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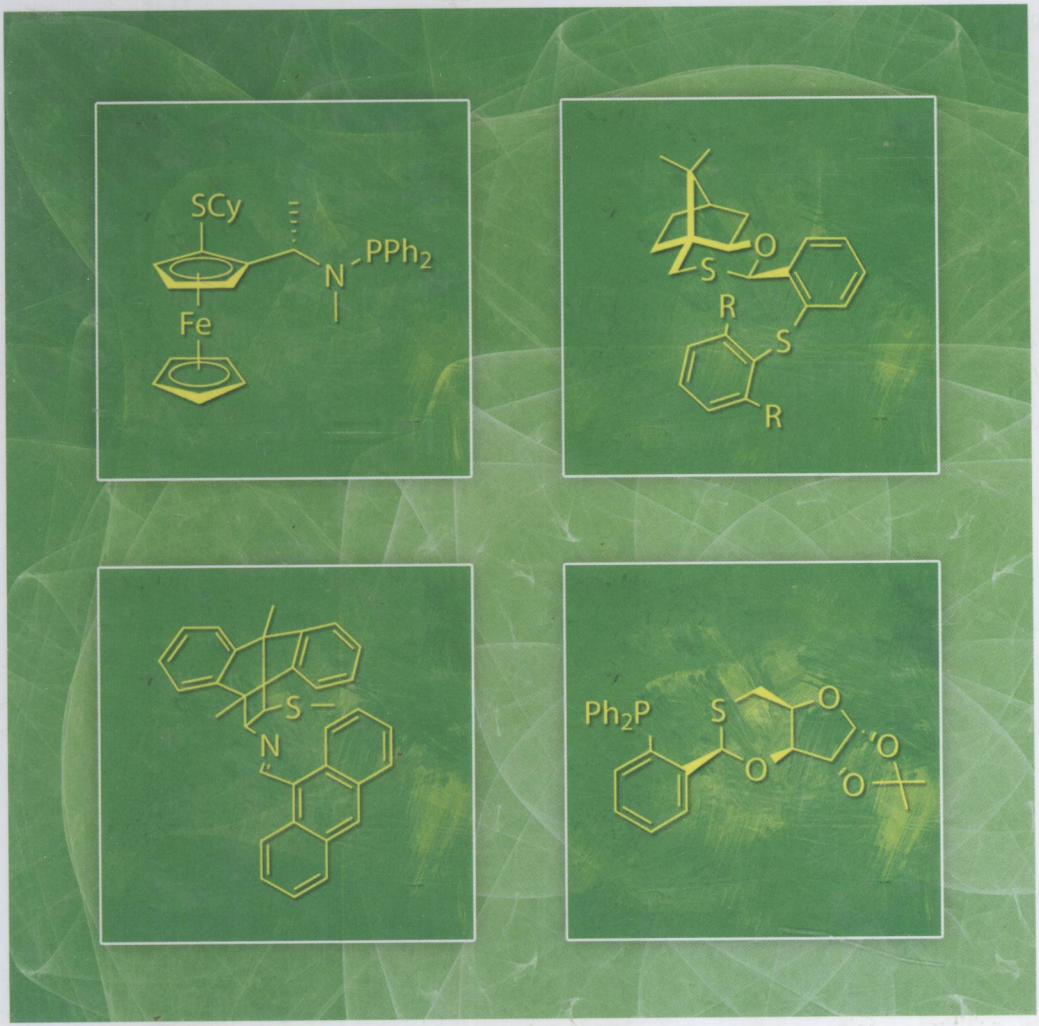
Hélène Pellissier

Chiral Sulfur Ligands

Asymmetric Catalysis



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Hélène Pellissier
CNRS and Paul Cézanne University Aix-Marseille III, Institute of Molecular Sciences, Marseille, France

RSC Publishing

RSC Catalysis Series No. 2

ISBN: 978-1-84755-924-1
ISSN: 1757-6725

A catalogue record for this book is available from the British Library

Published by The Royal Society of Chemistry,
Thomas Graham House, Science Park, Milton Road,
Cambridge CB4 0WF, UK

Registered Charity Number 207890

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In loving memory of Cyril and Valérie Pellissier
Dedicated to their so little children, Tess and Clément

Preface

The preparation of chiral compounds is an important and challenging area of contemporary synthetic organic chemistry, mainly in connection with the fact that most natural products are chiral and their physiological or pharmacological properties depend upon their recognition by chiral receptors, which will interact only with molecules of the proper absolute configuration. The use of chiral drugs in enantiopure form is now a standard requirement for virtually every new chemical entity, and the development of new synthetic methods to obtain enantiopure compounds has become a key goal for pharmaceutical companies. Indeed, the growing economic importance of chiral compounds has spurred major research efforts towards the selective preparation of chiral compounds. The synthesis of optically active chiral compounds, which play an important role in medicine and materials, is one of the most fascinating aspects of modern organic synthesis. Over the last three decades an explosive growth of research in the field of asymmetric synthesis has occurred. Asymmetric synthesis constitutes one of the main strategies to gain access to enantioenriched compounds, involving the use of either chiral auxiliaries or catalysts derived preferentially from cheap chiral pool sources. In particular, asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry.

In this context, the development of chiral ligands for asymmetric catalytic reactions is a subject of considerable interest in the field of asymmetric synthesis. Extensive efforts have been made for the development of new advantageous chiral ligands applicable in a broad variety of reaction types and their preparation continues to be an important area of synthetic organic research. Indeed, the ligand design is becoming an increasingly important part of the synthetic activity in chemistry. This is, of course, because of the subtle control that ligands exert on the metal centre to which they are coordinated. The impressive number of reports dealing with the use of chiral

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sulfur-containing ligands for asymmetric catalysis is well representative of the success of such ligands to promote numerous catalytic transformations. Nowadays, these ligands have become fairly renowned competitors to more usual phosphorus- or nitrogen-containing ligands. Indeed, chiral sulfur-containing ligands represent a highly efficient class of ligands applicable in a broad variety of reaction types, also in view of some peculiar properties, which differentiate them from more popular ligands such as phosphorus- or nitrogen-containing ligands. In particular, the stereoelectronic assistance of organosulfur functionalities and the possibility of stereocontrol through stereogenic sulfur atoms can provide interesting results in many applications. The key advantages of these new types of ligands are their easy synthesis, mostly starting from readily available commercial compounds, and their high stability, which allows easy storage and handling, especially compared to phosphine derivatives. Whereas the synthesis of chiral phosphorus ligands is often complex and difficult, the preparation of chiral sulfur compounds is much more convenient. Consequently, a wide diversity of chiral sulfur-containing ligands, more than forty different classes, is easily available either directly from the chiral pool or by facile modifications of other heteroatomic ligands. Many of the sulfur-containing ligands have only recently appeared in the literature, and it is clear that their application in asymmetric catalysis will undoubtedly increase in the near future for a number of additional asymmetric reactions, due in part to their easy synthesis. Moreover, due to their great stability, asymmetric heterogeneous catalysis seems to be a good way to develop the potential of these ligands in an economic and environmentally friendly manner.

The goal of this book is to provide to researchers and professionals of academic and industrial laboratories a broad overview of the works concerning the use of chiral sulfur-containing ligands in one of the most important focal areas in organic synthesis, asymmetric catalysis. The book is divided into ten chapters corresponding to the different types of reactions based on the use of complexes containing chiral sulfur ligands, such as allylic substitution, conjugate addition, addition of organometallic reagents to aldehydes, addition of organozinc reagents to ketones, Diels–Alder reaction, cyclopropanation, Heck-type reactions, hydrogenation, hydrogen transfer and miscellaneous reactions.

Abbreviations

Ac:	acetyl
Acac:	acetylacetone
Ad:	adamantyl
AIBN:	2,2′-azobisisobutyronitrile
Ar:	aryl
BDMPB:	2,6-bis(dimethylphenoxy)borane
BDPP:	2,4-bis(diphenylphosphino)pentane
BINAM:	1,1′-binaphthalenyl-2,2′-diamine
BINAP:	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Binas:	1,1′-binapthalene-2,2′-dithiol
BINOL:	1,1′-bi-2-naphthol
BITIANP:	2,2′-bis(diphenylphosphino)-3,3′-bi(benzo[b]thiophene)
BITIOP:	4,4′-bis(diphenylphosphino)-3,3′-bithiophene
Bn:	benzyl
Boc:	tert-butoxycarbonyl
Box:	bisoxazoline
BSA:	bis-(trimethylsilyl)acetamide
Bu:	butyl
Bz:	benzoyl
Cbz:	benzyloxycarbonyl
Chiraphos:	2,3-bis(diphenylphosphine)butane
Cod:	cyclooctadiene
Cp:	cyclopentadienyl
CPG:	controlled-pore glass
Cy:	cyclohexyl
DABCO:	1,4-diazabicyclo[2.2.2]octane
DAIB:	dimethylamino isoborneol
Dba:	(E,E)-dibenzylideneacetone
de:	diastereomeric excess
Dec:	decyl
DIBAL:	diisobutylaluminium hydride
DIOP:	2,3-(isopropylidenedioxy)-2,3-dihydroxy-l,4-bis(diphenylphosphanyl)butane)
DIOS:	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(methylsulfinyl)butane

DMF:	dimethylformamide
DMSO:	dimethylsulfoxide
DOSP:	N-p-dodecylbenzenesulfonylprolinate
DPEN:	1,2-diphenylethylenediamine
Dppe:	1,2-bis(diphenylphosphine)ethane
Dppp:	1,3-bis(diphenylphosphine)propane
EDA:	ethyl diazoacetate
ee:	enantiomeric excess
Et:	ethyl
Fm:	fluorenylmethyl
Fu:	furyl
Hept:	heptyl
Hex:	hexyl
HMPA:	hexamethylphosphoramide
HOCSAC:	bis(camphorsulfonyl)-substituted trans-cyclohexane-1,2-diamine ligand
L:	ligand
Me:	methyl
Menth:	menthyl
Mes:	mesyl
MTBE:	methyl tert-butyl ether
NADH:	nicotinamide adenine dinucleotide
NADPH:	nicotinamide adenine dinucleotide phosphate
Naph:	naphthyl
Nbd:	norbornadiene
NMO:	N-methylmorpholine N-oxide
NOBIN:	2-amino-2-hydroxy-1,1′-binaphthalene
Non:	nonyl
Nu:	nucleophile
Oct:	octyl
Pent:	pentyl
Ph:	phenyl
PHOX:	phosphinooxazoline
Piv:	pivalate
PMHS:	polymethylhydrosiloxane
Pr:	propyl
Py:	pyridine
SES:	2-(trimethylsilyl)ethanesulfonyl
Siam:	bis(sulfinyl)imidoamidine
Suc:	succinimide
TADDOL:	a,a,a′,a′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol
TBAB:	tetra-n-butylammonium bromide
TBDPS:	tert-butyldiphenylsilyl
TBS:	tert-butyldimethylsilyl
TEA:	triethylamine
Tf:	trifluoromethanesulfonyl

TFA:	trifluoroacetic acid
Tfbb:	tetrafluorobenzobarrelene
THF:	tetrahydrofuran
Thio:	thiophene
TIPS:	triisopropylsilyl
TMBTP:	4,4′-bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene
TMS:	trimethylsilyl
Tol:	tolyl
Tr:	triphenylmethyl (trityl)
Ts:	4-toluenesulfonyl (tosyl)

Contents

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General Introduction

The preparation of chiral compounds is an important and challenging area of contemporary synthetic organic chemistry.[1] Asymmetry is ubiquitous in every part of Nature and has a great impact on many fields, not only chemistry but also even the arts. In pharmaceuticals, as well as in related industries,[2] asymmetry plays an important role, since both enantiomers of a determinate drug do not necessarily have the same activity. The disastrous incident of thalidomide, in which each enantiomer has a totally different biological effect in humans, has had an impact on the society. The public demands for avoiding similar tragedies have been transferred first to the pharmaceutical and related companies, mainly through the questions of regulatory agencies, and second to the scientific community, which in turn has to provide highly efficient and reliable methods of asymmetric synthesis. In fact, these demands have already had an important response, since the worldwide sales of single-enantiomer drugs are continuously growing. For example, approximately 50 per cent of the drugs launched from 1992 to 2003 contain at least one stereogenic element and indeed, there appeared to be an increasing trend in the production of such drugs.[3] In addition, the policy of regulatory agencies (FAD, EMEA, *etc.*) on stereoisomers has triggered a move away from the development of racemates to the development of single enantiomer drugs. Moreover, the additional cost of producing a single enantiomer is almost always lower than the development work that is necessary to elucidate the toxicological and pharmaceutical profile of the undesired enantiomer. Among the different strategies of asymmetric synthesis, enantioselective approaches have many advantages compared to other strategies. For example, the annoying attachment and detachment of chiral auxiliaries is not necessary. In addition, the atom efficiency of preparing an enantiomer by enantioselective catalysis is much higher than either the diastereoselective or the racemate resolution approach. The development of efficient methods for enantioselective synthesis remains at the centre of modern-day organic

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chemistry; as such methods have many important applications, from the total synthesis of natural products[4] to the preparation of analogues of lead compounds in the pharmaceutical industry. In particular, catalytic asymmetric synthesis is a valuable and general method for preparing optically active substances.[5] In contrast to stoichiometric methods, the chiral information of a ligand molecule is transferred to several product molecules, through a catalytic cycle; in addition, the reactivity of the active species bearing the chiral ligand is, in general, enhanced, compared to that of the nonchiral ligand, due to the so-called "ligand acceleration effect".[6] Among the enantioselective catalytic transformations, those involving carbon–carbon bond formation are probably the most attractive for synthesis, compared to functional group conversions on a given carbon skeleton. Asymmetric catalysis is a topic of increasing interest and is one of the most important focal areas in organic synthesis. In the last three decades, the number and the quality of reports dealing with asymmetric synthesis have undergone a true revolution with the coronation being the awarding of the 2001 Nobel Prize in Chemistry to Professors Sharpless, Knowles, and Noyori for their studies on enantioselective synthesis. In particular, the development of chiral ligands for asymmetric catalytic reactions is a subject of considerable interest in the field of asymmetric synthesis.[7] Much attention has been devoted in the pharmaceutical field to catalytic asymmetric synthesis for the preparation of biologically active chiral compounds with complete optical purity and high efficiency.[8] Extensive efforts have been made for the development of new advantageous chiral ligands applicable in a broad variety of reaction types,[9] and their preparation continues to be an important area of synthetic organic research.[10,11]

Practical asymmetric catalysis using transition-metal complexes was initially inspired by the studies of Kagan[12] and Knowles.[13] Their important results, based on the use of chiral phosphines as ligands for asymmetric hydrogenation, have induced a tremendous amount of work, dealing with the synthesis and use of new chiral phosphine-containing complexes as catalysts. Numerous catalytic asymmetric reactions have been discovered over the last 30 years, often with spectacular results in terms of efficiency and selectivity, allowing the access to numerous biologically important molecules. Nevertheless, the contribution of asymmetric catalysis in the overall production of chiral chemicals is much lower than originally expected, which is surprising given the huge amount of work devoted to this subject. Factors such as the price of the catalyst precursor and the difficulties encountered in the separation and recycling of the catalyst are responsible for this lack of practical application. Only a few processes have, however, permitted high turnovers. Apart from these economic considerations, it is almost impossible to recycle, for example, phosphine-containing catalysts, due to their low stability towards oxidation. Indeed, the chemical and economic characteristics of these catalysts were partly responsible for problems encountered in the development of catalytic asymmetric processes in general. The field of asymmetric catalysis is witnessing an ever-growing interest, and several highly efficient catalytic methods are

nowadays known in the literature. Despite the positive results, knowledge in this field is still limited, and much work will be needed to make this methodology a comprehensive and well-established technique. The nature of the ancillary ligands used for a given metal-catalysed process is central, with chiral phosphorus- and nitrogen-based ligands occupying an incontestable leading position. In particular, chiral C_1- and C_2-symmetric phosphorus ligands possessing the axially chiral 1,1′-binaphthyl framework, are among the most widely used chiral ligands.[14] Moreover, oxazolines have also played a key role as efficient ligands for various types of catalytic asymmetric reactions.[15]

New classes of ligands that might offer new opportunities for applications or provide insight into fundamental chemical processes are always of interest. One relatively rare class of ligands is that in which stereogenicity resides not at carbon atoms, but at heteroatomic sites such as sulfur atoms. Compared to ligands having phosphorus, nitrogen or oxygen as donor atoms, sulfur-containing chiral mixed ligands have received much less attention. A possible reason is that sulfur has a tendency to poison transition-metal catalysts. On the other hand, the sulfur moiety creates additional possibilities compared to nitrogen- and oxygen-containing ligands since sulfur can become chiral when coordinated to a metal. Compared to phosphorus, sulfur has less donor and acceptor character. In addition to these electronic considerations, the sulfur atom, in thioether ligands for example, has only two substituents, which can create a less hindered environment than trivalent phosphorus. The formation of mixtures of diastereomeric complexes and the difficulty to control their interconversion in solution have been regarded as a problem for asymmetric induction in catalytic reactions. Nevertheless, in recent years, chiral bidentate S-donor ligands, in particular, have proved to be as useful as other classical asymmetric ligands, especially when combined with other donor atoms.[16] Whereas the synthesis of chiral phosphorus ligands is often complex and difficult, the preparation of chiral sulfur compounds is more convenient. In addition, sulfur possesses higher oxidation states available and can form some compounds that have different functional groups, such as thiol, sulfide, thioamide, sulfoxide, sulfinyl, thiocarbonyl and thiocarbamide. Furthermore, it's empty relatively low-energy *d* orbitals can accept back-donation of π-electron density from the metal, leading to a stabilisation of the metal–S bond. On complexation to a metal, chirality can be induced at sulfur.[17] These key structural features exemplify very rich coordination chemistry towards transition metals and they serve as powerful stereodirecting ligands in asymmetric synthesis. In addition to the vast knowledge on sulfur-metal interactions in coordination chemistry,[18] the study of sulfur-containing ligands has increased considerably over the last three decades.[19] Indeed, more than 40 different classes of chiral sulfur compounds have been described in the literature, and a large number of useful procedures for the synthesis of enantiomerically pure sulfur compounds have been developed.[20] The coordination chemistry of sulfur ligands has shown a unique variety of structures with most of the transition metals in different oxidation states.[18,21]