



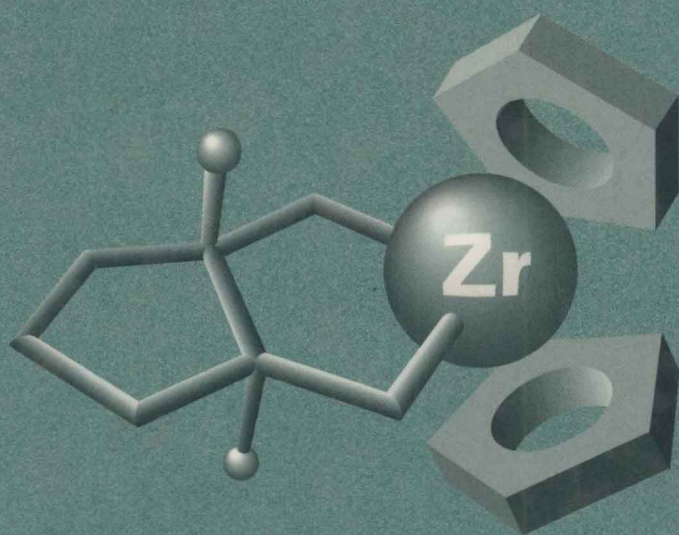
PRACTICAL
APPROACH IN
CHEMISTRY

TRANSITION METALS IN ORGANIC SYNTHESIS

A PRACTICAL APPROACH

EDITED BY

SUSAN E. GIBSON (NÉE THOMAS)



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Transition Metals in Organic Synthesis

A Practical Approach

Edited by

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Transition metals in organic synthesis

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Preface

The use of transition metals in organic synthesis has increased so dramatically in recent years that the importance and value of this area of chemistry is now beyond question. The teaching of the practical aspects of this topic, however, has lagged behind developments in the research laboratories, perhaps because some of the techniques associated with this area of chemistry have not traditionally been dealt with in organic chemistry undergraduate laboratories. It was with this omission in mind that this volume in the Practical Approach in Chemistry Series was compiled. Many of the protocols are suitable for advanced undergraduate experiments or short projects, whilst others are designed to provide guidance to more experienced research workers interested in applying a specific area of transition metal chemistry to their own particular research problem.

The coverage of the use of transition metals in organic synthesis in this volume is necessarily highly selective. The areas included, however, have been chosen to provide insight into the practical techniques associated with both catalytic and stoichiometric applications of transition metal complexes. Each chapter contains many valuable practical 'tips' on specific reagents, reactions, and techniques.

The chapters in this volume have been written by scientists with considerable expertise and experience in both laboratory practice and University teaching. I am indebted to all of them not only for their enthusiasm at the start of the project but also for their subsequent dedication to what at times seemed like a rather distant goal. The chapter authors and I are very grateful to the following people, all of whom provided invaluable advice and comments on the protocols described: Waldemar Adam, Howard Alper, Angela Brickwood, Ann Cotterill, Timothy N. Danks, Stephen G. Davies, Vittorio Farina, Alan Ford, Mike Harris, Laurence M. Harwood, Mark E. Howells, Eric N. Jacobsen, Richard F. W. Jackson, Russell James, Suresh Kapadia, Tsutomu Katsuki, Steven V. Ley, Robin Lord, Tim Luker, Jason Macro, David J. Miller, Norio Miyaura, Christopher J. Moody, Andy Mulvaney, Gareth Probert, Greg P. Roth, K. Barry Sharpless, Kenkichi Sonogashira, Lee Spence, Elizabeth Swann, Julie S. Torode, Barry M. Trost, Simon Tyler, Motokazu Uemura, Edwin Vedejs and Tohru Yamada. Finally, we also thank Domenico Albanese, Stephen A. Benyunes, Stefano C. G. Biagini, Miguel Gama Goicochea, Siân L. Griffiths, Nathalie Guillo, Gary R. Jefferson, Liang K. Ke, Stephen P. Keen, Patrick Metzner, Mark A. Peplow, Ellian Rahimian and Adam T. Wierzychlejski for proofreading the manuscript at various stages of production.

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Abbreviations

acac	acetylacetonate
AD	asymmetric dihydroxylation
AE	asymmetric epoxidation
Binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOC	<i>t</i> -butyloxycarbonyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cp	cyclopentadienyl
dba	dibenzylideneacetone
de	diastereomeric excess
DET	diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DMAP	<i>p</i> -dimethylaminopyridine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
dppe	1,2-bis(diphenylphosphino)ethane
ee	enantiomeric excess
Fc	ferrocenyl
hex	hexyl
HLADH	horse liver alcohol dehydrogenase
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
LDA	lithium diisopropylamide
macH	3-methyl-2,4-pentanedione
NADH	reduced nicotinamide adenine dinucleotide
NBS	<i>N</i> -bromosuccinimide
NMP	<i>N</i> -methylpyrrolidine
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
p.s.i.	pounds per square inch
py	pyridine
<i>R</i> _f	retention factor
salen	<i>N,N'</i> -disalicylidene-ethylenediaminato
SAMP	[(<i>S</i>)-1-amino-2-(methoxymethyl)pyrrolidine]
TBS	<i>t</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

Abbreviations

TMEDA	<i>N,N,N',N'</i>-tetramethylethylenediamine
TMM	trimethylenemethane
TMS	trimethylsilyl

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Transition metal-promoted oxidations

SIMON WOODWARD

1. Introduction

Few other areas of modern synthetic organic chemistry offer the diversity shown by homogeneous catalytic oxidation reactions. Practically all the transition metals have complexes showing oxidation activity; widely disparate mechanisms of action are standard.

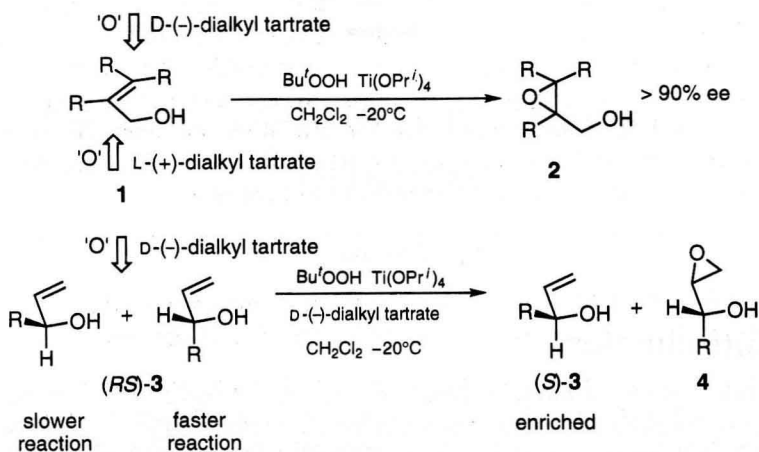
It is the aim of this chapter to present in detail a few selected examples of useful organic transformations promoted by Group 4–11 (Ti–Cu) metals rather than to give a comprehensive listing of all possible transformations, as this information is available in several other excellent books.^{1,2} The protocols are selected to demonstrate the most common oxygenation (addition of O atoms) or oxidation (removal of H atoms) pathways encountered in transition metal-promoted reactions of organic substrates.

Caution! As all oxidation reactions represent controlled highly exothermic reactions, and most involve the handling of toxic materials, all of the protocols in this chapter should be carried out in an efficient hood with explosion resistant sashes. Eye protection and disposable gloves must be worn. Clean reaction flasks are essential to avoid the accidental inclusion of materials known to bring about the rapid decomposition of high energy oxidants.

2. Group 4 metal-promoted oxidations: Sharpless–Katsuki asymmetric epoxidation

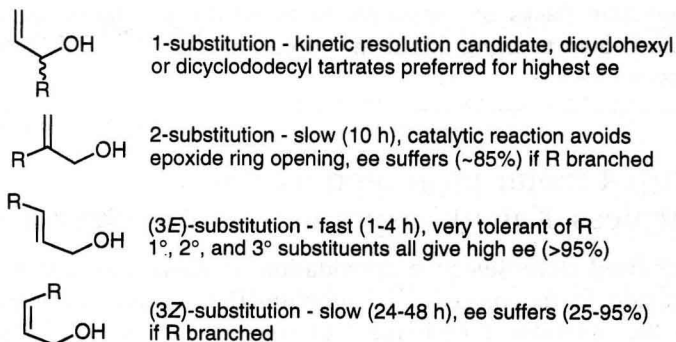
The generalised stereoselective epoxidation of allylic alcohols **1** by *t*-butyl hydroperoxide in the presence of titanium(IV) isopropoxide and tartrate esters to the epoxides **2** (Scheme 1.1) constitutes a seminal landmark in metal-mediated asymmetric oxidations. The catalytic version of this reaction is often the most effective procedure and is especially useful for the kinetic

resolution of 1-substituted allylic alcohols, as in the transformation of **3** to **4**. The epoxidation of (*E*)-2-hexen-1-ol is demonstrated here to allow comparison with a stoichiometric protocol described in *Organic Synthesis*.³



Scheme 1.1

Full mechanistic details of asymmetric epoxidation (AE) reactions can be found in a comprehensive review.⁴ The features of the transition state which leads to high enantioselectivities over such a wide range of allyl functions have been intensively studied,^{5,6} but it is arguably more instructive from a practical point of view to indicate the behaviour of some commonly encountered substrates with this catalyst. Tri- and tetra-substituted allylic alcohols with their electron-rich double bonds react rapidly, even at -35°C . 3-(*E*)-Monosubstituted allylic alcohols also react rapidly (1–4 h, as in Protocol 1) while other mono-substitution patterns dramatically slow down the reaction (10–50 h), necessitating the use of cryostatic cooling units. These reactivity patterns are summarised in Scheme 1.2.



Scheme 1.2

1: Transition metal-promoted oxidations

Although the AE reaction tolerates many functional groups, it is incompatible with RCO_2H , RSH , ArOH , PR_3 , and most amines. If the substrate is free of these functions and the procedure fails, moisture contamination of the dialkyl tartrate or Bu^tOOH solution is usually to blame. The former should be distilled quickly below 100°C (higher temperatures lead to tartrate polymerisation, resulting in lower product optical yields). The latter should be dried over a fresh supply of molecular sieves just before use. Cumene hydroperoxide may be substituted for Bu^tOOH in most AE reactions. Although its removal can complicate workup of the reaction mixture, its use normally results in slightly improved enantioselectivities.

Protocol 1.

Preparation of (2*S*,3*S*)-3-propyloxiranemethanol. Catalytic Sharpless–Katsuki asymmetric epoxidation (AE) (Scheme 1.1)

Caution! Employ the standard precautions outlined in the introduction to this chapter for this reaction. Strong acids, transition metal salts, or metal syringe needles should **never** be added to concentrated Bu^tOOH stock solutions. Aliquots of Bu^tOOH remaining after use in reactions should **not** be returned to the stock solutions. 1,2-Dichloroethane should **not** be used as a solvent with Bu^tOOH , despite early recommendations.⁷

Equipment

- Three-necked, round-bottomed flask (250 mL)
- Teflon-bladed overhead mechanical stirrer and ∇ 24/40 sleeve adapter
- Low temperature thermometer and ∇ 19/22 cone/screw thread adapter
- ∇ 19/22 socket/cone adapter with T connection
- Well-insulated low-temperature bath
- Septa
- All-glass Luer syringes (2 mL and 20 mL)
- Needles (10 cm, 20 or 22 gauge)
- Pressure-equalising addition funnel (50 mL)
- Glass funnel
- Beaker (50 mL)
- Erlenmeyer flasks (3×50 mL)
- Source of dry inert gas (nitrogen or argon)
- Separating funnel (1 L)

Materials

- Dry dichloromethane,^a ca. 120 mL total
 - Activated powdered 4 Å molecular sieves, 4.0 g
 - Activated pelleted 4 Å molecular sieves, ca. 10 g
 - Titanium(IV) isopropoxide (tetraisopropyl orthotitanate) (FW 284.3), 1.5 mL, 1.45 g, 5.09 mmol (12.7 mol%)
 - Diethyl L-(+)-(R,R)-tartrate (FW 206.2), 1.27 g, 6.11 mmol (15.3 mol%)
 - Anhydrous t-butyl hydroperoxide, 5.5 M in nonane,^b 25 mL, 138 mmol
 - (E)-2-Hexen-1-ol (FW 100.2), 4.0 g, 40.0 mmol
 - Iron(III) sulfate heptahydrate (FW 278.0), 29.9 g, 0.11 mol
 - L-(+)-(R,R)-Tartaric acid (FW 150.1), 9.9 g, 0.05 mol
 - Technical diethyl ether for extraction
- volatile, toxic at high concentrations
hygroscopic
hygroscopic
corrosive, moisture sensitive
harmful
oxidising agent, flammable
harmful
flammable

1. Clean all glassware, syringes, and needles sequentially in soap solution, water, and acetone. Allow the acetone to evaporate^c and then dry every-