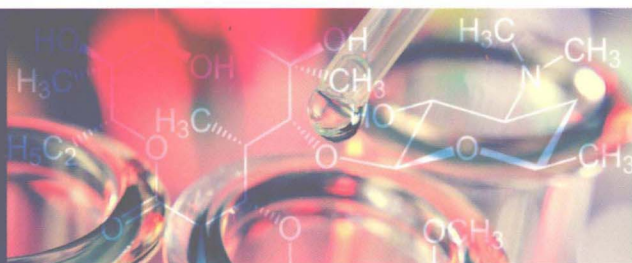
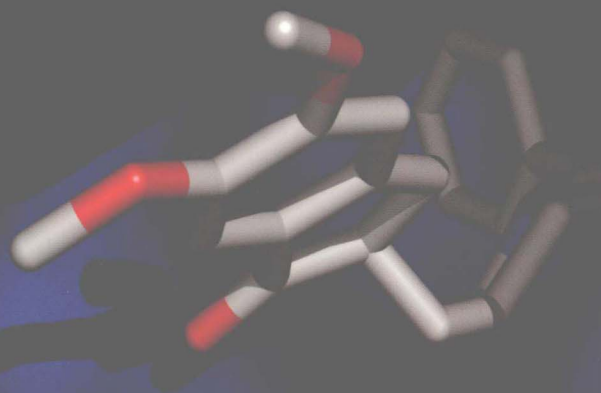


OXFORD

# AN INTRODUCTION TO DRUG SYNTHESIS



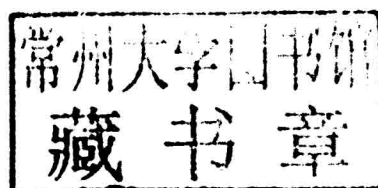
GRAHAM L. PATRICK



An Introduction to

# Drug Synthesis

Graham L. Patrick



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## **An Introduction to Drug Synthesis**



# Preface

This text is written for undergraduates and postgraduates who have a basic grounding in organic chemistry and are studying a module or degree in a chemistry-related field such as medicinal chemistry. It attempts to convey, in a readable and interesting style, an understanding about some of the issues and strategies relating to drug synthesis. In particular, the book aims to show the importance of organic synthesis to various aspects of the drug discovery process. For example, the kind of synthetic route chosen for a particular drug has an important bearing on what kind of analogues can be synthesized. These analogues can be used to study structure–activity relationships, as well as helping us to identify structures with improved activities and properties. Synthesis is also crucial to the economic and practical feasibility of manufacturing drugs on a commercial scale. Consequently, the book is of particular interest to students who might be considering a future career in research and development in the pharmaceutical industry.

The book is divided into three parts.

Part A contains six chapters that provide some general background on medicinal chemistry and organic synthesis. The first chapter gives an overview of the process involved in getting a drug to market and the impact that organic synthesis has at various stages of that journey. It also defines various medicinal chemistry terms that are used throughout the other chapters.

Chapter 2 identifies the different types of reactions that are involved in a drug synthesis, highlighting the importance of five general categories—coupling reactions, functional group transformations, functionalizations, functional group removals, and the use of protecting groups. Throughout the chapter, simple examples of drug syntheses are provided to illustrate these different reaction categories, and how the structure of a target compound has a crucial impact on the complexity of the overall synthesis.

Chapters 3–5 are overviews of retrosynthesis, cyclization reactions, and the synthesis of chiral compounds, where the emphasis is on explaining the key principles of these topics and relating them to the synthesis of important drug structures.

Finally, Chapter 6 describes the role of combinatorial and parallel synthesis in drug synthesis.

There are also three case studies. Two of these look at reactions that are particularly important in drug synthesis. Case study 1 considers the role of protecting groups and coupling agents in peptide synthesis, while case study 2 provides an overview of palladium-catalysed coupling reactions. Case study 3 provides an example of how retrosynthesis is used in designing a synthesis. In this case, the target structure is a natural product called huperzine A, which has interesting pharmacological properties.

Part B contains five chapters that describe how synthesis impacts on various stages of the drug design and development process. Chapter 7 focuses on the synthesis of novel structures as potential lead compounds in medicinal chemistry, whereas Chapter 8 looks at synthetic approaches to the analogues of known active compounds.

Chapter 9 covers synthetic and semi-synthetic approaches to the synthesis of medicinally important natural products and their analogues, and also describes how biosynthesis and genetic engineering has been used to generate such compounds.

Chapter 10 describes chemical and process development, and identifies many of the key issues that have to be considered in the synthesis of drugs on a commercial scale.

Finally, Chapter 11 describes the synthesis of isotopically labelled drugs, and the uses of such drugs in therapy, diagnosis, and scientific study.

A case study on gliotoxin provides an example of the use of radiolabelling studies to determine the biosynthesis of an important natural product.

Part C contains three chapters that focus on the design, synthesis, and activities of particular antibacterial agents. Chapters 12 and 13 describe tetracyclines and macrolides, respectively, while Chapter 14 describes different synthetic approaches to quinolones and fluoroquinolones.

In addition to the three main parts of the textbook, there are several appendices that summarize many of the most commonly used reactions in drug synthesis. Further information about these reactions is provided in the Online Resource Centre, as explained in the guide to the book that follows.

G. L. P.  
June 2014

# About the book

An *Introduction to Drug Synthesis* and its Online Resource Centre contain many learning features which will help you to understand this fascinating subject. This section explains how to get the most out of these features.

## Emboldened key words

Terminology is emboldened within the main text and defined in a glossary at the end of the book, helping you to become familiar with the language of drug synthesis.

## Boxes

Boxes are used to present in-depth material and to explore how the concepts of drug synthesis are applied in practice.

## Key points

Summaries at the end of major sections within chapters highlight and summarize key concepts, and provide a basis for revision.

## Questions

End-of-chapter questions allow you to test your understanding and apply concepts presented in the chapter to solve the problems presented to you.

## Further reading

Selected references allow you to easily research those topics that are of particular interest to you.

## Case studies

Case studies within several chapters and at the end of Parts A and B demonstrate the practical application of drug synthesis by exploring the synthesis of a number of drugs in detail.

## Appendix

There are seven appendices which summarize many of the most commonly used reactions in drug synthesis.

target to the one being tested in the *in vitro* test. Physiological effects are often the result of a variety of different biological mechanisms, and carrying out specific *in vitro* tests alone may miss an important new lead compound. Furthermore, it may not be known what role a newly discovered protein has in the body. An *in vitro* test will show whether a compound interacts with that novel target, while an *in vivo* test will identify the overall effect of that interaction on the organism.

Secondly, *in vitro* tests are excellent at establishing whether a drug interacts with its target to produce a pharmacological effect (pharmacodynamics), but they

### 1.5.3 Pharmacokinetics

If a drug is to be effective, it must not only interact with a particular molecular target, but must also reach that target. However, there are many different factors which can prevent that happening. The main ones are **absorption**, **distribution**, **metabolism**, and **excretion** (commonly referred to as ADME). Another factor which is commonly considered is **toxicity** (ADMET).

#### Absorption

### BOX 6.2 Dynamic combinatorial synthesis of vancomycin dimers

Vancomycin is an antibiotic that works because it masks the building blocks required for bacterial cell wall synthesis. Binding takes place specifically between the antibiotic and a peptide sequence (L-Lys-D-Ala-D-Ala) which is present in the building block. It is also known that this binding promotes dimerization of the vancomycin-target complex, which suggests that covalently linked vancomycin dimers might be more effective antibacterial agents than vancomycin itself. A dynamic combinatorial synthesis was carried out to synthesize a variety of different vancomycin dimers covalently linked by bridges of different

The tripeptide target was present to accelerate the rate of bridge formation and to promote formation of vancomycin dimers having the ideal bridge length. As shown in Figure 2, the vancomycin monomers bind the tripeptide, which encourages the self-assembly of non-covalently linked dimers. Once formed, those dimers having the correct length of substituent are more likely to react together to form the covalent bridge (Fig. 2).

Having established the optimum length of bridge, another experiment was carried out on eight vancomycin monomers which had the correct length of 'tether' but varied slightly in

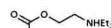
#### KEY POINTS

- Tagging involves the construction of a tagging molecule on the same solid support as the target molecule. Tagging molecules are normally peptides or oligonucleotides. After each stage of the target synthesis, the peptide or oligonucleotide is extended and the amino acid or nucleotide used defines the reactant or reagent used in that stage.

- Dynamic combinatorial chemistry involves the equilibrium formation of a mixture of compounds in the presence of a target. Binding of a product with the target amplifies that product in the equilibrium mixture.
- Diversity-orientated synthesis aims to produce compounds with as wide a diversity as possible in order to fully explore the conformational space around a molecule when it interacts with a target binding site.

### QUESTIONS

1. Carry out a retrosynthetic analysis of the muscle relaxant **piritrolol** and propose a possible synthesis.
2. **Proparacaine** (**proxymetacaine**) is a local anaesthetic that is used in ophthalmology and is applied in eye drops. Carry out a retrosynthetic analysis of its structure and propose a possible synthesis.



### FURTHER READING

#### General references

Patrick, G.L. (2013) *An introduction to medicinal chemistry* (5th edn). Oxford University Press, Oxford (Chapter 24, 'The opioid analgesics'; Chapter 23, 'Drugs acting on the adrenergic nervous system'; Section 19.5.1, 'Penicillins'; Section 21.6.2, 'Protein kinase inhibitors').

analgesic', *Journal of Medicinal Chemistry*, **29**, 2290–7 (alfentanil).

Lawrence, H.R., et al. (2005) 'Novel and potent 17 $\beta$ -hydroxysteroid dehydrogenase type I inhibitors', *Journal of Medicinal Chemistry*, **48**, 2759–62 (estrone analogues).

#### Specific syntheses

Lipkowski, A.W., et al. (1986) Peptides as receptor selectivity modulators of opiate pharmacophores. *Journal of Medicinal Chemistry*, **29**, 1111–1118.

### CS1.1 Introduction

Peptide synthesis has been an important area of organic synthesis for many years. Many of the body's neurotransmitters and hormones are peptides or proteins, and the ability to carry out peptide synthesis has allowed the medicinal chemist to prepare these structures, as well as their analogues. This provided an understanding of structure-activity relationships and led to useful drugs. The same holds true for peptides and proteins that have

there are several examples where peptide-like drugs have proved clinically useful.

### CS1.2 Amino acids—the building blocks for peptide synthesis

Amino acids are the building blocks used for the biosynthesis and synthesis of peptides and proteins. They all contain an amine and a carboxylic acid functional group.

## Appendix 1

### Functional group transformations

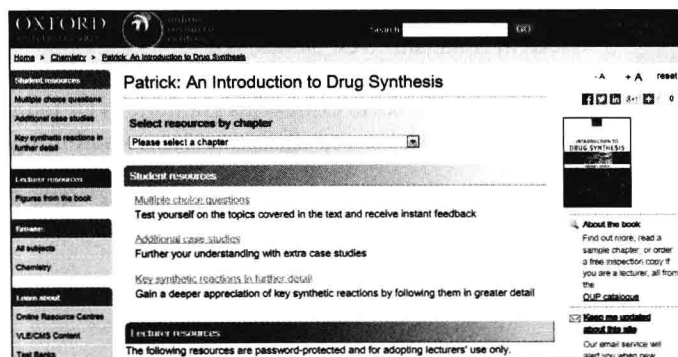
There are a large number of possible functional group transformations (FGTs) in organic synthesis. The following are examples of the most commonly used FGTs in

drug synthesis. Further details on each reaction are available in the book's Online Resource Centre.

# About the Online Resource Centre

Online Resource Centres provide students and lecturers with ready-to-use teaching and learning resources to augment the printed book.

You will find the material to accompany *An Introduction to Drug Synthesis* at:  
[www.oxfordtextbooks.co.uk/orc/patrick\\_synth/](http://www.oxfordtextbooks.co.uk/orc/patrick_synth/)



## Student resources

### Multiple-choice questions

Test yourself on the topics covered in the text and receive instant feedback.

### Additional case studies

Further your understanding with extra case studies.

### Key synthetic reactions in further detail

Gain a deeper appreciation of key synthetic reactions by following them in greater detail.

## Lecturer resources

*For registered adopters of the book*

### Figures from the book

All of the figures from the textbook are available to download electronically for use in lectures and handouts.



# Acknowledgements

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The author would like to express his gratitude to Dr John Spencer of the University of Sussex for co-authoring Chapter 6.

# Abbreviations and acronyms

<b>aa</b>	amino acid	<b>CoA</b>	coenzyme A
<b>Ac</b>	acetyl	<b>COD</b>	cyclooctadiene
<b>7-ACA</b>	7-aminocephalosporinic acid	<b>COX</b>	cyclooxygenase
<b>AcCl</b>	acetyl chloride	<b>cyclic AMP</b>	cyclic adenosine 5'-monophosphate
<b>ACE</b>	angiotensin-converting enzyme	<b>CYP</b>	cytochrome P450
<b>ACh</b>	acetylcholine	<b>DAGO or DAMGO</b>	[D-Ala <sup>2</sup> ,MePhe <sup>4</sup> ,Glyol <sup>5</sup> ]enkephalin
<b>AChE</b>	acetylcholinesterase	<b>DAST</b>	diethylaminosulphur trifluoride
<b>Ac<sub>2</sub>O</b>	acetic anhydride	<b>dba</b>	dibenzylidene acetone
<b>ACP</b>	acyl carrier protein	<b>DBTA</b>	dibenzoyl tartaric acid monohydrate
<b>AD</b>	Alzheimer's disease	<b>DBU</b>	1,8-diazobicyclo[5.4.0]undec-7-ene
<b>ADH</b>	aldehyde dehydrogenase	<b>DCC</b>	dicyclohexylcarbodiimide
<b>ADHD</b>	attention deficit hyperactivity disorder	<b>DCM</b>	dichloromethane
<b>ADME</b>	absorption, distribution, metabolism, excretion	<b>DCU</b>	dicyclohexylurea
<b>ADMET</b>	absorption, distribution, metabolism, excretion, toxicity	<b>DEAD</b>	diethyl azodicarboxylate
<b>ADP</b>	adenosine 5'-diphosphate	<b>DEBS</b>	6-deoxyerythronolide B synthase
<b>AIDS</b>	acquired immune deficiency syndrome	<b>DET</b>	diethyl tartrate
<b>AMD</b>	amorphadiene synthase	<b>DH</b>	dehydratase
<b>AMP</b>	adenosine 5'-monophosphate	<b>DIBAL or DIBAL-H</b>	diisobutylaluminium hydride
<b>cAMP</b>	cyclic adenosine 5'-monophosphate	<b>DIC</b>	<i>N,N'</i> -diisopropylcarbodiimide
<b>amu</b>	atomic mass unit	<b>DIOP</b>	<i>O</i> -isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
<b>6-APA</b>	6-aminopenicillanic acid	<b>DIPAMP</b>	ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]
<b>AT</b>	acyltransferase	<b>DIPC</b>	<i>N,N'</i> -diisopropylcarbodiimide
<b>ATP</b>	adenosine 5'-triphosphate	<b>DIPEA</b>	<i>N,N</i> -diisopropylethylamine
<b>BBB</b>	blood-brain barrier	<b>DIU</b>	diisopropylurea
<b>BINAP</b>	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	<b>DMA</b>	dimethylacetamide
<b>BnBr</b>	Benzyl bromide	<b>DMAP</b>	4-dimethylaminopyridine
<b>Boc</b>	<i>tert</i> -butoxycarbonyl	<b>DMF</b>	dimethylformamide
<b>Boc anhydride or (Boc)<sub>2</sub>O</b>	di- <i>t</i> -butyl dicarbonate	<b>DMSO</b>	dimethylsulphoxide
<b>BOP</b>	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate	<b>DNA</b>	deoxyribonucleic acid
<b><i>n</i>-Bu</b>	<i>n</i> -butyl	<b>DOR</b>	delta opioid receptor
<b><i>t</i>-Bu</b>	<i>tertiary</i> -butyl	<b>DPDPE</b>	tyr-c(D-Pen-Gly-Phe-D-Pen)
<b>cbz</b>	benzyloxycarbonyl or carboxybenzyl	<b>DPP-4</b>	dipeptidyl peptidase-4
<b>CDI</b>	<i>N,N'</i> -carbonyldiimidazole	<b>EC<sub>50</sub></b>	concentration of drug required to produce 50% of the maximum possible effect
<b>CHIRAPHOS</b>	bis(diphenylphosphino)butane	<b>EDC or EDCI</b>	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
<b>ClogP</b>	calculated logarithm of the partition coefficient	<b>EDU</b>	1-ethyl-3-(3-dimethylaminopropyl)urea
<b>CNS</b>	central nervous system	<b>ee</b>	enantiomeric excess

<b>EGF</b>	epidermal growth factor	<b><sup>d</sup>Ipc<sub>2</sub>BCl</b>	d-enantiomer of diisopinocampheylchloroborane
<b>EGF-R</b>	epidermal growth factor receptor	<b><sup>l</sup>Ipc<sub>2</sub>BCl</b>	l-enantiomer of diisopinocampheylchloroborane
<b>EMA</b>	European Agency for the Evaluation of Medicinal Products	<b>IpcBH<sub>2</sub></b>	diisopinocampheylborane
<b>ER</b>	enoyl reductase	<b>K<sub>d</sub></b>	binding affinity or dissociation binding constant
<b>Et</b>	ethyl	<b>K<sub>i</sub></b>	inhibition constant
<b>F-SPE</b>	fluorous solid phase extraction	<b>KIE</b>	kinetic isotope effect
<b>FDA</b>	US Food and Drug Administration	<b>KN(TMS)<sub>2</sub></b>	potassium bis(trimethylsilyl)amide
<b><sup>18</sup>F-FDG</b>	[ <sup>18</sup> F]fluorodeoxyglucose	<b>KOR</b>	kappa opioid receptor
<b>FG</b>	functional group	<b>KR</b>	ketoreductase
<b>FGI</b>	functional group interconversion	<b>KS</b>	ketosynthase enzyme
<b>FGT</b>	functional group transformation	<b>LDA</b>	lithium diisopropylamide
<b>Fmoc</b>	fluorenylmethyloxycarbonyl	<b>LDH</b>	lactate dehydrogenase
<b>Fmoc-Cl</b>	fluorenylmethyloxycarbonyl chloride	<b>LiHMDS or LiN(TMS)<sub>2</sub></b>	lithium bis(trimethylsilyl)amide
<b>FPP</b>	farnesyl pyrophosphate	<b>LogP</b>	logarithm of the partition coefficient
<b>F-SPE</b>	fluorous solid phase extraction	<b>LUMO</b>	lowest unoccupied molecular orbital
<b>FT</b>	farnesyl transferase	<b>M-receptor</b>	muscarinic receptor
<b>G-protein</b>	guanine nucleotide binding protein	<b>MAA</b>	Marketing Authorization Application
<b>GABA</b>	γ-aminobutyric acid	<b>MAOS</b>	microwave-assisted organic synthesis
<b>GABA-R</b>	benzodiazepine receptor	<b>mcpba</b>	meta-chloroperbenzoic acid
<b>GCP</b>	Good Clinical Practice	<b>Me</b>	methyl
<b>GDP</b>	guanosine 5'-diphosphate	<b>MIBK</b>	methyl isobutyl ketone (4-methylpentan-2-one)
<b>GIT</b>	gastrointestinal tract	<b>MOR</b>	mu opioid receptor
<b>GLP</b>	Good Laboratory Practice	<b>mRNA</b>	messenger RNA
<b>GMP</b>	Good Manufacturing Practice	<b>Ms</b>	mesyl
<b>GMP</b>	guanosine 5'-monophosphate	<b>MsCl</b>	methanesulphonyl chloride
<b>GTP</b>	guanosine 5'-triphosphate	<b>MWt</b>	molecular weight
<b>H-R</b>	histamine receptor	<b>N-Receptor</b>	nicotinic receptor
<b>HATU</b>	N-[(dimethylamino)-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i> ]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate	<b>NAD or NADH</b>	nicotinamide adenine dinucleotide
<b>HBA</b>	hydrogen bond acceptor	<b>NADP or NADPH</b>	nicotinamide adenine dinucleotide phosphate
<b>HBD</b>	hydrogen bond donor	<b>NaN(TMS)<sub>2</sub></b>	sodium bis(trimethylsilyl)amide
<b>HFC-134a</b>	1,1,1,2-tetrafluoroethane	<b>NBS</b>	N-bromosuccinimide
<b>HIV</b>	human immunodeficiency virus	<b>NCE</b>	new chemical entity
<b>HMG-CoA</b>	3-hydroxy-3-methylglutaryl-coenzyme A	<b>NDA</b>	New Drug Application
<b>HMPA</b>	hexamethylphosphoramide	<b>NH(TMS)<sub>2</sub></b>	bis(trimethylsilyl)amine
<b>HOBt</b>	1-hydroxybenzotriazole	<b>Ni(cod)<sub>2</sub></b>	bis(cyclooctadiene)nickel(0)
<b>HOMO</b>	highest occupied molecular orbital	<b>Ni(dppp)Cl<sub>2</sub></b>	dichloro(1,3-bis(diphenylphosphino)propane)nickel
<b>HPLC</b>	high performance liquid chromatography	<b>NIS</b>	N-iodosuccinimide
<b>17β-HSD1</b>	17β-dehydroxysteroid dehydrogenase type 1	<b>NME</b>	new molecular entity
<b>HTS</b>	high throughput screening	<b>NMP</b>	N-methylpyrrolidinone
<b>IC<sub>50</sub></b>	concentration of drug required to inhibit a target by 50%	<b>NMR</b>	nuclear magnetic resonance

<b>NNRTI</b>	non-nucleoside reverse transcriptase inhibitor	<b>RNA</b>	ribonucleic acid
<b>nor-BNI</b>	norbinaltorphimine	<b>rRNA</b>	ribosomal RNA
<b>NRPS</b>	non-ribosomal peptide synthase	<b>SAR</b>	structure–activity relationships
<b>NRTI</b>	nucleoside reverse transcriptase inhibitor	<b>SCAL</b>	safety catch acid-labile linker
<b>NSAID</b>	non-steroidal anti-inflammatory drug	<b>SOP</b>	standard operating procedure
<b>NVOC</b>	nitroveratryloxycarbonyl	<b>SPA</b>	scintillation proximity assay
<b>P</b>	partition coefficient	<b>SPE</b>	solid phase extraction
<b>PBS</b>	phosphate-buffered saline	<b>SPECT</b>	single photon emission computer tomography
<b>Pd/C</b>	palladium charcoal catalyst	<b>SSRI</b>	selective serotonin reuptake inhibitor
<b>Pd<sub>2</sub>(dba)<sub>3</sub></b>	tris(dibenzylideneacetone) dipalladium(0)	<b>TBAF</b>	tetrabutylammonium fluoride
<b>PEG</b>	polyethylene glycol	<b>TBDMS or TBS</b>	<i>tert</i> -butyldimethylsilyl
<b>PET</b>	positron emission tomography	<b>TCA</b>	tricyclic antidepressant
<b>Ph</b>	phenyl	<b>TFA</b>	trifluoroacetic acid
<b>PI</b>	protease inhibitor	<b>TfOH</b>	triflic acid or trifluorosulphonic acid
<b>PKS</b>	polyketide synthase	<b>THF</b>	tetrahydrofuran
<b>PLP</b>	pyridoxal phosphate	<b>TIPS</b>	triisopropylsilyl
<b>PMP</b>	1,2,2,6,6-pentamethylpiperidine	<b>TLC</b>	thin layer chromatography
<b>PPA</b>	polyphosphoric acid	<b>TMEDA</b>	tetramethylethylenediamine
<b>PPE</b>	polyphosphoric ethyl ester	<b>TMSCN</b>	trimethylsilyl cyanide
<b>PPI</b>	proton pump inhibitor	<b>(TMS)<sub>2</sub>NLi</b>	lithium bis(trimethylsilyl)amide
<b>PPTs</b>	pyridinium <i>para</i> -toluenesulphonate or pyridinium 4-toluenesulphonate	<b>TMSOMe</b>	methoxytrimethylsilane
<b>PTFE</b>	polytetrafluoroethylene	<b>T<sub>2</sub>O</b>	tritiated water
<b>P(o-Tol)<sub>3</sub></b>	tri( <i>o</i> -tolyl)phosphine	<b>o-Tol</b>	<i>ortho</i> -tolyl
<b>ptsa</b>	<i>para</i> -toluenesulphonic acid	<b>Tris</b>	tris(hydroxymethyl)aminomethane
<b>PyBOP</b>	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate	<b>Tris-HCl</b>	tris hydrochloride
<b>PyBrOP</b>	bromotripyrrolidinophosphonium hexafluorophosphate	<b>tRNA</b>	transfer RNA
<b>Q-phos</b>	pentaphenyl(di- <i>tert</i> -butylphosphino) ferrocene	<b>TsCN</b>	<i>para</i> -toluenesulphonyl cyanide or 4-toluenesulphonyl cyanide
<b>R</b>	symbol used to represent the rest of the molecule	<b>TsDAEN</b>	<i>N</i> -[2-amino-1,2-bis(4-methoxyphenyl)ethyl]-4-methylbenzenesulphonamide
<b>Rapid</b>	random peptide integrated discovery	<b>UTI</b>	urinary tract infection
<b>RedAl or Red-Al</b>	sodium bis(2-methoxyethoxy) aluminiumhydride	<b>Vdw</b>	van der Waals
		<b>Voc-Cl</b>	vinylloxycarbonyl chloride
		<b>X</b>	halogen or leaving group
		<b>Z</b>	benzyloxycarbonyl



# Brief contents

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# Detailed contents

## Abbreviations and acronyms

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## PART A Concepts

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