Aziridines and Epoxides in Organic Synthesis

Edited by
Andrei K. Yudin

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To Jovana

Foreword

Epoxides have fascinated me since my days as an undergraduate at the Massachusetts Institute of Technology. I vividly remember taking a course in organic chemistry, watching an inspiring (if unconventional) professor, Barry Sharpless, perform a demonstration in which a cage that contained a collection of gypsy moths was opened, allowing them to respond to the presence of a nearby sample of (+)-disparlure (an epoxide-containing sex pheromone for the gypsy moth). The result was memorable, and it was in fact this class that led to my decision to pursue a career in organic chemistry.

Of course, (+)-disparlure is only one of the many natural products that contain either an epoxide or an aziridine. Important and intriguing biologically active compounds such as the mitomycins, azinomycins, and epothilones also bear these functional groups.

Interest in epoxides and aziridines has been amplified because, not only are they significant synthetic endpoints, but they are also tremendously useful synthetic intermediates. Due to the strain associated with the three-membered ring, they are "spring-loaded" for reactions with nucleophiles, allowing a wide array of powerful functionalizations to be achieved. Thus, ring-openings of aziridines and epoxides have been applied industrially to produce a variety of bulk chemicals, including polyethylenimine, ethylene glycol, and epoxy resins. Furthermore, aziridines and epoxides serve as versatile intermediates in natural product and pharmaceutical synthesis. Reactions with a broad range of nucleophiles proceed cleanly with excellent regioselectivity and/or stereoselectivity, furnishing products that bear useful amino and hydroxyl groups.

Discovering effective new methods for the synthesis of aziridines and epoxides, as well as developing novel transformations of these heterocycles, has been an extremely active area of research in recent years. The publication of this book, Aziridines and Epoxides in Organic Synthesis, is therefore timely, since there have been no monographs on this topic in quite some time. Prof. Andre Yudin has brought together a set of insightful reviews by leading researchers that nicely illustrate a rich diversity of chemistry. The twelve chapters cover a broad spectrum, including methods for the synthesis of aziridines and epoxides, functionalization reactions, applications in natural product synthesis, and biosynthesis studies. I anticipate that this highly readable book will be the "go to" resource for those

interested in learning about the state-of-the-art in this important field. Equally significantly, the monograph will no doubt inspire further exciting developments in this area.

Gregory C. Fu, Cambridge, MA
October 2005

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Preface

Aziridines and epoxides are among the most versatile intermediates in organic synthesis. In addition, a number of biologically significant molecules contain these strained three-membered rings within their structures. The synthetic community has been fascinated with prospects of selective synthesis and transformations of aziridines and epoxides. Recent years have witnessed a number of important advances in this area and I felt that a book that summarizes these achievements would be a valuable addition to the chemistry literature. I was very glad to receive enthusiastic support from my colleagues from around the World. Roughly divided into equal number of chapters dedicated to epoxides and aziridines, this volume will serve as a useful resource. The synthesis part covers additions to aldehydes and imines, olefin transformations, cyclizations, and metal catalysis. The applications encompass chemistry of vinyl aziridines and epoxides, aziridinecarboxylates and phosphonates, metalated epoxides and aziridines, asymmetric ring opening chemistry, complex target-oriented synthesis, and click chemistry. Another important area discussed in this book is the biosynthesis of aziridines and epoxides.

This project has turned into a wonderful compilation of outstanding manuscripts and I am very grateful to the authors who contributed to it. Last, but not least, I want to express my gratitude to Dr. Evgenii Blyumin, Iain Watson, and Lily Yu for their valuable editorial comments at the revision stages.

Andrei K. Yudin
Toronto, November 2005

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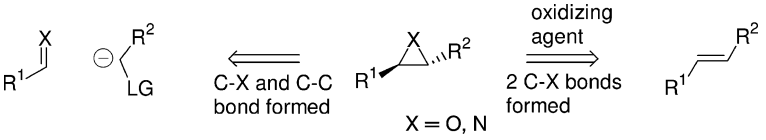
1
Asymmetric Synthesis of Epoxides and Aziridines from Aldehydes and Imines

Varinder K. Aggarwal, D. Michael Badine, and Vijayalakshmi A. Moorthie

1.1
Introduction

Epoxides and aziridines are strained three-membered heterocycles. Their synthetic utility lies in the fact that they can be ring-opened with a broad range of nucleophiles with high or often complete stereoselectivity and regioselectivity and that 1,2-difunctional ring-opened products represent common motifs in many organic molecules of interest. As a result of their importance in synthesis, the preparation of epoxides and aziridines has been of considerable interest and many methods have been developed to date. Most use alkenes as precursors, these subsequently being oxidized. An alternative and complementary approach utilizes aldehydes and imines. Advantages with this approach are: *i*) that potentially hazardous oxidizing agents are not required, and *ii*) that both C–X and C–C bonds are formed, rather than just C–X bonds (Scheme 1.1).

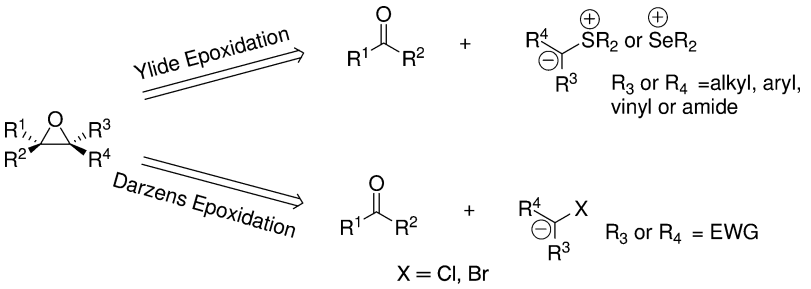


Scheme 1.1

This review summarizes the best asymmetric methods for preparing epoxides and aziridines from aldehydes (or ketones) and imines.

1.2
Asymmetric Epoxidation of Carbonyl Compounds

There have been two general approaches to the direct asymmetric epoxidation of carbonyl-containing compounds (Scheme 1.2): ylide-mediated epoxidation for the construction of aryl and vinyl epoxides, and α-halo enolate epoxidation (Darzens reaction) for the construction of epoxy esters, acids, amides, and sulfones.



Scheme 1.2

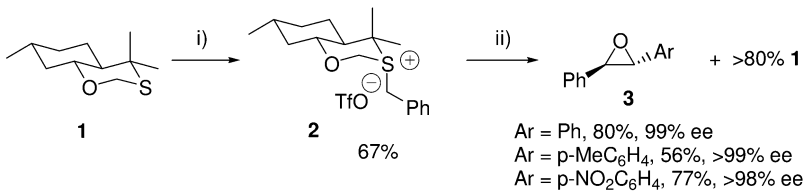
1.2.1 Aryl, Vinyl, and Alkyl Epoxides

1.2.1.1 Stoichiometric Ylide-mediated Epoxidation

Solladié-Cavallo's group used Eliel's oxathiane **1** (derived from pulegone) in asymmetric epoxidation (Scheme 1.3) [1]. This sulfide was initially benzylated to form a single diastereomer of the sulfonium salt **2**. Epoxidation was then carried out at low temperature with the aid of sodium hydride to furnish diaryl epoxides **3** with high enantioselectivities, and with recovery of the chiral sulfide **1**.

Using a phosphazene (EtP_2) base, they also synthesized aryl-vinyl epoxides **6a-c** (Table 1.1) [2]. The use of this base resulted in rapid ylide formation and efficient epoxidation reactions, although it is an expensive reagent. There is potential for cyclopropanation of the alkene when sulfur ylides are treated with α,β-unsaturated aldehydes, but the major products were the epoxides, and high selectivities could be achieved (Entries 1–4). Additionally, heteroaromatic aryl-epoxides could be prepared with high selectivities by this procedure (Entries 5 and 6) [3]. Although high selectivities have been achieved, it should be noted that only one of the two enantiomers of **1** is readily available.

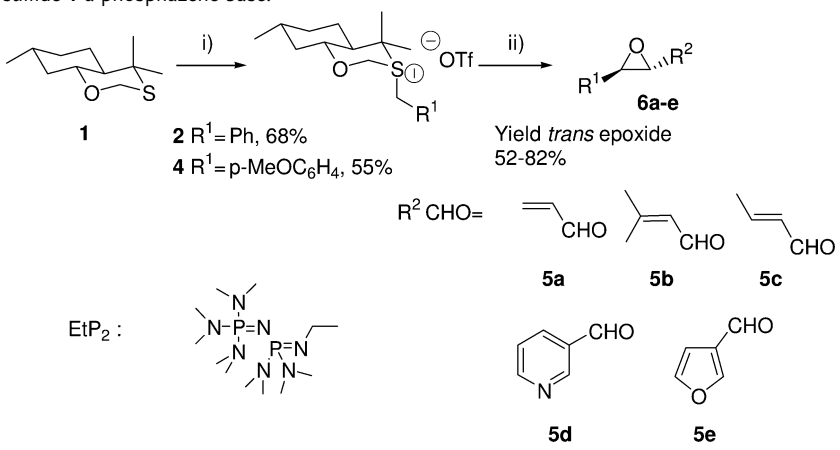
The Aggarwal group has used chiral sulfide **7**, derived from camphorsulfonyl chloride, in asymmetric epoxidation [4]. Firstly, they preformed the salt **8** from either the bromide or the alcohol, and then formed the ylide in the presence of a range of carbonyl compounds. This process proved effective for the synthesis of aryl-aryl, aryl-heteroaryl, aryl-alkyl, and aryl-vinyl epoxides (Table 1.2, Entries 1–5).



i) BnOH, Tf_2O, pyridine, CH_2Cl_2, -10 °C; ii) NaH, CH_2Cl_2, ArCHO, -40 °C, 24 - 48 h.

Scheme 1.3

Table 1.1 Synthesis of aryl-vinyl epoxides by use of chiral sulfide **1** a phosphazene base.



i) BnOH, Tf_2O, pyridine, CH_2Cl_2, -10 °C; ii) EtP_2, **5a-e** (R^2CHO), -78 °C, CH_2Cl_2.

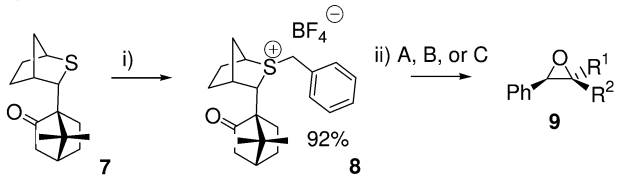
Entry	R^1 (ylide)	R^2CHO	Epoxide: epoxycyclop.: cyclop.	Epoxide *trans: cis*	Epoxide *ee trans* (*cis*) (%)
1	Ph	**5a**	77:11:12	100:0	97
2	*p*-$MeOC_6H_4$	**5a**	100:0:0	77:23	95 (98)
3	Ph	**5b**	100:0:0	97:3	100
4	Ph	**5c**	100:0:0	97:3	100
5	Ph	**5d**	–	100:0	96.8
6	Ph	**5e**	–	100:0	99.8

Until this work, the reactions between the benzyl sulfonium ylide and ketones to give trisubstituted epoxides had not previously been used in asymmetric sulfur ylide-mediated epoxidation. It was found that good selectivities were obtained with cyclic ketones (Entry 6), but lower diastereo- and enantioselectivities resulted with acyclic ketones (Entries 7 and 8), which still remain challenging substrates for sulfur ylide-mediated epoxidation. In addition they showed that aryl-vinyl epoxides could also be synthesized with the aid of α,β-unsaturated sulfonium salts **10a-b** (Scheme 1.4).

1.2.1.2 **Catalytic Ylide-mediated Epoxidation**

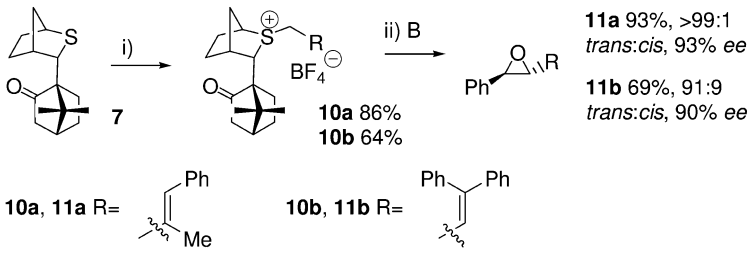
The first attempt at a catalytic asymmetric sulfur ylide epoxidation was by Furukawa's group [5]. The catalytic cycle was formed by initial alkylation of a sulfide (**14**), followed by deprotonation of the sulfonium salt **15** to form an ylide **16** and

Table 1.2 Application of the chiral sulfide **7** in asymmetric epoxidations.



i) BnBr, $AgBF_4$, CH_2Cl_2; ii) **A**: KOH, R^1R^2CO, MeCN:H_2O (9:1), rt ; **B**: EtP_2 R_1R_2CO, CH_2Cl_2, -78 °C; **C**: KHMDS, THF, -78 °C.

Entry	R^1COR^2	Method	Yield (%)	d. r. *trans* : *cis*	*ee* trans (%)
1	PhCOH	A	75	98:2	98
2	2-PyrCOH	B	88	98:2	99
3	C_4H_9COH	C	87	90:10	>99
4	CH_2=C(Me)COH	B	52	>99:1	95
5	(*E*)-MeCH=CH_2COH	B	90	>99:1	95
6	cyclohexanone	B	85	–	92
7	$MeCOC_6H_4$-p-NO_2	B	73	>1:99	71
8	MeCOPh	B	77	33:67	93 (50)

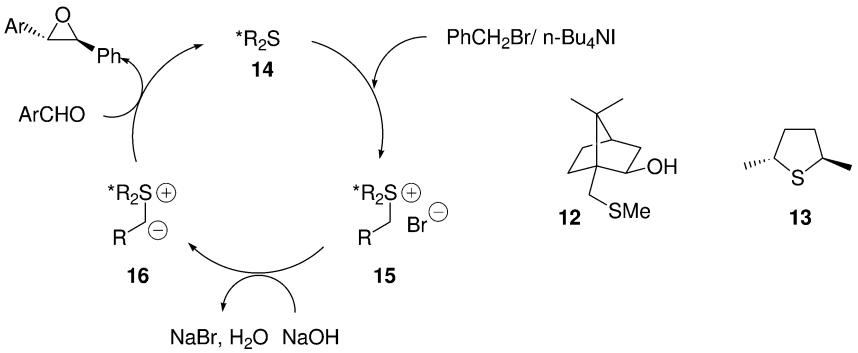


i) RCH_2OH, HBF_4, Et_2O; ii) **B**: EtP_2, PhCHO, CH_2Cl_2, -78 °C.

Scheme 1.4

subsequent reaction with an aldehyde to furnish the epoxide with return of the sulfide **12** (Scheme 1.5). However, only low yields and selectivities resulted when the camphor-derived sulfide **12** was employed. Metzner improved the selectivity of this process by using the C_2 symmetric sulfide **13** [6].

Although reactions required 2 days to reach completion in the presence of stoichiometric amounts of sulfide, they became impracticably long (28 days) when 10 % sulfide was employed, due to the slow alkylation step. The alkylation step was

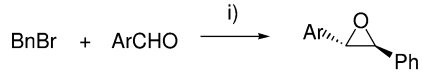


Scheme 1.5

accelerated upon addition of iodide salts, however, and the reaction times were reduced (Table 1.3). The yields and selectivities are lower than for the corresponding stoichiometric reactions (compare Entry 1 with 2, Entry 4 with 5, and Entry 6 with 7). The use of iodide salts proved to be incompatible with allylic halides, and so stoichiometric amounts of sulfide were required to achieve good yields with these substrates [7].

Metzner et al. also prepared the selenium analogue **17** of their C_2 symmetric chiral sulfide and tested it in epoxidation reactions (Scheme 1.6) [8]. Although good enantioselectivities were observed, and a catalytic reaction was possible without the use of iodide salts, the low diastereoselectivities obtained prevent it from being synthetically useful.

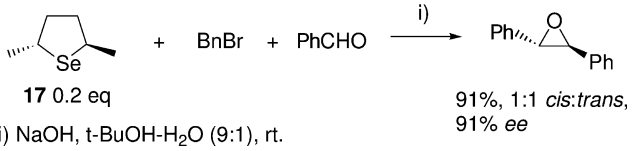
Table 1.3 Catalytic ylide-mediated epoxidations.



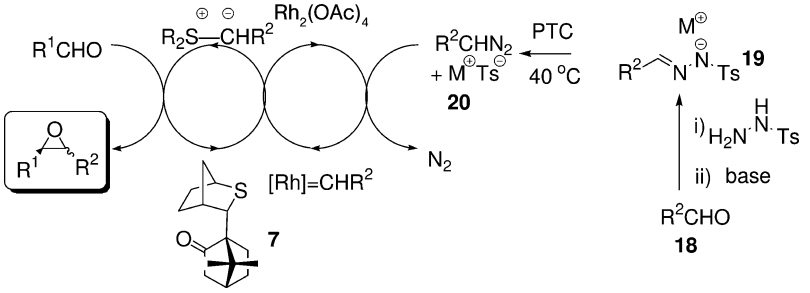
i) NaOH,n-Bu_4NI, **13**, t-BuOH-H_2O (9:1), rt.

Entry	Ar in ArCHO	Eq. 13	Time (days)	Yield (%)	d.r.	*ee* (%)
1	PhCHO	1[a]	1	92	93:7	88
2	PhCHO	0.1	4	82	93:7	85
3	*p*-ClC_6H_4	0.1	6	77	80	72
4	cinnamyl	1[a]	2	93	98:2	87
5	cinnamyl	0.1	6	60	89:11	69
6	2-thiophenyl	1[a]	4	90	91:9	89
7	2-thiophenyl	0.1	6	75	88:12	80

[a] Without *n*-Bu_4NI.



Scheme 1.6



Scheme 1.7

Aggarwal and co-workers have developed a catalytic cycle for asymmetric epoxidation (Scheme 1.7) [9]. In this cycle, the sulfur ylide is generated through the reaction between chiral sulfide **7** and a metallocarbene. The metallocarbene is generated by the decomposition of a diazo compound **20**, which can in turn be generated *in situ* from the tosylhydrazone salt **19** by warming in the presence of phase-transfer catalyst (to aid passage of the insoluble salt **19** into the liquid phase). The tosylhydrazone salt can also be generated *in situ* from the corresponding aldehyde **18** and tosylhydrazine in the presence of base.

This process thus enables the coupling of two different aldehydes together to produce epoxides in high enantio- and diastereoselectivities. A range of aldehydes have been used in this process with phenyl tosylhydrazone salt **19** (Table 1.4) [10]. Good selectivities were observed with aromatic and heteroaromatic aldehydes (Entries 1 and 2). Pyridyl aldehydes proved to be incompatible with this process, presumably due to the presence of a nucleophilic nitrogen atom, which can compete with the sulfide for the metallocarbene to form a pyridinium ylide. Aliphatic aldehydes gave moderate yields and moderate to high diastereoselectivities (Entries 3 and 4). Hindered aliphatic aldehydes such as pivaldehyde were not successful substrates and did not yield any epoxide. Although some α,β-unsaturated aldehydes could be employed to give epoxides with high diastereo- and enantioselectivities, cinnamaldehyde was the only substrate also to give high yields (Entry 5). Sulfide loadings as low as 5 mol% could be used in many cases.

Benzaldehyde was also treated with a range of tosylhydrazone salts (Table 1.5). Good selectivities were generally observed with electron-rich aromatic salts (Entries 1–3), except in the furyl case (Entry 7). Low yields of epoxide occurred when a hindered substrate such as the mesityl tosylhydrazone salt was used.