preferred, especially at the end of the synthesis because of their low toxic potential (see Chapter 8).

In general, high-concentration reactions are desired because not only do the reactions at high concentrations afford high throughput, but they also produce less downstream wastes.

Anhydrous reaction conditions can be reached by using anhydrous reagents and solvents. In addition, azeotropic distillation is the most commonly used technique to remove moisture from a reaction system. In the case of the presence of temperature-sensitive species, a moisture scavenger, such as acetic anhydride, is employed.

P.4.3 Isolation and Purification

Direct isolation and extractive workup are two commonly used isolation approaches. Direct isolation is preferred over extractive workup in terms of process wastes, processing times, and costs.

An isolated reaction product usually needs to be purified in order to meet a predetermined purity criteria. The purification methods include distillation, recrystallization/precipitation, and column chromatography. Owing to the intensive labor requirement, column chromatography is generally not recommended in large scale.

Obviously, the product yield and quality, including chiral and chemical purity and solid form (for solid materials), are two important parameters in determining the efficiency of a given process. Generally, reaction product yields of around 100% are considered quantitative, yields between 90% and 100% are considered excellent, yields between 80% and 90% are considered very good, yields between 60% and 80% are considered good, yields between 40% and 50% are considered moderate, and yields below 40% are considered poor.[21] A product failing to meet the predetermined purity criteria may contain impurities, such as residual processing solvents, undesired products, or metals (see Chapter 15 for various isolation/purification strategies).

P.5 CONCLUSION

This book is designed to provide readers with unprecedented R&D approaches, which will help process chemists and graduate students who plan to become industrial chemists to develop chemical processes in an efficient manner. Based on the mechanism-guided process development (MPD) strategy, this book consists of 17 chapters, and each chapter contains numerous case studies. Each case study focuses on a mechanistic diagnosis of reaction problems, giving readers an opportunity of independent thinking and ultimately the ability to solve process problems in the real world.

NOTES

1. Blacker, A. J.; Williams, M. T. *Pharmaceutical Process Development, Current Chemical and Engineering Challenges,* Ch. 5, Royal Society of Chemistry: Cambridge, UK, 2011, p. 92.
2. (a) Luo, F.-T.; Jeevanandam, A. *Tetrahedron Lett.* 1998, *39*, 9455. (b) Connolly, T. J.; Considine, J. L.; Ding, Z.; Forsatz, B.; Jennings, M. N.; MacEwan, M. F.; McCoy, K. M.; Place, D. W.; Sharma, A.; Sutherland, K. *Org. Process Res. Dev.* 2010, *14*, 459. (c) Connolly, T. J.; Constantinescu, A.; Lane, T. S.; Matchett, M.; McGarry, P.; Paperna, M. *Org. Process Res. Dev.* 2005, *9*, 837. (d) Peters, R.; Waldmeier, P.; Joncour, A. *Org. Process Res. Dev.* 2005, *9*, 508.
3. Anastas, P. T.; Warner, J. C. *Green Chemistry, Theory and Practice*, Oxford University Press: New York, 1988.
4. Trost, B. *Science* 1991, *54*, 1471.
5. Sheldon, R. A. *Chem. Ind.* 1992, *56*, 903.
6. Dunn, P. J.; Hughes, M. L.; Searle, P. M.; Wood, A. S. *Org. Process Res. Dev.* 2003, *7*, 244.
7. (a) Dunn, P. J. *Org. Process Res. Dev.* 2005, *9*, 88. (b) Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* 2000, *4*, 17. (c) Dunn, P. J.; Wood, A. S. European Patent, EP 0 812845, 1997.
8. Dunn, P. J.; Galvin, S.; Hettenbach, K. *Green Chem.* 2004, *6*, 43.
9. Itoh, T.; Kato, S.; Nonoyama, N.; Wada, T.; Maeda, K.; Mase, T.; Zhao, M. M.; Song, J. Z.; Tschaen, D. M.; McNamara, J. M. *Org. Process Res. Dev.* 2006, *10*, 822.
10. Srimani, D.; Leitus, G.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* 2014, *53*, 11092.
11. Zi, W.; Wang, Y.-M.; Toste, F. D. *J. Am. Chem. Soc.* 2014, *136*, 12894.
12. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley & Sons: New York, 1999.
13. Min, L.; Zhang, Y.; Liang, X.; Huang, J.; Bao, W.; Lee, C.-S. *Angew. Chem. Int. Ed.* 2014, *53*, 11294.
14. Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* 2007, *446*, 404.
15. Prashad, M.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* 1999, *3*, 409.
16. Zhao, W.; Chen, F.-E. *Curr. Org. Synth.* 2012, *9*, 873.
17. (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* 1996, *29*, 123. (b) Ugi, I. *Pure Appl. Chem.* 2001, *73*, 187. (c) Zhu, J.; Bienaime, H. *Multicomponent Reactions,* Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005.
18. For reviews on cascade reactions in organic synthesis, see: (a) Tietze, L. F. *Chem. Rev.* 1996, *96*, 115. (b) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* 2004, *76*, 1967.
19. (a) Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* 2002, *124*, 14544. (b) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* 2002, *124*, 13390. (c) Denmark, S. E. Thorarensen, A. *Chem. Rev.* 1996, *96*, 137. (d) Winkler, J. D. *Chem. Rev.* 1996, *96*, 167. (e) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* 1996, *96*, 177. (f) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* 2006, *45*, 7134.
20. Curzons, A. D.; Constable, D. C.; Cunningham, V. L. *Clean Prod. Process* 1999, *1*, 82. (b) Jimenez-Gonzalez, C.; Curzons, A. D.; Constable, D. J. C.; Cunningham, V. L. *Clean Technol. Environ. Pol.* 2005, *7*, 42. (c) Capello, C.; Fischer, U.; Hungerbuhler, K. *Green Chem.* 2007, *9*, 917.
21. Vogel, A. I.; Tatchell, A. R.; Furnis, B. S.; Hannaford, A. J.; Smith, P. W. G. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman Scientific & Technical: London, UK, 1989.

Acknowledgments

I thank all my friends and family members for their support, especially my wife, Felicity, for her support and infinite patience.

Author

Wenyi Zhao earned a BSc and an MSc at Lanzhou University and a PhD in physical organic chemistry at Nanjing University, China. He spent two years at the Institute of Chemistry, Chinese Academy of Sciences, as a postdoctoral associate. In 1995 he joined Dr. Shine's group at Texas Tech University, Lubbock, Texas, as a senior research associate. He started his industrial career at Roche Carolina in 2001 as a process chemist. His research interests are focused on organic synthesis, reaction mechanism, and development of chemical processes for the large-scale production of pharmaceutical intermediates and APIs. He has developed a mechanism-guided process development (MPD) strategy and applied it toward his process research and development.

List of Abbreviations

ACE-Cl	1-Chloroethyl chloroformate
API	Active pharmaceutical ingredient
ARC	Accelerating rate calorimeter
9-BBN	9-Borabicyclo[3.3.1]nonane
BDMAEE	Bis[2-(*N*,*N*-dimethylamino)ethyl] ether
BHT	Butylated hydroxy toluene (2,6-bis(1,1-dimethylethyl)-4-methylphenol)
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Boc	*tert*-Butyloxycarbonyl
BOP	(Benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate
BQ	1,4-Benzoquinone
***m*CBA**	*m*-Chlorobenzoic acid
***m*CBPO**	*m*-Chlorobenzoyl peroxide
Cbz	Benzyloxycarbonyl
CDI	1,1-Carbonyl diimidazole
CDMT	2-Chloro-4,6-dimethoxy-1,3,5-triazine
CIDR	Crystallization-induced dynamic resolution
CLD	Chord length distribution
CMCS	Chloromethyl chlorosulfate
COBC	Continuous oscillatory baffled crystallizer
***m*CPBA**	*m*-Chloroperbenzoic acid
CPME	Cyclopentyl methyl ether
CSA	Camphorsulfonic acid
CSD	Crystal size distribution
CSI	*N*-Chlorosulfonylisocyanate
CTP	4-Chlorothiophenol
DABCO	1,4-Diazabicyclo[2.2.2]octane
DABSO	1,4-Diazabicyclo[2.2.2]octane (DABCO)–sulfur dioxide charge-transfer complex
1,2-DAP	1,2-Diaminopropane
DAS	Dipolar aprotic solvent
DAST	Diethylaminosulfur trifluoride
DBDMH	Dibromodimethylhydantoin
DBH	1,3-Dibromo-5,5-dimethylhydantoin
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCH	1,3-Dichloro-5,5-dimethylhydantoin
DCM	Dichloromethane
DEA	Diethanolamine
DEAD	Diethyl azodicarboxylate
DEAN	*N*,*N*-Diethylaniline
DEG	Diethylene glycol
DEM	Diethoxymethane
DEMS	Diethoxy(methyl)silane
Deoxo-Fluor	Bis(2-methoxyethyl)aminosulfur trifluoride
DFI	2,2-Difluoro-1,3-dimethylimidazolidine
DHP	3,4-Dihydro-2*H*-pyran
DIAD	Diisopropyl azodicarboxylate

DIBAL-H Diisobutylaluminum hydride
DIC 1,3-Diisopropylcarbodiimide
DIPEA Diisopropylethylamine
DIPT Diisopropyl tartrate
DKR Dynamic kinetic resolution
DMAc Dimethylacetamide
DMAP 4-Dimethylaminopyridine
DMC Dimethyl carbonate
DMCC Dimethylcarbamoyl chloride
DME Dimethoxyethane
DMEDA *N,N*-Dimethylethylenediamine
DMF Dimethyl formamide
DMI Dimethylimidazolidinone
DMP Dess–Martin periodinane
2,2-DMP 2,2-Dimethoxypropane
DMPU 1,3-Dimethyl tetrahydropyrimidin-2(1*H*)-one
DMS Dimethyl sulfide
DMSO Dimethyl sulfoxide
DPEphos Bis[(2-diphenylphosphino)phenyl]ether
DPPA Diphenylphosphoryl azide
DPPB 1,4-Bis(diphenylphosphino)butane
DPPE 1,2-Bis(diphenylphosphino)ethane
DSC Differential scanning calorimetry
DTA Differential thermal analysis
DTAD Di-*tert*-butyl azodicarboxylate
DTBP 2,6-Di-*tert*-butyl pyridine
DTTA Di-*p*-toluoyl-tartaric acid
DVS Dynamic vapor sorption
EDC 1-Ethyl-3-(3-dimethyl-aminopropyl)carbodiimide
EDCI 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride
EDTA Ethylenediamine tetraacetic acid
EEDQ 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EH&S Environment, health, and safety
EMA European Medicines Agency
EPA Environmental Protection Agency
FBRM Focused beam reflectance measurement
FDA Food and Drug Administration
Fmoc Fluorenylmethyloxycarbonyl
FTIR Fourier transform infrared spectroscopy
GSK GlaxoSmithKline Pharmaceuticals
HATU 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HBTU *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HDMT 2-Hydroxy-4,6-dimethoxy-1,3,5-triazine
HFIP Hexafluoro-2-propanol
HKR Hydrolytic kinetic resolution
HMDS Hexamethyldisilazane
HMTA Hexamethylenetetramine
HNB 2-Hydroxy-5-nitrobenzaldehyde
HOAt 1-Hydroxy-7-azabenzotriazole
HOBt 1-Hydroxybenzotriazole

HOSu	*N*-Hydroxysuccinimide
HPLC	High-performance liquid chromatography
HSA	Hydroxylamine-*O*-sulfonic acid
HWE	Horner–Wadsworth–Emmons olefination
IBCF	Isobutyl chloroformate
ICH	International Conference on Harmonization
IMS	Industrial methylated spirit
INCB	International Narcotics Control Board
IPA	2-Propanol
IPAc	Isopropyl acetate
IPE	Diisopropyl ether
LAH	Lithium aluminum hydride
LC/MS	Liquid chromatography/mass spectrometry
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidin-1-ide
MCR	Multicomponent reaction
MEK	Methyl ethyl ketone
MEMCl	2-Methoxyethoxymethyl chloride
MeTHF	2-Methyl tetrahydrofuran
MIBK	Methyl isobutyl ketone
MIDA	*N*-Methyl iminodiacetic acid
MPD	Mechanism-guided process development
MP-TMT	Macroporous polystyrene-2,4,6-trimercaptotriazine
MPV	Meerwein–Ponndorf–Verley reduction
MSA	Methanesulfonic acid
MSDS	Material safety data sheet
MTBE	Methyl *tert*-butyl ether
NBS	*N*-Bromosuccinimide
NCP	*N*-Chlorophthalimide
NCS	*N*-Chlorosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
NIS	*N*-Iodosuccinimide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methyl-2-pyrrolidone
P-BiAA	Polymer-supported bis(2-aminoethyl)-amine
PBPB	Pyridinium bromide perbromide
PBS	Phosphate buffered saline
PCC	Pyridinium chlorochromate
PCP	Purity control point
P-EDA	Polymer-supported ethylenediamine
PEPPSI	Pyridine-enhanced precatalyst preparation stabilization and initiation
L-PGA	L-Pyroglutamic acid
PGIs	Potential genotoxic impurities
PGME	Propylene glycol monomethyl ether
PICB	2-Picoline borane
PKA	Porcine kidney
PLE	Pig liver esterase
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl