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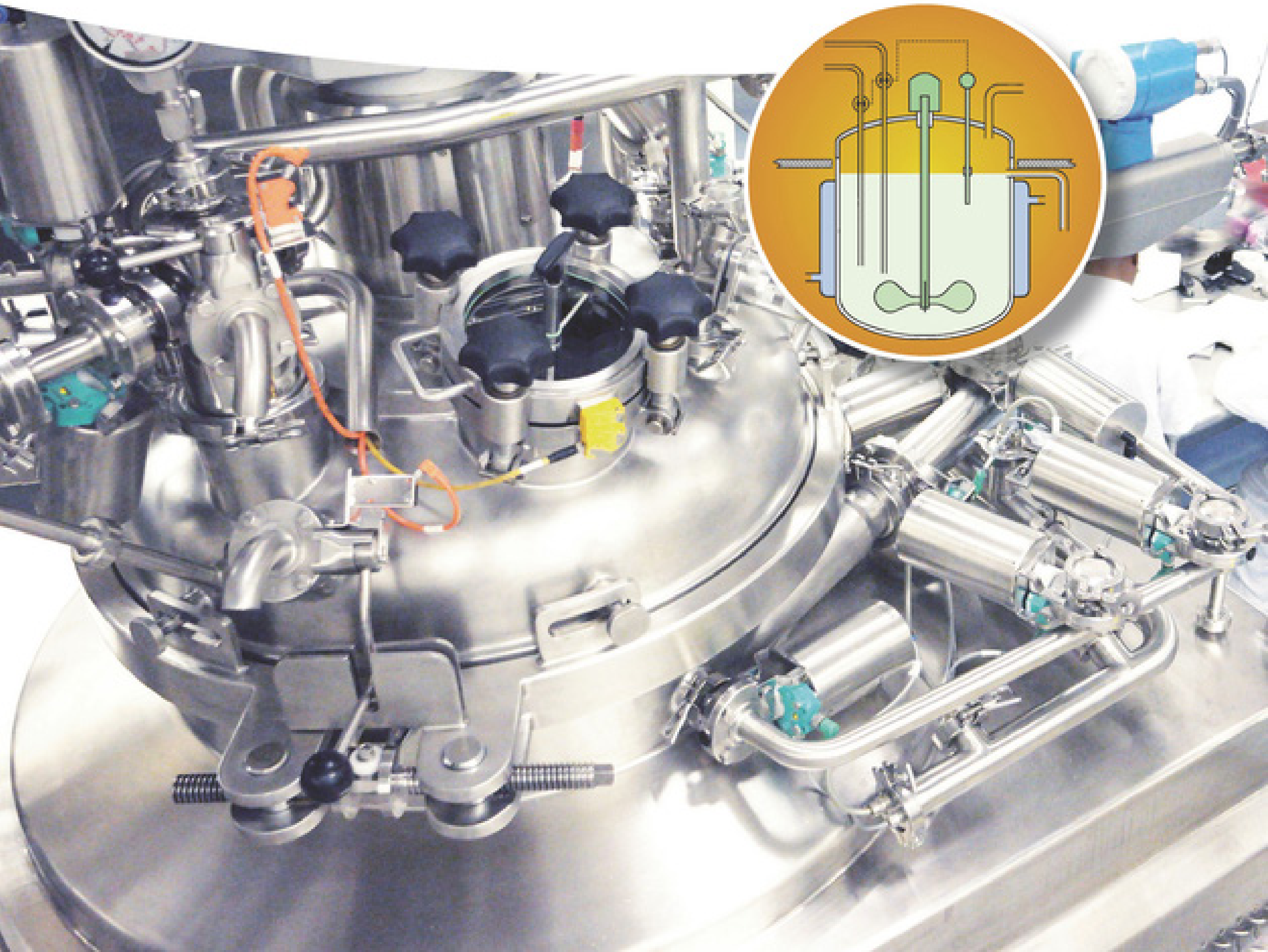
Catalytic Processes in Research and Development



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Carolina S. Marques dedicates this book to an amazing man, her grandpa João, the greatest storyteller ever, who encouraged her to follow her dreams.

Anthony J. Burke dedicates this book to Olívia, Simon, and Dan.

Contents

Foreword

The molecules coming out of drug discovery pipelines are becoming increasingly complex due to the fact that more intricate structures are required for achieving specific interactions with proteins, hence more efficacious medicines with fewer side effects. Development chemists, who are tasked to supply bulk active pharmaceutical ingredients (APIs) for preclinical and clinical studies, must constantly look to new technologies, in particular catalytic technologies, in order to produce these new molecular entities in a practical, cost-effective, and environmentally responsible manner.

As the authors of the book have eloquently described in the introductory chapters, developing catalytic reactions for large-scale API synthesis presents its own set of challenges ranging from securing intellectual property (IP) and ligand supply, achieving scalability and high turnover number/turnover frequency (TON/TOF) to controlling the residual toxic metals in the final drug substances. To ensure reproducibility on large scales, detailed understanding of reaction kinetics is also required. These challenges are often not fully appreciated from an academic perspective. For this reason, we are particularly pleased to see this book by Burke, Marques, Hermann, and Turner integrating unique views on industrial catalysis from their predominant academic background. We anticipate that this book will certainly inspire enhanced collaboration between academia and industry to further advance practical catalysis.

Development chemists in industry are not only focusing on applying and optimizing known catalytic reactions reported in the literature but also inventing novel catalysts. A number of pharmaceutical companies and technology vendors have very strong in-house R&D capability to address tough catalysis challenges through their own original research. The authors of the book discussed numerous examples where new ligands were engineered by industrial chemists in response to challenging transformations encountered in API manufacturing. As a matter of fact, the many practical problems we face in our daily research in industry provide a fertile ground for chemical innovation.

In summary, the book “Active Pharmaceutical Ingredients in Synthesis: Catalytic Processes in Research and Development” presents a comprehensive survey and detailed analysis of modern chemical catalysis and its application to industrial processes. The treatise also clearly illustrates the importance of catalysis to society by narrating key historical events in this fascinating field, including a number of Nobel Prize–winning catalytic reactions. We believe that this book would serve as a great resource and highly useful research guide for graduate students, postdoctoral researchers, as well as practicing scientists in pharmaceutical industry and the broader chemical field.

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Preface

Catalysis is everywhere!

It is an area of activity that has certainly improved our standard of living and the well-being of our planet as a whole. It impacts many areas of activity that include agriculture and the production of everyday common materials like plastics, polymers, and textiles. It also has a significant role in energy production and, of course, has an enormous role in the production of essential medicines, or, more appropriately, active pharmaceutical ingredients (APIs), which is the focus of this book.

More than 2400 APIs are known, and many of these are obtained using catalytic methods [1].

The "grand plan" of this book is to give the reader an insight into the key catalytic reactions which have been used to produce important APIs. This approach is different from other books, generally written by industrial chemists, where the focus is the actual API, where the processes giving the API are discussed. This is a book that, besides recounting the importance of the API, discusses in detail the importance of the principle catalytic processes involved in the API preparation. The key catalytic reactions discussed in our book are listed later, and include hydrogenation, epoxidation, cycloaddition reactions, metal-catalyzed couplings, biocatalysis, and phase-transfer catalysis. Both metal-based and organocatalysis are discussed at length. The book concentrates on the developments of APIs by both industrial and nonindustrial or academic laboratories.

Considering the fact that about 80% of the drugs on the market consist of a single enantiomeric species, naturally, a significant number of examples using asymmetric catalysis are described in this book. There has been a recent paradigm shift affecting the production of APIs by the pharmaceutical industry, where greater emphasis has been placed on process intensification, sustainability, and waste mitigation, and where catalysis has a central role. Catalytic methods coupled with continuous manufacturing processes like continuous-flow methods have become and will become vital, enabling technologies for accessing APIs.

This book provides the reader with an updated clear view of the current state of the challenging field of catalysis for API production. The book consists of 12 chapters seamlessly interwoven and spanning most of the spectrum of catalytic reactions used in modern API synthesis. Recent patent literature is also included for completeness; this facet will be of particular interest to industrial chemists.

The book's focus is on the application of catalytic methods for the synthesis of known APIs; however, for completeness, we also have covered important lead compounds that have got to clinical trials, but whose studies were discontinued for different reason (generally for safety reasons). We also have included some very promising molecules with demonstrated biological activities. We include, to a lesser extent, some examples of promising and interesting biologically active compounds.

This is a body of work written by a quartet of highly motivated chemists with diverse experience in the field of catalysis, which includes industrial catalysis, biocatalysis, asymmetric catalysis, metal-catalyzed coupling and organocatalysis, etc.

Chapters 1, 3, 4, and 8 were written by Anthony Burke; Chapters 5, 6, 9, and 10 by Carolina Marques; Chapters 2, 7, and 11 by Gesine Hermann; and Chapter 12 by Nicholas Turner. NT acknowledges the assistance he received from Dr. Scott France and Jin Xu from the School of Chemistry and the Manchester Institute of Biotechnology, University of Manchester for writing Chapter 12.

Chapter 1 is a general "review-type" chapter that explores the history of catalysis, which includes a time line of key discoveries and the impact it has had on the development of chemistry and on the chemical industry over the past 120 years. More importantly, it also addresses the importance it has had on the discovery of APIs by the pharmaceutical industry. To show its significance, a number of case examples are described, which include *naproxen* (obtained using a catalytic asymmetric hydrogenation), *indinavir* (obtained via a Jacobsen–Katsuki epoxidation), *L-699,392* (from a Mizoroki–Heck coupling), and *losartan* (from a Suzuki–Miyaura reaction). This chapter also looks at the future of manufacturing of APIs by the pharmaceutical industry and emerging technologies such as continuous-flow processes.

Chapter 2 is a more specific chapter that looks at the factors involved in implementing one or more catalytic processes in the manufacture of an API. The factors that go into the planning of a catalytic process to be scaled up are considered, which include the option of conducting a homogeneous or heterogeneous catalysis, safety aspects, catalyst recycling, and removal issues including the control of residual metals, particularly when they are toxic, to ensure product safety and their effect on the environment, methods for improving the manufacturing process, like the use of design of experiment (DoE) and enabling technologies that allow better streamlining of the manufacturing process. In order to hammer home the concept and the application, case studies are given.

Chapter 3 deals with the catalytic hydrogenation, hydroformylation, and other reductions including hydrosilylation and the reduction of nitro groups (which is a very important undertaking considering the presence of amino groups in many APIs). Organocatalytic methods are discussed in the context of the hydrosilylation of imines. Asymmetric catalytic methods are strongly emphasized in this chapter.

Chapter 4 looks at catalytic oxidation methods, which includes the Sharpless–Katsuki reaction, the Jacobsen–Katsuki reaction, catalytic nucleophilic methods (which include the Juliá–Colonna–Roberts poly-Leucine method, the Sharpless dihydroxylation and amino-hydroxylation methods, including the formation of sulfones and sulfoxides that are present in many APIs, including *omeprazole.* Asymmetric catalytic methods are also strongly emphasized in this chapter.

Chapter 5 is a short chapter that looks at the impact both catalytic 1,2- and 1,4-additions have had on the manufacture of APIs. Some of the important reactions considered are the 1,4-addition of arylboronic acids to nitroolefins as in the case of Merck's synthesis of *telcagepant,* or the Nozaki–Hiyama–Kishi reaction which is a 1,2-addition used in Eisai's synthesis of the cancer drug *eribulin,* the use of the catalytic Henry reaction in the production of (*R*)-*salmeterol*, and the asymmetric Michael addition reaction in Abbott's process for *ABT-546* used for cancer and congestive heart failure. Asymmetric catalytic methods are also strongly emphasized in this chapter.

Chapter 6 is the longest chapter in the book, and, of course, it looks at the application of metal-catalyzed coupling procedures, which include the "usual suspects" like the Heck–Mizoroki reaction (as is the case of *montelukast* and *L-699,392* by Merck), the Suzuki–Miyaura reaction (as in the case of *CI-1034* by Pfizer), the Buchwald–Hartwig reaction (*AR-A2* by AstraZeneca), and the Sonogashira–Hagihara reaction (*terbinafin* by Sandoz) as well as, C—H activation processes that have been used for the synthesis of *anacetrapib* by Merck.

Chapter 7 is another short chapter that looks at catalytic metathesis reactions in the synthesis of APIs. Both Ru- and Mo-based catalysts have been used. In the case of the former, APIs such as *relacatib* (GSK), *simeprevir* (Medivir and Janssen), and *vaniprevir* (Merck, Sharp & Dohme) are obtained through a catalytic metathesis step, the latter-based catalyst has received much less interest for the synthesis of APIs, but nonetheless, has been used for the synthesis of *balanol* and *KRN7000.*

Chapter 8 is concerned with the application of catalytic cycloaddition reactions for accessing APIs. The most predominant methods used for API production have been the Diels–Alder (DA) reaction (including the hetero-Diels–Alder (hDA) reaction) and 1,3-dipolar azomethine ylide cycloadditions. Some of the examples described include *LY235959* by Eli Lilly (DA), *MK-1256* by Merck (hDA) and *vabicaserin* by Pfizer (Wyeth) (1,3-dipolar azomethine ylide cycloadditions). The copper-catalyzed azide-alkyne (CuAAC) and the ruthenium-catalyzed azide-alkyne (RuAAC) reactions also feature in this chapter. Although few APIs have been produced to date with these methods, a vast array of interesting biologically active compounds have been obtained, and are discussed. Asymmetric catalytic methods are also emphasized in this chapter.

Chapter 9 addresses the issue of catalytic cyclopropanation reactions. This reaction is important considering the relevance of the cyclopropyl unit as a crucial pharmacophore in many APIs. Some of the examples include Eli Lilly's *LY2140023,* and Pfizer's *TRPV1.* Asymmetric catalytic methods are also emphasized in this chapter.

Chapter 10 deals with catalytic C—H insertion reactions or, more specifically, carbene (derived from diazo groups) insertion into C—H bonds. Some of the APIs discussed include (+)-*cetiedil,* (*S*)-*venlafaxine,* (+)-*indatraline,* and *methylphenidate.* Many other bioactive compounds are also described.

Chapter 11 looks at phase-transfer catalytic (PTC) routes to APIs. This, in fact, is a chapter that embraces the impact organocatalysis has had on API production. Both non-asymmetric and asymmetric PTC routes are discussed. APIs like *donepezil* (Eisei), *iloperidone* (Hoechst Marion Roussel), *tenofovir disoproxil* (Gilead), and *roflumilast* (Nycomed/Takeda Pharmaceuticals) are discussed.

Chapter 12 is a specific chapter on the burgeoning area of biocatalysis in the context of API production. This chapter gives the reader a glimpse of the enormous potential biocatalysis has for the production of APIs. It looks at the four main areas of biocatalysis used for API manufacture, which encompasses hydrolysis, oxidation, reduction, and C—X bond formation. A cross-section of APIs obtained with these methods includes *esomeprazole*, *atorvastatin*, *rivastigmine*, and *rasagline*.

We also include an API index, which is basically a list of the APIs that have been accessed with the catalytic methods discussed in this book. This gives the reader an off-hand glimpse of the importance of the discussed catalytic methods in accessing these APIs. It will be noticed by the reader that several of the APIs discussed in this book appear in more than one chapter, and wherever possible we have tried to cross-reference the APIs between the chapters.

We thank the following colleagues for their feedback and opinions on several parts of the book, including Dr. Christoph Sklorz (Lonza) and Dr. Olivier Dirat (Pfizer). Dr. Chris. Senanayake and Dr. Jeff Song from Boehringer Ingelheim Pharmaceuticals Inc. are gratefully acknowledged for the very nice Foreword.

We also thank the superb assistance we have received from our very competent editors Elke Masse, Kishore Sivakolundu, and Lesley Jebaraj from Wiley-VCH.

AJB thanks his family for their patience and consideration during the writing and preparation of this book.

We hope you enjoy the read.

May 2018

Anthony J. Burke
Carolina S. Marques
Gesine J. Hermann
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Reference

1 Kleeman, A., Engel, J., Kutscher, B., and Reichert, D. (2008). *Pharmaeutical Substances: Syntheses, Patents and Applications of the Most Relevant APIs*, 5e. Stuttgart: Thieme.

Abbreviations

AADH	amino acid dehydrogenase
AAH	asymmetric aminohydroxylation
ABNO	9-azabicylo[3.3.1]nonane *N*-oxyl
Ac	acetyl
ACAE	asymmetric catalytic allylic epoxidation
ACE	angiotensin-converting enzyme
AD	asymmetric dihydroxylation
ADH	alcohol dehydrogenase
ADiH	asymmetric dihydroxylation
ADMEP	acyclic diene metathesis polymerization
AHAS	acetohydroxyacid synthase
AHF	asymmetric hydroformylation
ALOX	aluminum oxide
AmDH	amine dehydrogenase
AmPhos	di-*tert*-butyl(4-dimethylaminophenyl)phosphine
ANDA	abbreviated new drug applications
API	active pharmaceutical ingredient
ARB	angiotensin II receptor blocker
ARC	accelerating rate calorimetry
ATH	asymmetric transfer hydrogenation
AZADO	2-azaadamantane-*N*-oxyl
9-BBN	(9-borabicyclo[3.3.1]nonane)
B_2Pin_2	bis(pinacolate)diboron
BAr_F	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BAT	best available technology
BBE	berberine bridge enzyme
BIBOP	bisdihydrobenzooxaphosphole
BINAP	1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
BippyPhos	5-(di-*tert*-butylphosphino)-1′, 3′, 5′-triphenyl-1′H-[1,4′] bipyrazole
Bn	benzyl
BNA	bisnoraldehyde
Boc	*tert*-butyloxycarbonyl
Bpin	pinacol borane
BPTTL	*N*-benzene-fused-phthaloyl-tert-leucinate

bpy	2,2′-bipyridyl
BrettPhos	2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
Brosyl(Brs)	*p*-bromobenzenesulfonyl
BSA	*N,O*-bis(trimethylsilyl)acetamide
BsOH	benzenesulfonic acid
Bu	butyl
BVMO	Baeyer–Villiger monooxygenase
Bz	benzoyl
CA	cycloadditon
CAGR	compound annual growth rate
CALB	*Candida antarctica* lipase B
cap	caprolactamate
Cbz	carboxybenzyl
CCK	cholecystokinin
CCR	chemokine receptor
CDI	carbonyl diimidazole
CETP	cholesterol ester transfer protein
CEYM	cross ene–yne metathesis
CFC	continuous-flow conditions
cGMP	current good manufacturing practice
CGRP	calcitonin gene-related peptide
CHP	cumene hydroperoxide
CM	cross-metathesis
CNS	central nervous system
COD	cyclooctadiene
COPD	chronic obstructive pulmonary disease
Cp	cyclopentadienyl
CPA	(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamine
CQA	critical quality attribute
CSA	camphorsulphonic acid
CuAAC	copper-catalyzed azide-alkyne cycloaddition
Cy	cyclohexyl
CyDMEDA	*trans-N,N′*-dimethyl-1,2-cyclohexanediamine
DA	Diels–Alder
DAAO	D-amino acid oxidase
DABCO	1,4-diazabicyclo[2.2.2]octane
DAP	diaminopropane
DavePhos	2-dicyclohexylphosphino-2′-(*N,N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DBDTC	dibenzylthiodicarbamate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCHA	dicyclohexylamine
DCM	dichloromethane
DCP	dicumyl peroxide
d.e.	diastereomeric excess
DEANB	*N,N*-diethylanilineborane

DEM	diethoxymethane
DERA	deoxyribose aldolase
DET	diethyl tartrate
DHP	dihydropyran
DiaPhox	diaminophosphine oxide
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DiPAMP	1,2-bis[(2-methoxyphenyl)(phenylphosphino)]ethane
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DKR	dynamic kinetic resolution
DMDMH	dibromodimethyldentoin
DME	dimethoxyethane
DMF	dimethylformamide
DMT	dimercaptotriazine
DoE	design of experiment
DOSP	(+)-*N*-(*p*-dodecylphenylsulfonyl)prolinate
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
DPPA	diphenylphosphoryl azide
dppb	1,4-bis(diphenyl)phosphinobutane
DPPE	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
dppp	1,2-bis(diphenyl)phosphinopropane
dr	diastereomeric ratio
DSC	differential scanning calorimetry
dtbpf	di-*tert*-butylphosphino)ferrocene
DTTA	(*S,S*)-di-*p*-toluyltartaric acid
DYKAT	dynamic kinetic asymmetric transformation
ee	enantiomeric excess
EDA	ethyl diazoacetate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EN	ethylenediamine
er	enantiomeric ratio
ERED	ene reductase
ERK	extracellular-signal-regulated kinase
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
FDA	Food and Drug Administration
FDH	formate dehydrogenase
FOXAP	ferrocenyloxazolinylphosphines
FTIR	Fourier transform infrared
GC	gas chromatography
GDH	glucose dehydrogenase
GSK3β	glycogen synthase kinase-3β inhibitor
HBV	hepatitis B virus
HCV	hepatitis C virus

hDA	Hetero-Diels-Alder
Hex	hexane
hfacac	hexafluoroacetylacetonate
HHD	halohydrin dehalogenase
HLADH	horse liver alcohol dehydrogenase
HMG-Co	3-hydroxy-3-methylglutaryl coenzyme A
HMPA	hexamethylphosphoramide
HNL	hydroxynitrile lyase
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
ICH	International Council of Harmonization
IP	intellectual property
IPA	isopropylalcohol
IPPL	poly-L-leucine
ip-Pybox	2,6-bis(isopropyl-2-oxazolin-2-yl)pyridine
IQNQ	isoquinoline *N*-oxide
IRED	imine reductase
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
KF	Karl Fischer
KRED	ketoreductase
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LDH	lactate dehydrogenase
LUMO	lowest unoccupied molecular orbital
MAO-N	monoamine oxidase N
MAEP	1-(2-dimethylaminoethyl)-4-methylpiperazine
MAP	mitogen-activated protein
MBHA	methylbenzhydrylamine
mCPBA	*m*-chloroperbenzoic acid
MDM2	mouse double minute 2
MeOBIPHEP	6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine)
MePhos	2-dicyclohexylphosphino-2′-methylbiphenyl, 2-Methyl-2′-dicyclohexylphosphinobiphenyl
MEPY	methylpyrrolidone-5-carboxylate
MeTHF	2-methyltetrahydrofuran
MIBK	methyl isobutyl ketone
MNA	mercaptonicotinic acid
MOM	methoxymethylacetal
MR	mineralocorticoid receptor
Ms	methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butylether
N-DMB	*N*-2,4-dimethoxybenzyl
NAC	*N*-acetyl cysteine
NAD^+	nicotinamide adenine dinucleotide (oxidized form)
NADH	nicotinamide adenine dinucleotide (reduced form)
$NADP^+$	nicotinamide adenine dinucleotide phosphate (oxidized form)

NADPH	nicotinamide adenine dinucleotide phosphate (reduced form)
NaHDMS	sodium bis(trimethylsilyl)amide
NAM	negative allosteric modulator
NANA	*N*-acetyl neuraminic acid aldolase
NBD	norbornadiene
NBS	N-bromosuccinimde
NDSA	1,5-naphthalenedisulfonic acid
NHC	N-heterocyclic carbene
NHK	Nozaki-Hiyama-Kishi
NIR	near infrared
NIS	*N*-iodosuccinimide
NMDA	*N*-methyl-ᴅ-aspartate
NMI	*N*-methylimidazole
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
NRI	norephedrine reuptake inhibitor
NSAID	nonsteroidal anti-inflammatory drug
oct	octanoate
OD	oxidative dehydrogenation
OpDH	opine dehydrogenase
OSN	organic solvent nanofiltration
OVAT	one variable a time
P450	P450 monooxygenase
PAL	phenylalanine ammonia lyase
PARP	poly (ADP-ribose) polymerase
PAT	process analytical technology
PCA	principal component analysis
PCR	polychelated resin
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$PdCl_2(dtbpf)$	[1,1′-bis(di-*tert*-butylphosphino)ferrocene] dichloropalladium(II)
PDE	permitted daily exposure
PDE4	phosphodiesterase type 4
PEEK	polyetheretherketone
PEG	polyethyleneglycol
pfm	perfluorobutyramide
PhanePhos	4,12-bis(diphenylphosphino)-[2.2]-paracyclophane
phd	1,10-Phenanthroline-5,6-dione
PheDH	phenylalanine dehydrogenase
pin	pinacolate
PIX	potassium isopropyl xanthate
PLP	pyridoxal-5′-phosphate
PMB	*p*-methoxybenzyl ether
PMI	process mass intensity
PMP	*para*-methoxyphenyl
PNB	*p*-nitrobenzyl
PPI	proton pump inhibitor

ppm	parts per million
PPNO	3-phenylpropyl *N*-oxide
PTA	phosphotungstic acid
PTC	phase-transfer catalysis
PTFE	polytetrafluoroethylene
PTSA	*p*-toluenesulfonic acid
PTTEA	*N*-phthaloyl-triethylalaninate
PTTL	*N*-phthaloyl-tert-leucinate
p-ABSA	4-acetamidobenzenesulfonyl azide
QA	quality assurance
QbD	quality by design
QC	quality control
RCM	ring-closing metathesis
RedAm	reductive aminase
RI	renin inhibitor
ROMP	ring-opening-metathesis polymerization
RuAAC	ruthenium-catalyzed azide-alkyne cycloaddition
Salen	*N,N′*-bis(salicylidene)ethylenediamine
scCO_2	supercritical carbon dioxide
SFE	supercritical fluid extraction
SHE	safety, health, and environment
SHD	simulated high dilution
SMB	simulated moving bed
SPT	serine palmitoyl transferase
S/C	substrate-to-catalyst ratio
T3P	1-propylphosphonic acid cyclic anhydride
TaDiAS	tartrate-derived diammonium salt
TBAB	tetrabutylammonium bromide
TBDMS	*tert*-butyldimethylsilyl ether
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butyl methyl ether
TBHP	*tert*-butylhydroperoxide
TBPB	tetrabutylphosphonium bromide
TBS	tributylsilane
TCFP	TriChickenFootPhos
TCPTAD	*S*-2-adamanthyl-2-(1,3-dioxo-isoindolin-2-yl) acetate
TEAB	tetraethylammonium bromide
TEBAC	benzyltriethylammonium chloride
TEBAC (TEBA)	benzyltriethylammonium hydroxide
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
Tf	triflate
TFA	trifluoroacetic acid
ThDP	thiamine diphosphate
THF	tetrahydrofurane
THMP	tris(hydroxymethyl)phosphine
THP	tetrahydropyran
TIPS	tri-isopropyl-silyl

TM	transition metals
TMBSK	potassium 2,4,6-trimethylbenzene-sulfonate
TMSA	trimethylsilylacetylene
TMSCl	trimethylsilyl chloride
TMT	2,4,6-trimercaptotriazine
TOF	turnover frequency
Tol	toluene
TON	turnover number
TPPP	tetraphenylphosphonium monoperoxysulfate
TPPTS	triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt
TRPV1	transient receptor potential cation channel, subfamily V, member 1
TTR	amyloid polyneuropathy
ω-TA	ω-transaminase
UHP	urea-hydrogen peroxide
Walphos	(*R*)-1-{(R_P)-2-[2-(diphenylphosphino)phenyl]ferrocenyl} ethylbis[3,5-bis-(trifluoromethyl)phenyl]phosphine
wt	weight
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos Pd G2	chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II)
Xyliphos	1-[2-(diphenylphosphanyl)ferrocenyl]ethyldi(3,5-xylyl) phosphane

1

Catalysis and Prerequisites for the Modern Pharmaceutical Industry Landscape

> *In the sum of the parts there are only the parts*
>
> Wallace Stevens, Poet

1.1 Introduction

The global market for active pharmaceutical ingredients (APIs) is in a very good state. The market was valued at US $119.7 billion in 2014 and is predicted to rise to US $185.9 billion by 2020 [1]. It is expected to increase at a compound annual growth rate (CAGR) of 6.50% from 2014 to 2020. The global API market is driven by the rising abbreviated new drug applications (ANDAs) [1]. It was also noted in 2011 that 90% of chemicals are derived from catalytic processes, and that the worldwide demand for catalysts was estimated to be about 850 000 tons in 2007 and the market value of products generated by catalysis reached about US $900 billion [2].

In the history of humanities' brief time on this planet, the need for more potent and efficient APIs has never been more critical than it is today. This has become a crucial issue particularly due to the exponential increase in the world population, the ever-increasing aging world population, the impact of global climate change on world health, the ever-diminishing set of natural resources, the greater propensity for the spread of disease, the rise in urban pollution, as well as lifestyle changes that are leading to serious health issues, such as obesity, and neurological problems, such as depression. For these reasons, there is an increased demand on world governments to improve their health care services. Within this context there is the requirement to provide new and efficacious drugs to treat a large panoply of diseases, including emerging ones, that are generally viral or spread by other microorganisms. This is no easy task, and two of the parameters that have to be considered are the cost of the drug (so that it can be acquired by governments and patients alike) and the speed of putting such entities on the market. However, quality is also a very important factor, and catalytic methods allowing for cleaner reaction conditions can make this an easier and more cost-effective task. In both cases, catalysis can provide the answer as both economical and efficient/rapid catalytic routes can reduce the cost and accelerate the time to market.

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Without a doubt during the past number of decades, catalysis has played a very important role in the development of APIs. When working at its optimum level, it is one of the most efficient and desirable ways of accessing APIs, particularly at the large scale over a prolonged period of time. Catalysis is desirable for accessing APIs, particularly in the pharmaceutical industry, for a number of reasons: it reduces waste, so the environmental footprint is reduced; the catalysts can be recycled, so that the process becomes more economical in the long run; low loadings can be attained for a number of metal-based catalysts (like palladium), so that the overall cost is reduced; chiral catalysts can be used to afford enantiomerically pure chiral APIs [3]; specific catalysts that are eco-friendly like enzymes (whether used as part of a whole cell, or as the isolated enzymes) with no metal contamination, organocatalysts can also be used which require facile working conditions (air reactions and water as solvent, and with no metal contamination issues); and catalysis can be easily integrated in continuous manufacturing processes, such as continuous-flow chemistries (see subsequent text) that can really speed up production times.

However, with the new developments in enabling technologies, catalytic methods leading to APIs are undergoing a major revolution; the great advances in continuous-flow methods in the context of continuous manufacturing [4] have certainly enhanced the effectiveness of catalytic routes in the past number of years (we return to this topic in Section 1.3) [5]. This technology is now highly integrated in an automatic or back-to-back setup, which includes not only the actual chemical transformation but the separations, crystallizations, drying, and formulations, as well! [4, 5].

It should also be noted that over the past three decades, there has been an increased application of the principles of green chemistry, particularly the incorporation of catalytic steps in API production [6, 7]. Catalysis is one of the 12 principles of green chemistry – i.e. principle 9 – [6] and for inherent sustainable catalytic processes it is crucial that it is integrated with the other key principles like atom economy (No. 2), safer solvents (No. 5), design for energy efficiency (No. 7), use of renewable feedstocks (No. 7), and inherently safer chemistry for accident prevention (No. 12). These issues are addressed in Chapter 2.

The impact of catalysis for the synthesis of APIs by the pharmaceutical industry has been reviewed previously [2, 3, 8]. In the context of green engineering for sustainable manufacture, both biocatalysis and continuous processing have been identified as key enabling technologies [4].

Before describing some of the landmark API synthesis that have been accomplished over the past number of decades, in the next section we describe the historical development of the field of catalysis as a major scientific area, and include some of the key discoveries in the area and their industrial applications over the past 100 years or so.

1.2 Key Historical Moments in Catalysis Development

A catalyst is a substance that when added to a chemical reaction in small quantities affects the reaction rate (generally increasing it) and the selectivity (generally improving it) but without being consumed. Historically, it was Wilhelm Ostwald who introduced chemical thermodynamics into the physical chemical definition of catalysis, and stated that it was a substance that did not effect the equilibrium of the reaction or, in Ostwald's exact words, "a catalyst is a substance which affects the rate of a chemical reaction without being part of its end products" [9, 10]. Oswald won the Nobel Prize in Chemistry in 1909, for his work on catalysis and on the conditions of chemical equilibria and velocities of chemical reactions (see Table 1.1). He also developed the industrial-scale catalytic oxidation of ammonia to nitric acid (known as the Ostwald process (Table 1.2)) [12]. This area gained traction with the work of Paul Sabatier who studied the heterogeneous catalytic hydrogenation of organic compounds using finely divided metals, and who won the Nobel Prize in Chemistry in 1912, for his method of hydrogenating organic compounds in the presence of finely divided metals (Table 1.1). (In fact, it would be several decades later that homogeneous catalytic hydrogenation became a stable academic and industrial process with the work of Fischer and Wilkinson using organometallic compounds; see subsequent text).

Sabatier introduced the concept of formation of reaction intermediates of intermediate stability on the surface of the catalyst; if they were too stable, they would not decompose into products and if too unstable, the products would not be formed [10]. He introduced for the first time the notion of a catalytic cycle, with the formation of transient complexes between the catalyst and the reagent. Together with the thermodynamic and physical chemical concepts of Oswald, this led to a greater understanding of the molecular basis of catalysis [10]. The area of catalysis began to build up steam and gain much importance with the development of the Haber–Bosch (HB) process – essentially the reaction of hydrogen with nitrogen to form ammonia over a metal catalyst – which was invented in 1913 by Fritz Haber in collaboration with Carl Bosch (Table 1.2) [10]. With this technology, large quantities of fertilizer for global food production could be obtained. In this process, dinitrogen from the air is split using a catalyst – which is usually iron – to synthesize ammonia [10]. Fritz Haber won the Nobel Prize in Chemistry for this discovery in 1918 (actually Carl Bosch won the Nobel Prize jointly with Friedrich Bergius for the invention and development of chemical high-pressure methods in chemistry in 1931) for the synthesis of ammonia (Table 1.1). It was in fact the first high-pressure industrial process on record [10]. However, insight into the actual mechanism of this process was only obtained by the groundbreaking, careful, and painstaking experiments of Gerhard Ertl – one of the fathers of modern surface chemistry – who was the recipient of the Nobel Prize in Chemistry in 2007 [13]. Ertl, having been inspired by developments in the semiconductor field in the 1960s and 1970s, conducted groundbreaking experimental studies of chemical processes, mainly catalytic, on surfaces (http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2007/advanced-chemistryprize2007.pdf). When asked at his first interview – after been informed that he had received the prize – if it was possible to improve the efficiency of the HB process, he responded by saying that it was impossible to improve the process from the chemical side, as it had undergone so many improvements/optimizations over the past 90 years; the only improvements possible would be in the engineering context [12]. Ertl not only clarified the

Table 1.1 Relevant Nobel Prizes in Chemistry with a link to catalysis (https://www.nobelprize.org/nobel_prizes/chemistry/laureates/) [11].

Years	Winner	Theme
1907	Eduard Buchner	For biochemical researches and his discovery of cell-less formation
1909	Wilhelm Ostwald	For his work on catalysis and on the conditions of chemical equilibrium and velocities of chemical reactions
1912	Paul Sabatier (one half) Victor Grignard (one half)	For his methods of hydrogenating organic compounds in the presence of finely divided metals (PS). For the discovery of the so-called Grignard reagent, which in recent years has greatly advanced the progress of organic chemistry (VG)
1913	Alfred Werner	For his work on the linkage of atoms in molecules by which he has thrown new light on earlier investigations and opened up new fields of research, especially in inorganic chemistry
1918	Fritz Haber	For the synthesis of ammonia from its elements, nitrogen and hydrogen
1932	Irving Langmuir	For discoveries and investigations in surface chemistry
1946	James B. Sumner/John H. Northrop/Wendell M. Stanley	For his discovery that enzymes could be recrystallized (JBS) For the preparation of enzyme and virus proteins in a pure form (JHN/WMS)
1963	Karl Ziegler/Giulio Natta	Catalytic polymer synthesis
1973	Geoffrey Wilkinson Ernst Otto Fischer	For pioneering work on the chemistry of the organometallic so-called sandwich compounds
1983	Henry Taube	For work on electron transfer reactions, especially in metal complexes
1989	Sidney Altman Thomas R. Cech	For their discovery that RNA acts as a biological catalyst as well as a carrier of genetic information
1993	Kary B. Mullis	For his invention of the polymerase chain reaction (PCR) method
2001	K.B. Sharpless/R. Noyori/W. Knowles	For their work on chirally catalyzed hydrogenation and oxidation reactions
2005	Robert H. Grubbs/ Richard R. Schrock/ Yves Chauvin	For the development of the metathesis method in organic synthesis
2007	Gerhard Ertl	For studies of chemical processes on solid surfaces
2010	Richard F. Heck/Ei-ichi Negishi/Akira Suzuki	For palladium-catalyzed cross couplings in organic synthesis

mechanism of the HB process but also provided a road map for the elucidation of heterogeneous catalytic processes in general [12]. It should be noted that prior to Ertl, Irving Langmuir (known for Langmuir–Blodgett films, Langmuir circulation, Langmuir waves, and the Langmuir probe) who incidentally originally