CHIRAL SULFOXIDES: SYNTHESIS AND UTILITY

Andrew Young April 24, 2008

INTRODUCTION

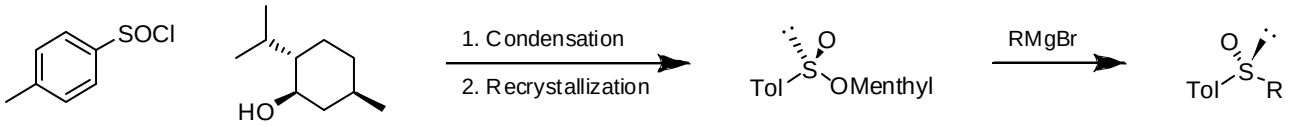
The past two decades have seen an explosion in interest in the synthesis and utility of molecules containing a stereogenic sulfur center.[1] An important subclass of this category is the sulfoxides. Though this structural motif is typically represented in Lewis structures as analogous to a carbonyl moiety, the sulfur atom of the sulfoxide is in fact a stereogenic center when $R_1 \neq R_2$ (Fig. 1). The oxygen and sulfur do not share a typical p-orbital pi bond which would enforce a planar conformation, but rather the oxygen donates electron density from a lone pair into a d-orbital of sulfur. This d-π bonding allows the sulfur to assume tetrahedral sp^3 hybridization, with a lone pair of electrons from sulfur as "place holders" in the fourth quadrant. Sulfoxides are conformationally stable at room temperature and therefore can be separated into pure enantiomers. The barrier to inversion via a bipyramidal intermediate for most sulfoxide compounds is in the range of 38-41 kcal/mol.[2] Sulfoxides will only racemize under rather harsh conditions, including temperatures in excess of 200°C, irradiation to induce C-S bond scission, and radical transfer reagents.

Figure 1

Sulfoxides are found in a variety of natural products. They have also been employed as chiral auxiliaries in a range of reaction classes, and more recently as chiral ligands. Sulfur is well-suited to the role of an agent for transfer of chirality for several reasons. The faces of a sulfoxide are highly differentiated due to the large steric difference between its substituents, which range from an electron lone pair to large alkyl groups like *tert*-butyl. Both sulfur and oxygen have lone pairs of electrons available to coordinate to Lewis acidic functionality, often promoting highly ordered transition states. Finally, sulfur can readily form covalent bonds, including to heteroatoms, and can be cleaved under relatively mild conditions. These properties have inspired considerable investigation into the synthetic applications of sulfoxides. A diverse array of techniques for the synthesis of enantiomerically enriched sulfoxides has been developed. These methods generally fall into two categories: chiral auxiliary-directed functionalizations and catalytic enantioselective oxidations. The greater availability of chiral sulfoxides in turn spurs further investigations into their utility.

CHIRAL AUXILIARY-BASED METHODOLOGIES & APPLICATIONS

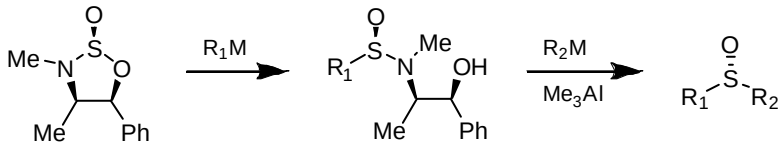
The most straightforward route to enantiomerically enriched sulfoxides involves preparation and



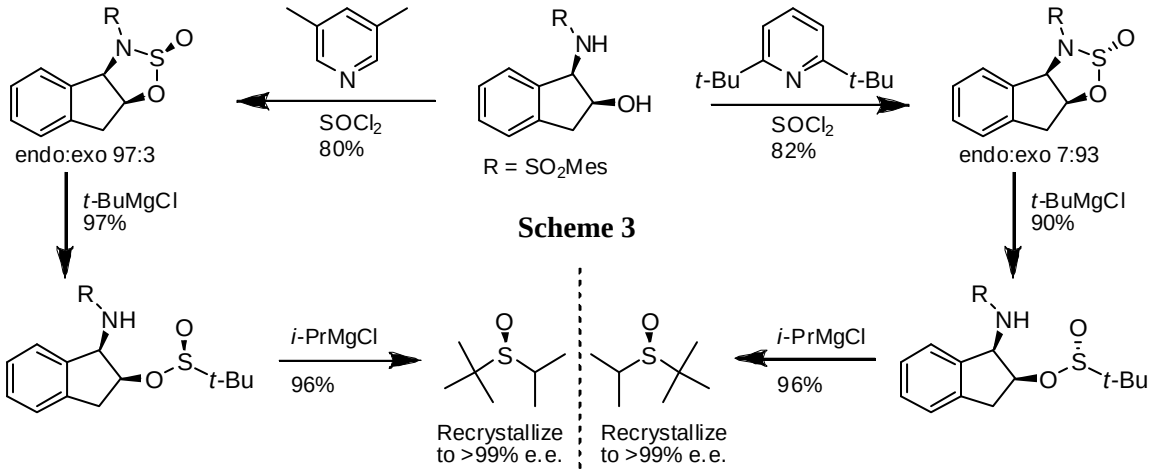
Scheme 1

substitution of a pure diastereomer using a chiral reagent. Following pioneering work by Gilman on the attack by Grignard reagents on sulfonic esters,[3] Andersen reported the first practical synthesis of chiral sulfoxides in 1962 (Scheme 1).[4] Condensation of toluene sulfinyl chloride with optically pure (-)-menthol yields a mixture of diastereomers which can be separated by recrystallization. Nucleophilic attack by an organomagnesium halide reagent displaces mentholate with clean inversion at the sulfur center. Though this is still a widely used method, it suffers from limitations. The menthol sulfinate ester can only be recrystallized efficiently if it bears an aryl substituent, so dialkyl sulfoxides are not accessible by this method. Second, the initial condensation proceeds without diastereoselectivity. Though Solladié and coworkers have developed an epimerization equilibration method to improve the yield of the desired diastereomer,[5] repeated recrystallizations are often necessary.

Wuld and Lee pioneered the use of cyclic oxathiazolidines derived from ephedrine to obtain chiral sulfoxides through two sequential nucleophilic attacks (Scheme 2).[6] However this methodology was often stymied by an unreactive S-N bond, which Benson and Snyder found had to be activated by strong Lewis acids such as trimethyl aluminum in order to achieve good reactivity.[7] Senanayake and coworkers reasoned that replacing the methyl group on nitrogen with an electron withdrawing group could activate the S-N bond and perhaps even reverse the selectivity of S-N versus S-O bond cleavage.[8] This vision was realized using the N-sulfonylated amino



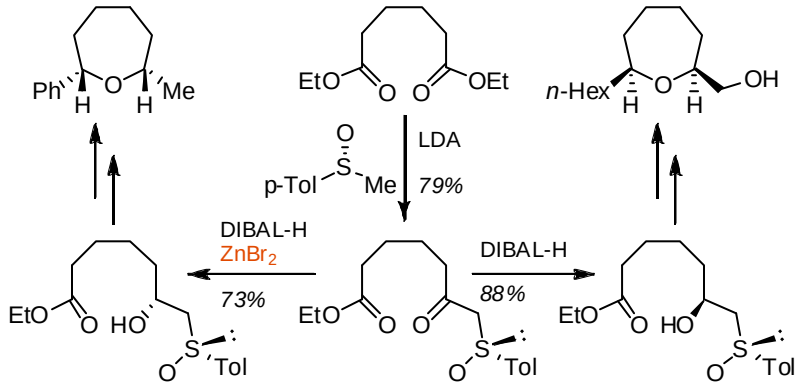
Scheme 2



Scheme 3

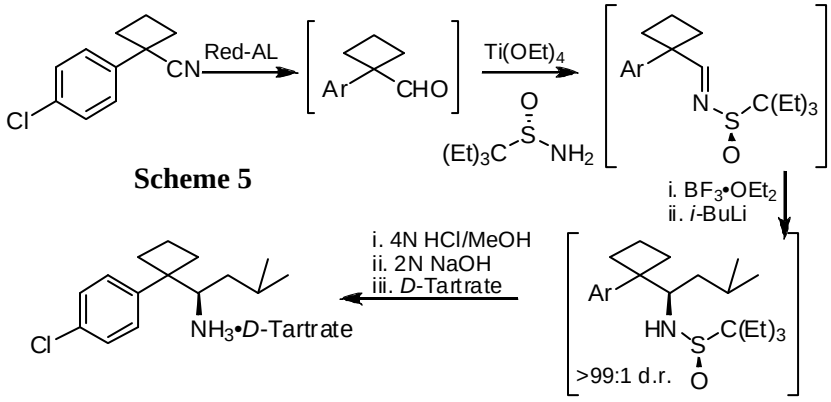
indanol scaffold (Scheme 3). Senanayake discovered that by varying conditions in the condensation of the amino indanol with thionyl chloride, both diastereomers of oxathiazolidine could be obtained selectively.[9] This has allowed access to a wide variety of enantiomerically pure sulfoxides.

Chiral auxiliary methodologies characteristically produce relatively simple sulfoxides with very high enantiomeric purity. These products are ideally suited for use as chiral ligands or chiral auxiliaries. Sulfoxide auxiliaries are commonly in the diastereoselective reductions of β-ketones, as typified by Solladié's formal synthesis of (+)-isolaurepan (Scheme 4).[10] The diastereoselectivity of the reaction can be switched by addition of Lewis acids ZnX_2, a phenomenon readily explained by familiar chair-like transition state analysis.[1c]



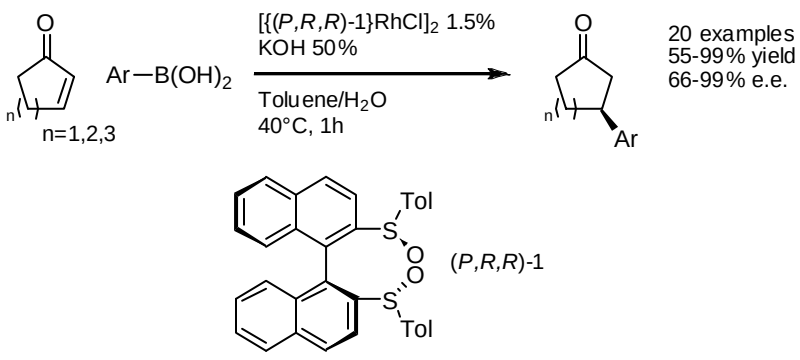
Scheme 4

Senanayake has developed a modular synthesis of sulfinamide auxiliaries based on the reported amino indanol oxathiazolidine. This tunable auxiliary approach was demonstrated in the synthesis of (*R*)-didesmethylsibutramine, a reuptake inhibitor for several neurotransmitters.[11] In an efficient and stereoselective one-pot procedure, the target compound was isolated in 83% yield and 99% e.e. (Scheme 5).



Scheme 5

The application of chiral sulfoxides as ligands for transition metals has been less thoroughly explored to date than their use as chiral auxiliaries. Recently, Dorta reported the first highly enantioselective reaction using a bis-sulfoxide ligand.[12] The



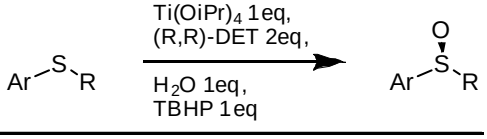
Scheme 6

rhodium/bis-sulfoxide catalyzed conjugate addition of aryl boronic acids to α,β-unsaturated ketones proceeded in excellent yields and enantioselectivities (Scheme 6). The bis-sulfoxide ligand was synthesized by the Andersen procedure from dibromobinaphthalene.

CATALYTIC ENANTIOSELECTIVE OXIDATION METHODOLOGIES & APPLICATIONS

The methods to synthesize enantioenriched sulfoxides using chiral auxiliaries are remarkably efficient and have been widely utilized. However, inherent limitations in the methodology have generally restricted their application to simple sulfoxides. Given the prevalence of sulfoxides in complex organic molecules including many drug targets, the development of asymmetric oxidations of sulfides has generated considerable interest. The first synthetically useful systems were reported nearly simultaneously by Kagan[13] and Modena.[14] Both involve modifications to Sharpless' titanium catalyzed asymmetric epoxidation reaction. Kagan and coworkers discovered that addition of stoichiometric water to the catalyst was crucial to achieve enantioselectivity in the oxidation of sulfides. Yields and enantioselectivities were high for aryl alkyl sulfoxides and moderate for dialkyl sulfoxides (Table 1). The reaction reported by Modena and coworkers modified the Sharpless method by addition of excess diethyl tartrate. Yields and selectivities were nearly identical to those reported by Kagan, and experimental evidence suggested that the excess tartrate may in fact serve only to introduce an uncontrolled amount of water. Though the nature of the active water-modified catalyst species is unknown, kinetic studies suggest the presence of a dimeric titanium complex. Kagan has proposed a μ-oxo bridged titanium dimer, which could differentiate the two substituents on the incoming sulfide (Fig. 2). Further optimizations have allowed for a decrease in catalyst loading and modest improvement in enantioselectivity.[15]

Table 1



entry	Ar	R	Yield (%)	e.e. (%)
1	p-$CH_3C_6H_4$	Me	90	90
2	p-$MeO_2CC_6H_4$	Me	50	91
3	p-$MeOC_6H_4$	Me	72	86
4	p-$CH_3C_6H_4$	Et	71	74
5	p-$CH_3C_6H_4$	*i*-Pr	56	63
6	$(CH_3)_3C$	Me	72	53

Figure 2

Proposed catalytic species

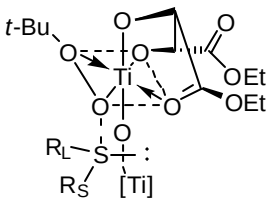
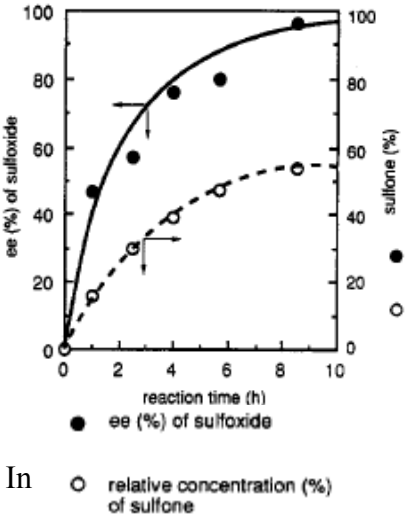
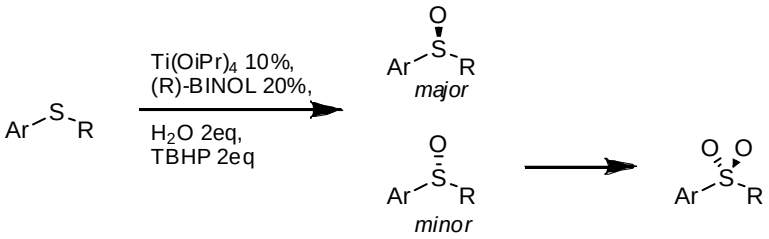


Figure 3



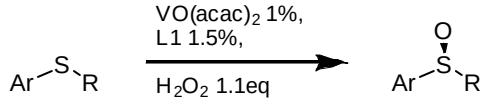
Uemura reported a significant advance in the titanium-catalyzed oxidation of sulfides.[16] Substituting binaphthol for tartrate, Uemura and coworkers achieved improved enantioselectivities with reduced catalyst loadings for the synthesis of aryl alkyl sulfoxides. In



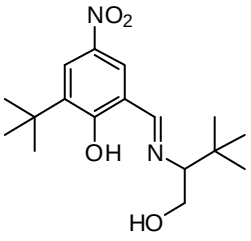
contrast to the reactions reported by Kagan and Sharpless, a large positive nonlinear effect was observed, implying a considerable difference in the structures of the respective active catalyst species. Additionally, it was observed that over time the concentration in the reaction mixture of sulfone, the product of a second oxidation, increased and the enantiomeric purity of the remaining sulfoxide also increased (Fig 3). This led Uemura to conclude that an initial moderately enantioselective oxidation process was benefitting from a secondary kinetic resolution in which the minor enantiomer was preferentially oxidized to sulfone (Scheme 7).

A second major class of catalysts used in enantioselective oxidations of sulfides consists of metallo-Schiff base complexes. Early efforts by Jacobsen[17] and Fujita[18] provided only low levels of enantioselectivity. Bolm reported the catalyst formed by $VO(acac)_2$ and N-salicylidene amino acid ligands, which could achieve good yields and moderate enantioselectivities of aryl alkyl sulfoxides under simple operational conditions and using hydrogen peroxide as a terminal oxidant (Table 2).[19] No evidence suggesting a kinetic resolution was found, indicating that the inherent enantioselectivity of the reaction is promisingly high. A switch to iron as the metal source and the use of lithium benzoates as additives has further optimized this method and expanded the substrate scope.[20]

Table 2

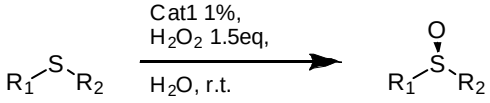


entry	Ar	R	Yield (%)	e.e. (%)
1	Ph	Me	94	70
2	Ph	*i*-Pr	64	62
3	p-$NO_2C_6H_4$	Me	55	63
4	Bn	*t*-Bu	91	65

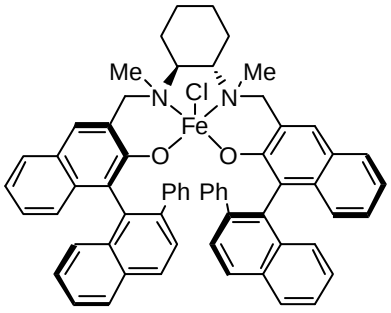


L1

Table 3



entry	R_2	R_2	Yield (%)	e.e. (%)
1	p-$CH_3C_6H_4$	Me	88	96
2	p-$MeOC_6H_4$	Me	88	95
3	p-ClC_6H_4	Me	72	94
4	Ph	Et	73	81
5	Bn	Me	85	87
6	$CH_3(CH_2)_7$	Me	73	89
7	Cy	Me	73	88

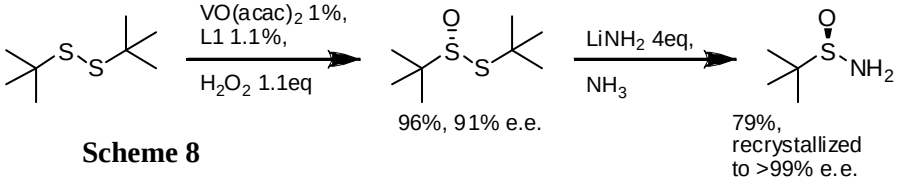


Cat1

Katsuki and coworkers have advanced the metallo-Schiff base methodology in recent reports.[21] Using a very bulky fully reduced salan ligand—a better donor than salen—complexed to iron,

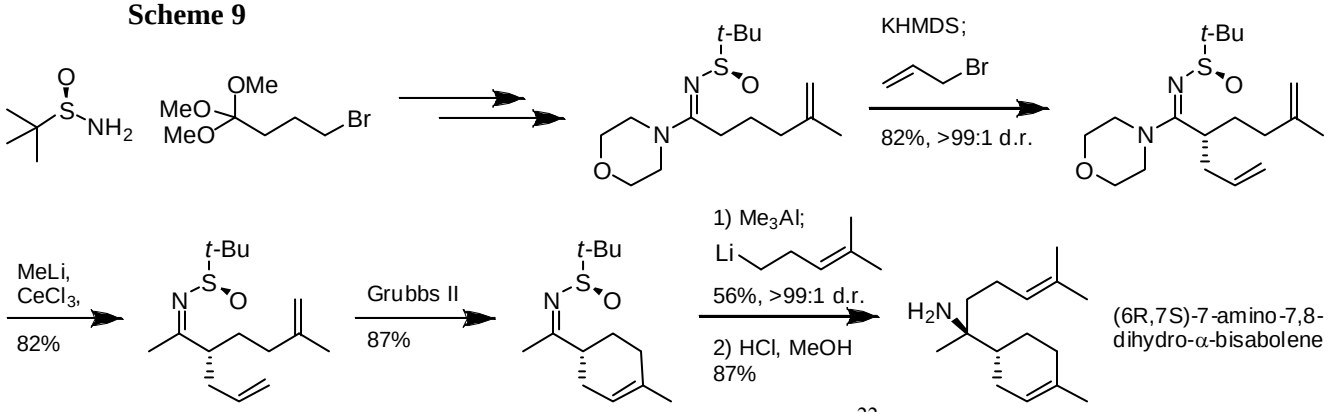
Katsuki has developed a reaction using aqueous hydrogen peroxide to oxidize a range of sulfides. Notably, this catalyst is capable of oxidizing dialkyl sulfides in addition to aryl alkyl sulfides in high enantioselectivities (Table 3). This is the most general example of enantioselective oxidation of dialkyl sulfides that has been reported. The mechanism of this reaction has yet to be investigated fully. However, in studies of an analogous titanium-salen catalytic system Katsuki observed evidence suggesting that the normally planar salen ligand is forced into a cis-β conformation by the η^2 coordination of peroxide. The approach of the sulfide is controlled by the bulky naphthyl substituents on the salen framework. Somewhat ambiguously, however, Katsuki also observed broadening of the sulfide resonances by NMR, implying that perhaps the sulfide is coordinated to the metal center.

The enantioselective catalytic oxidations to synthesize sulfoxides have found numerous applications in the literature. Ellman and coworkers have developed a method for the enantioselective synthesis of amines that employs *tert*-butanesulfinamide as a chiral auxiliary.[22] The sulfinamide is synthesized in two steps using Bolm's procedure to oxidize *tert*-butyl disulfide (Scheme 8). It is notable that this simple sulfinamide is readily accessible via previously described chiral auxiliary methods for synthesis of sulfoxides. The catalytic method is operationally superior and purification consists of a distillation and a recrystallization. The utility of this sulfinamide auxiliary has been demonstrated in a number of syntheses, including the remarkable enantioselective synthesis of (6*R*,7*S*)-7-amino-7,8-dihydro-α-bisabolene (Scheme 9).[23] The sulfur controls the formation of two stereogenic centers and is easily removed from the highly functionalized molecule.



Scheme 8

Scheme 9

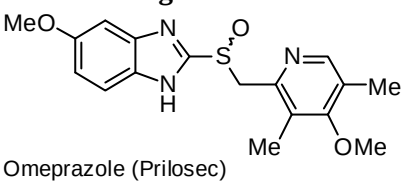


Perhaps the most significant applications of the catalytic oxidation methodology have occurred in the synthesis of complex natural products containing a stereogenic sulfoxide moiety. Many classes of

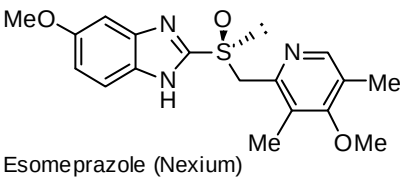
drug targets contain sulfoxide functionality, and an additional number contain sulfides which may be metabolized to sulfoxide.[24] Because resolution or derivatization from a chiral auxiliary would be an ineffective strategy to access these complex examples, catalytic enantioselective oxidation is uniquely suited to this challenge.

The most prominent drug target example of an enantioselective catalytic sulfide oxidation is that of the proton pump inhibitor omeprazole. Introduced in 1990 under the brand name Prilosec, omeprazole quickly became the most widely used drug for inhibition of gastric acid secretion with sales reaching $6 billion annually. Omeprazole was originally marketed as a racemate, with the final step in its industrial synthesis being a racemic oxidation by MCPBA (Scheme 10).[25] This was a relatively minor consideration because the molecule breaks down to an achiral sulfenamide, the active species, in the acidic environment of the stomach. However, continued studies showed inter-individual variability in omeprazole therapy, with some patients requiring much higher doses to effectively regulate acid secretion. This led to the investigation of esomeprazole, the S_S enantiomer of omeprazole, which demonstrated improved bioavailability in clinical studies. Esomeprazole was originally obtained by a resolution of racemic omeprazole.[26] In order to produce an industrially scalable process von Unge and coworkers at AstraZeneca investigated the application of the Kagan catalytic oxidation to the synthesis of esomeprazole.[27] Initial attempts using the conditions reported by Kagan led to nearly racemic omeprazole, a failure attributed to the similar steric demand of the two substituents of the sulfide precursor. However von Unge developed several modifications to the procedure which ultimately allowed for the synthesis of esomeprazole in yields exceeding 90% and e.e. of 94%, which was readily recrystallized to a single enantiomer (Scheme 11). It was found that the titanium, tartrate and water must be complexed in the presence of sulfide and at elevated temperature. Furthermore the use of N,N-diisopropylethylamine as an additive was discovered to improve enantioselectivity. This process was

Figure 5

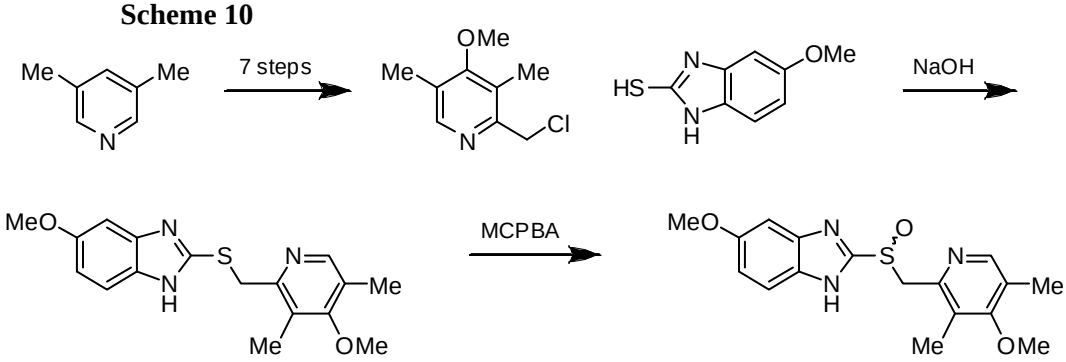


Omeprazole (Prilosec)



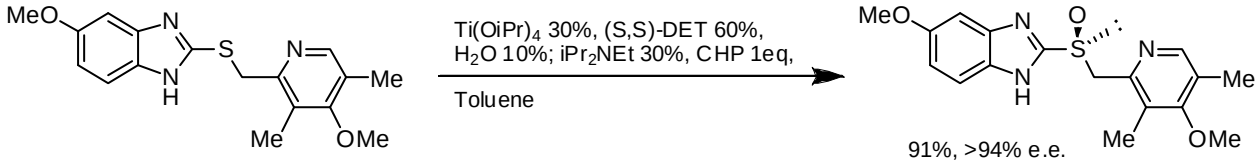
Esomeprazole (Nexium)

Scheme 10



employed for the industrial production of esomeprazole, marketed as Nexium, which in 2000 was the top-selling drug in the United States.

Scheme 11



The leading methods for the asymmetric synthesis of sulfoxide compounds have been presented and a number of applications have been detailed. Sulfoxides have been applied as chiral auxiliaries and chiral ligands to metals, and have been incorporated into a variety of natural products and their synthetic derivatives. Several challenges remain unsolved, however. Chiral sulfoxide ligands in catalytic systems clearly have not been developed to their full potential. A truly general catalytic asymmetric oxidation has yet to be described, though progress has been made. Chiral auxiliary methods, in order to compete, must become more efficient, perhaps through solid-supported auxiliaries.

---

[1] a) Pellissier, H. *Tetrahedron.* **2006**, *62*, 5559. b) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651. c) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717.
[2] Aurisicchio, C.; Baciocchi, E.; Gerini, M. F.; Lanzalunga, O. *Org. Lett.* **2007**, *9*, 1939.
[3] Gilman, H.; Robinson, J.; Beaber, N. J. *J. Am. Chem. Soc.* **1926**, *48*, 2715.
[4] Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93. b) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637.
[5] Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.
[6] a) Wuld, F.; Lee, T. B. K. *J. Chem. Soc., Chem. Comm.* **1972**, 61. b) Wuld, F.; Lee, T. B. K. *J. Am. Chem. Soc.* **1973**, *95,* 6349.
[7] Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5885.
[8] Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Senanayake, C. H.; *J. Am. Chem. Soc.* **2002**, *124*, 7880.
[9] a) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Su, X.; Lu, Z.-H.; Magiera, D.; Senanayake, C. H.; *Angew. Chem. Int. Ed.* **2003**, *42*, 2032. b) Lu, B. Z.; Jin, F.; Zhang, Y.; Wu, X.; Wald, S. A.; Senanayake, C. H.; *Org. Lett.* **2005**, *7*, 1465.
[10] Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 297.
[11] Han, Z.; Krishnamurthy, D.; Pflum, D.; Grover, P.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2002**, *4*, 4025.
[12] Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172.
[13] Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B.; *J. Am. Chem. Soc.* **1984**, *106*, 8188.
[14] Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325.
[15] Brunel, J. M.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1109.
[16] a) Komatsu, N.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *Tetrahedron Lett.* **1992**, *33*, 5391. b) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org.Chem.* **1993**, *58*, 4529.
[17] Palucki, M.; Hanson, P.; Jacobsen, E. N. *Tetrahedron Lett.* **1992**,*33*, 7111.
[18] Nakajima, K.; Kojima, M.; Fujita, J. *Chem. Lett.* **1986**, 1483.
[19] Bolm, C.; Bienewald, F. *Angew. Chem. Int. Ed. Engl.* **1996**, *34*, 2640.
[20] Legros, J.; Bolm, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 4225.
[21] a) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 8940. b) Masumoto, K.; Saito, B.; Katsuki, T. *Chem. Comm.* **2007**, 3619.
[22] Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.
[23] Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652.
[24] Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609.
[25] a) Carlsson, E. I.; Junggren, U. K.; Larsson, H. S.; von Wittken Sundell, G. W. Patent appl. EP 074341. (Priority date: Aug. 13, 1981) b) Lindberg, P.; Brändström, A.; Wallmark, B.; Mattsson, H; Rikner, L.; Hoffman, K.-J. *Med. Res. Rev.* **1990**, *1*, 1.
[26] Erlandsson, P.; Isaksson, R.; Lorentzon, P.; Lindberg, P. *J. Chromatogr*. **1990**, *532*, 305.
[27] Cotton, H.; Elebring, T.; Larsson, M.; Li, L.; Sörenson, H.; von Unge, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3819.