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Development of Chiral Sulfoxide Ligands for Asymmetric Catalysis

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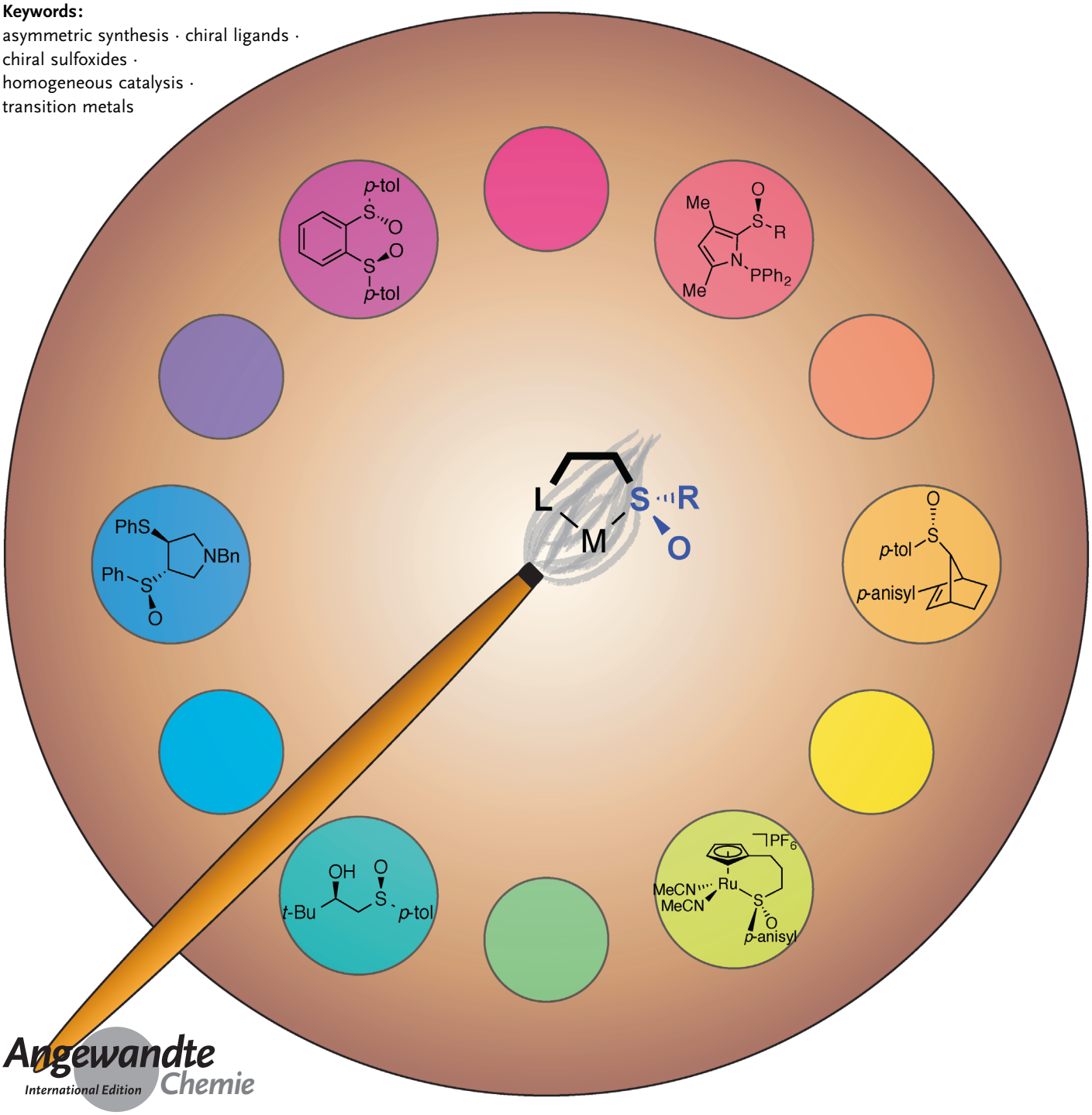


Nitrogen-, phosphorus-, and oxygen-based ligands with chiral backbones have been the historic workhorses of asymmetric transition-metal-catalyzed reactions. On the contrary, sulfoxides containing chirality at the sulfur atom have mainly been used as chiral auxiliaries for diastereoselective reactions. Despite several distinct advantages over traditional ligand scaffolds, such as the proximity of the chiral information to the metal center and the ability to switch between S and O coordination, these compounds have only recently emerged as a versatile class of chiral ligands. In this Review, we detail the history of the development of chiral sulfoxide ligands for asymmetric catalysis. We also provide brief descriptions of metal–sulfoxide bonding and strategies for the synthesis of enantiopure sulfoxides. Finally, insights into the future development of this underutilized ligand class are discussed.

From the Contents

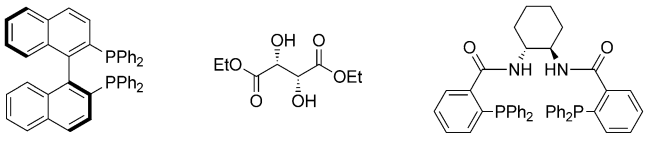
1. Introduction

The preparation of optically active materials has been a long-standing challenge in organic synthesis owing to the prevalence and utility of non-racemic molecules. Two main approaches exist for the construction of enantiopure compounds: 1) the use of chiral auxiliaries and 2) asymmetric catalysis. Reliance on the latter has the dual benefit of avoiding both the need to install and remove the chiral auxiliary (step economy) and the waste of stoichiometric amounts of chiral material (atom economy).[1,2] Among the methods used for asymmetric catalysis, reactions employing transition-metal catalysts with chiral ligands often benefit from high turnover numbers and frequencies, thereby lowering the amount of chiral material needed for the induction of asymmetry. The development of chiral ligands has primarily relied upon the use of phosphorus, nitrogen, or oxygen donor atoms with chiral carbon backbones. A few scaffolds of this type enjoy privileged status, including BINAP, tartrate-, and salen-derived scaffolds, such as the Trost standard ligand (Figure 1).

By contrast, the use of chiral sulfoxides as ligands for asymmetric catalysis has remained relatively unexplored, although they contain many potentially attractive features. First, as opposed to traditional ligands, which typically incorporate backbone chirality, the central chirality contained at the sulfur atom places the enantiodiscriminating substituents very close to the reaction center. Second, sulfoxides benefit from both a large steric and electronic differentiation between the oxygen and carbon substituents. Furthermore, a variety of methods exist for the facile synthesis of chiral sulfoxides, and both enantiomers of a given sulfoxide are typically readily available.[3] Finally, owing to their potential to switch from S to O coordination, sulfoxides may serve as ligands for both "hard" and "soft" transition metals (see Section 2).

Chiral sulfoxides have historically been used as auxiliaries in asymmetric synthesis, and this work has been discussed extensively.[4] This Review limits itself to a discussion of the use of chiral sulfoxides as ligands in asymmetric catalysis, and as such, the use of related sulfinamides, sulfilimines, and sulfoximines as ligands will not be discussed.[5] Many Reviews have dealt with chiral sulfur-containing ligands for asymmetric catalysis, even though only one Review, written before some of the major breakthroughs in the field, focused specifically on the development of sulfoxide ligands.[6,7]

This Review tracks the history of the development of chiral sulfoxide ligands for use in asymmetric transition-metal catalysis. A brief discussion of metal–sulfoxide bonding is followed by a description of early work in the field. As the vast majority of the chiral sulfoxide ligands developed to date are bidentate, the bulk of the Review is broken down by the atom of the second coordinating group (e.g., S,N ligands), and results are generally presented in chronological order. Within each category, the ligands are grouped by the type of reaction



(*S*)-binap (*R*,*R*)-diethyl tartrate (*R*,*R*)-Trost standard ligand

Figure 1. Privileged scaffolds for ligands used in asymmetric catalysis.

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studied. Finally, general methods for the preparation of enantiopure sulfoxides are discussed.

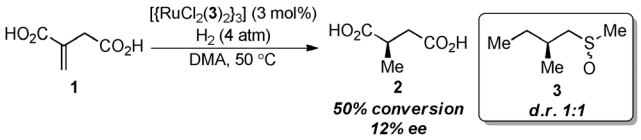
2. Metal–Sulfoxide Bonding

Much work has been done to study the nature and structure of metal–sulfoxide bonding, and several Reviews have been written on the topic.[8] Of particular interest for the development of ligands for asymmetric transition-metal catalysis is the question of whether the sulfoxide binds through the sulfur or oxygen atom. This is typically determined through an examination of the ^{1}H NMR shifts (sulfur binding results in a large downfield shift of the α-protons) and the sulfur–oxygen stretching frequencies as well as by X-ray crystallography. Sulfoxides generally prefer to bind "soft" transition metals (second and third row) through sulfur, both to maximize orbital overlap and take advantage of π-back-bonding. "Hard" transition metals (first row) prefer to ligate sulfoxides through the oxygen atom. These preferences, however, can change in response to the steric and electronic environment around the metal center.[8b]

3. Early Work

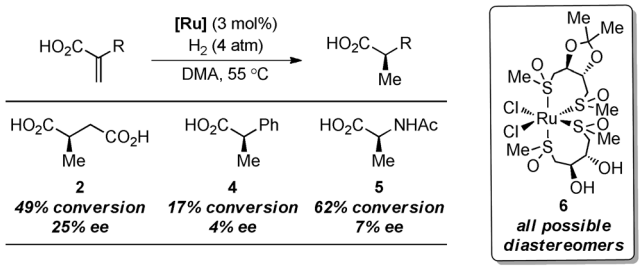
The idea of employing chiral sulfoxides as ligands for asymmetric catalysis was pioneered by James et al., who first reported their use in the context of Ru-catalyzed asymmetric hydrogenations in 1976.[9] Several complexes incorporating monodentate sulfoxide ligands only chiral at the sulfur atom were synthesized, but none were found to be catalytically active. Some activity was achieved using ligand **3**, which contained an additional stereocenter and was used as a diastereomeric mixture epimeric at sulfur. The exact structure of the catalyst was not determined, but mass spectrometry and ^{1}H NMR analysis indicated that the complex was a trimer possessing two ligands per metal center. Using this catalyst system, itaconic acid (**1**) could be hydrogenated to form methylsuccinic acid (**2**) in 12% *ee* (Scheme 1).

James and McMillan subsequently found that higher enantioselectivities could be obtained in the Ru-catalyzed hydrogenation using chelating bis(sulfoxide) ligands with tartrate-derived backbones.[10] Again, the ruthenium com-



Scheme 1. The first chiral sulfoxide ligand for asymmetric catalysis, which was developed by James et al. DMA = *N*,*N*-dimethylacetamide. The sulfur–oxygen bond of a sulfoxide is typically depicted as either a double bond (S=O) or a singly bonded ylide (S^+–O^-). For this Review, we have chosen to depict sulfoxides in their ylide form, but we have omitted the charges for clarity.

plexes were synthesized as mixtures of diastereomers epimeric at the sulfur atom. Even so, complex **6** was found to successfully hydrogenate itaconic acid to provide **2** in 49% conversion and 25% *ee* (Scheme 2). Hydrogenation to form **4** and **5** using the same catalyst, however, proceeded in only 4 and 7% *ee*, respectively. This disparity suggests that binding of the second carboxylate group of **2** is important for selectivity.



Scheme 2. Importance of carboxylate binding in a hydrogenation employing the bis(sulfoxide) ligands developed by James and McMillan.

This observed importance of carboxylate binding led James and co-workers to design a third-generation chiral sulfoxide ligand containing a tethered carboxylic acid.[11] The use of *N*-acetylmethionine sulfoxide (**8**), again as a mixture of epimers at the sulfur atom, with a rhodium precatalyst enabled the transfer hydrogenation of aryl alkyl ketones with up to 75% *ee* (Scheme 3). Unlike the complexes used in the Ru-catalyzed hydrogenations, the Rh catalysts were generated in situ. Inclusion of the free carboxylate and the electron-

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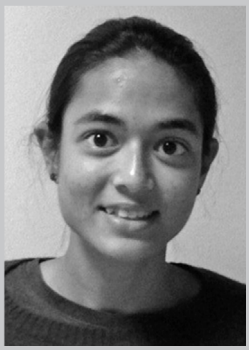
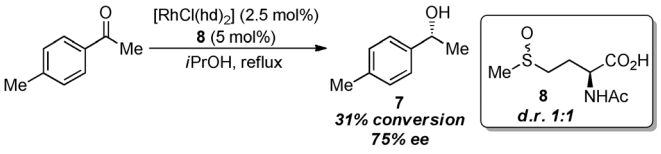


Meera Rao was born in Tampa, FL and studied chemistry at Northwestern University (BA, 2007). She completed her Ph.D. work in 2013 at Stanford University in the laboratory of Prof. Barry M. Trost where she worked on the development of chiral sulfoxide-ligated ruthenium complexes for use in asymmetric catalysis. She is currently a postdoctoral associate at UC Berkeley in the laboratory of Prof. Matthew B. Francis, where she is working on the development of polymer additives for enzymatic cellulose depolymerization.

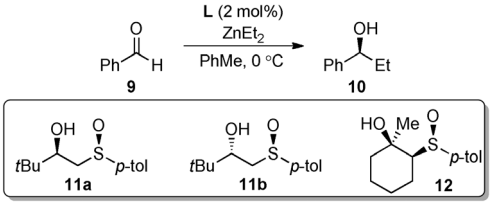


Scheme 3. Methionine-derived sulfoxide ligands for asymmetric hydrogenation developed by James et al. hd = 1,5-hexadiene.

withdrawing nitrogen protecting group were found to be critical for reactivity.

The first sulfoxide ligands that were employed as single sulfur epimers were developed in 1993 by Carreño and co-workers.[12] The diastereomeric β-hydroxysulfoxide ligands **11a** and **11b** were examined in the asymmetric addition of $ZnEt_2$ to benzaldehyde. Interestingly, the absolute configuration of product **10** was mainly controlled by the carbinol stereocenter (Table 1, entries 1 and 2). Use of cyclohexanol-

Table 1: Carreño and Ruano's ligands were the first that were employed as single sulfur epimers.

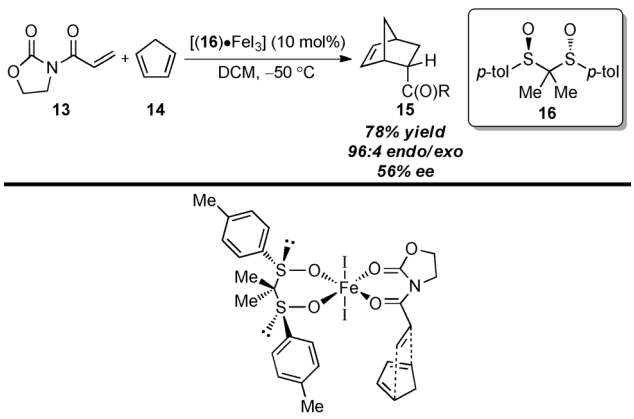


Entry	Ligand (**L**)	*ee* [%]
1	**11a**	9 (*R*)
2	**11b**	22 (*S*)
3[a]	**12**	55 (*S*)

[a] Ligand pretreated with $AlMe_3$.

containing ligand **12** and pre-treatment of the ligand with $AlMe_3$ provided alcohol **10** with the highest level of enantioselectivity (55% *ee*). Unlike the Ru- and Rh-catalyzed hydrogenations performed by James et al., these $ZnEt_2$ additions are believed to proceed via intermediates with O-bound sulfoxide ligands.

A major breakthrough was achieved in 1993 when Khiar et al. disclosed the use of a sulfoxide ligand with a chiral center only at the sulfur atom.[13] C_2-symmetric bis(sulfoxide) **16** was employed in the Fe-catalyzed Diels–Alder reaction between acrylamide **13** and cyclopentadiene (**14**). Bicycle **15** could be obtained with near-perfect diastereoselectivity in 78% yield and 56% *ee* (Scheme 4, top). As with the Carrreño system, the ligand is hypothesized to bind through the oxygen atoms of the sulfoxides to form a six/six-membered bicyclic complex (Scheme 4, bottom). The enantioselectivity arises from the selective approach of the diene *trans* to the bulky aryl sulfoxide substituent.



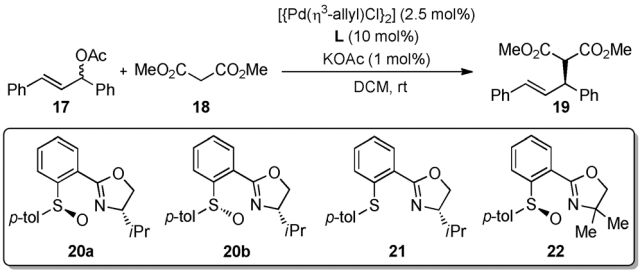
Scheme 4. Khiar's bis(sulfoxide) ligand was the first to contain chirality only at the sulfur atom. DCM = 1,2-dichloromethane.

4. S,N Ligands

4.1. Palladium-Catalyzed Asymmetric Allylic Alkylation

The earliest class of sulfoxide-containing ligands explored for use in asymmetric transition-metal catalysis incorporated pendant amines or imines. These ligands typically featured additional carbon-backbone stereocenters. The first such report was disclosed by Williams and co-workers in 1994.[14] A series of sulfoxide-oxazolidine ligands were prepared, with some containing chirality at the oxazolidine and others only with a chiral sulfur atom. These ligands were evaluated in the Pd-catalyzed asymmetric allylic alkylation (AAA) of 1,3-diphenylpropenyl acetate (**17**) with dimethyl malonate (Table 2). A clear matched/mismatched effect was observed when the diastereomeric ligands **20a** and **20b** were employed, with the *S*- and *R*-sulfoxide ligands providing product **19** in 88 and 55% *ee*, respectively. The presence of the sulfoxide stereocenter was found to be superfluous, however, as the use of sulfide ligand **21** provided product **19** in 93% *ee*. This finding indicates that palladium likely ligates one of the two enantiotopic lone pairs of sulfide **21** selectively, forming

Table 2: Williams' oxazolidine-sulfoxide ligands for Pd-catalyzed allylic alkylations.

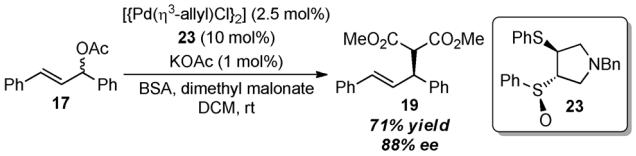


Entry	Ligand (**L**)	Yield [%]	*ee* [%]
1	**20a**	96	88 (*R*)
2	**20b**	42	55 (*R*)
3	**21**	69[a]	93 (*R*)
4	**22**	60	49 (*R*)

[a] Conversion; isolated yield not determined.

a diastereomerically pure Pd complex. Use of ligand **22**, which is only chiral at the sulfur atom, provided adduct **19** in a diminished 49% *ee*, demonstrating the importance of the oxazolidine chirality for the selectivity. Building on this report, Chelucci and co-workers reported the ability of tethered pyridine-sulfoxide ligands to catalyze the same reaction, even though the highest selectivity observed was 34% *ee*.[15]

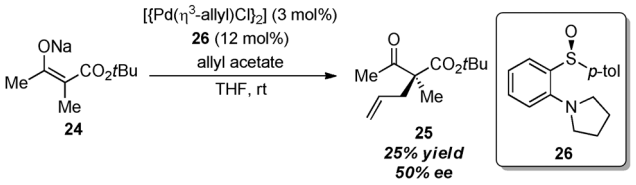
In 2004, Skarżewski et al. reported the employment of pyrrolidine-sulfoxide ligands in the same Pd-catalyzed asymmetric allylic alkylation (Scheme 5).[16] Use of ligand **23**



Scheme 5. Skarżewski's pyrrolidine-sulfoxide ligand. Bn = benzyl, BSA = *N*,*O*-bis(trimethylsilyl)acetamide.

afforded product **19** in 71% yield and 88% *ee*. The corresponding disulfide ligand gave similar results, whereas use of the corresponding bis(sulfoxide) shut down the desired transformation, indicating that the chiral sulfoxide element of **23** is not crucial for the reactivity or enantioselectivity. As with the ligands developed by the groups of Williams and Chelucci, the ligand backbone chirality remained the key structural element for selectivity.

A breakthrough was achieved in 1997 when Hiroi and Suzuki evaluated a large library of S,N-chelating ligands only chiral at the sulfur atom in the Pd-catalyzed asymmetric allylic alkylation of β-ketoester **24** (Scheme 6).[17] This report



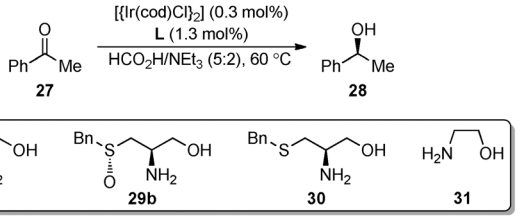
Scheme 6. Hiroi's chiral sulfoxide ligand for the Pd-catalyzed AAA of a prochiral nucleophile.

was both the first example of the use of S,N sulfoxide ligands without backbone chirality and the first and only example of the use of sulfoxide ligands in the asymmetric allylic alkylation of prochiral nucleophiles. Ligand **26** provided the highest level of selectivity, furnishing product **25** in 25% yield and 50% *ee*. In one case, switching the solvent from THF to 1,2-dimethoxyethane was found to reverse the absolute configuration of the product, and the authors speculated that a change in binding from S to O coordination could account for the observation.

4.2. Carbonyl Addition Reactions

More recently, chiral-sulfoxide-containing S,N ligands were developed for asymmetric carbonyl additions. The first report was disclosed in 2000 by van Leeuwen and co-workers, who studied the Ir-catalyzed transfer hydrogenation of acetophenone with formic acid.[18] Cysteine-derived sulfoxide ligands **29a** and **29b** displayed a marked matched/mismatched effect (Table 3), with *R*-sulfoxide ligand **29b** provid-

Table 3: Ligands used in asymmetric hydrogenation reactions with formate by van Leeuwen et al.[a]



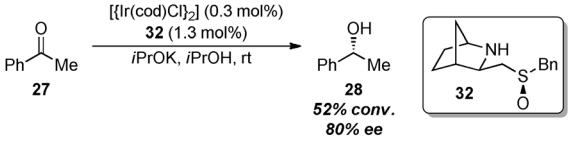
Entry	Ligand (**L**)	Conversion [%]	*ee* [%]
1	**29a**	56	27 (*R*)
2	**29b**	99	65 (*S*)
3	**30**	69	12 (*S*)
4	**31**	–	n/a

[a] cod = 1,5-cyclooctadiene; n/a = not applicable.

ing alcohol **28** in 65% *ee*. Elimination of the chirality at the sulfur atom through the use of sulfide ligand **30** led to a dramatic reduction in enantioselectivity (12% *ee*), demonstrating the importance of the sulfur stereocenter. The lack of reactivity observed with aminoalcohol ligand **31** indicated that sulfide and sulfoxide ligands **29** and **30** likely bind the metal center through the sulfur atom as opposed to the pendant alcohol.

Andersson et al. later developed a series of azanorbornyl-derived S,N ligands, also for use in the transfer hydrogenation of acetophenone.[19] Oddly, no hydrogenation was observed upon use of ligand **32** with formate as the reductant, in sharp contrast to the results obtained with the primary amine ligands developed by van Leeuwen and co-workers. Use of 2-propanol as the reductant proved successful, however, and alcohol **28** could be obtained in 52% conversion and 80% *ee* (Scheme 7). Using the diastereomer of **32** that is epimeric at the sulfur atom resulted in a sluggish reaction (10% conversion) and provided the enantiomer of alcohol **28** in a reduced 55% *ee*.

Very recently, Deng et al. developed a pair of tridentate ligands for the Ir-catalyzed asymmetric hydrogenation of



Scheme 7. Andersson's azanorbornane-tethered amine-sulfoxide ligand.

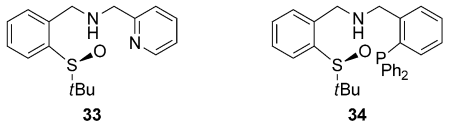
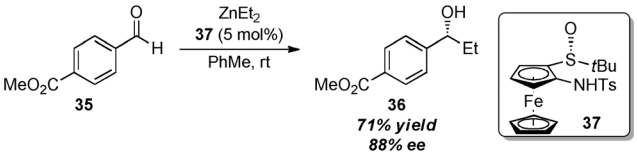


Figure 2. *tert*-Butylsulfinyl-containing ligands for hydrogenation developed by Deng et al.

acetophenone, each containing a *tert*-butylsulfinyl moiety only chiral at the sulfur atom (Figure 2).[20] Using 2-propanol as the reductant and pyridine-containing ligand **33**, benzyl alcohol **28** could be obtained in 96% conversion and 74% *ee*. Use of phosphine-containing ligand **34** resulted in significantly reduced conversions and enantioselectivities. Even though analogous ligands containing phosphorus and nitrogen binding sites have been shown to form Ru complexes with tridentate coordination, no evidence was given for the existence of tridentate coordination in the corresponding Ir sulfoxide complexes.

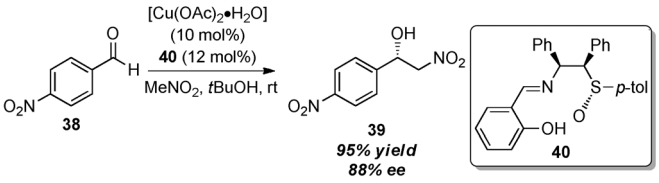
In 2001, Carretero et al. developed a series of ferrocene-based S,N ligands containing both planar chirality at the ferrocene unit and point chirality at the sulfur atom for use in the asymmetric addition of $ZnEt_2$ to benzaldehyde (Scheme 8).[21] Using ligand **37**, alcohol **36** could be obtained



Scheme 8. Carretero's ligands derived from planar-chiral ferrocenes. Ts = *para*-toluenesulfonyl.

in 71% yield and 88% *ee*. Employment of the sulfoxide fared no better than use of the corresponding sulfide or sulfone in terms of enantioselectivity, however, indicating that the planar chirality of the ferrocene moiety is the key structural element. Use of the sulfone ligand resulted in a more sluggish reaction, suggesting that the reaction is accelerated when the ligand is bound through the sulfur atom. Reboul, Metzner, and Grach later disclosed the use of similar ferrocenyl-sulfoxide S,N ligands containing an additional stereocenter for use in the same reaction, but the highest enantioselectivity achieved (65% *ee*) was lower than those obtained using the simpler Carretero ligands.[22]

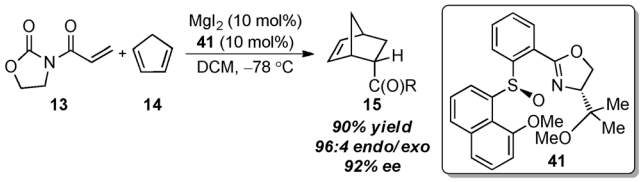
Very recently, Chen, Xiao, and co-workers examined a series of salen-derived imine-sulfoxide ligands for use in a Cu-catalyzed asymmetric Henry reaction between aldehyde **38** and nitromethane.[23] Impressively, use of ligand **40** was found to provide alcohol **39** in 95% yield and 88% *ee* (Scheme 9). Use of the corresponding sulfone was found to slow down the reaction considerably, indicating that the ligand likely binds the copper catalyst through the sulfur atom. Even though high levels of reactivity could be obtained through use of the corresponding sulfide ligand, the enantioselectivity of the process suffered (34% *ee*), implicating sulfur point chirality as a key structural element.



Scheme 9. Chen and Xiao's salen-based sulfoxide ligands utilized in a Henry reaction.

4.3. Other Reactions

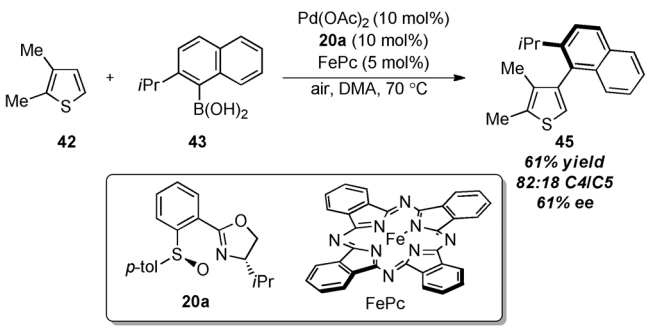
Oxazolidine-sulfoxide ligands were employed by Hiroi et al. in 2001 in a Mg-catalyzed Diels–Alder reaction between acrylamide **13** and cyclopentadiene.[24a] The highest enantioselectivity (92% *ee*) was obtained using ligand **41**, which contains a 2-methoxyisopropyl group at the oxazolidine ring (Scheme 10). Elimination of chirality at either the oxazolidine



Scheme 10. Oxazolidine-sulfoxide ligands employed in an asymmetric Diels–Alder reaction by Hiroi et al.

or the sulfoxide (through use of the corresponding sulfone) resulted in the formation of norbornene **15** with greatly reduced selectivities (6–36% *ee*). These data demonstrate the cooperative effects that can be obtained with structures containing point chirality at both sides of the bidentate ligand. Hiroi et al. also found that a combination of a $Cu(SbF_6)_2$ precatalyst and alkyl-tethered sulfoxide-oxazoline ligands could be used in the same asymmetric Diels–Alder reaction, though the selectivities were much lower ($\leq$66% *ee*).[25]

Very recently, Yamaguchi, Itami and co-workers utilized the same ligand scaffold originally developed by Williams et al. (see Section 4.1) in the oxidative coupling of electron-rich heterocycles with aryl boronic acids. Using *N,N*-dimethylacetamide (DMAc) as the solvent and air as the terminal oxidant, thiophene **42** and boronic acid **43** could be coupled to provide biaryl product **45** in 61% yield and 61% *ee* (Sche-



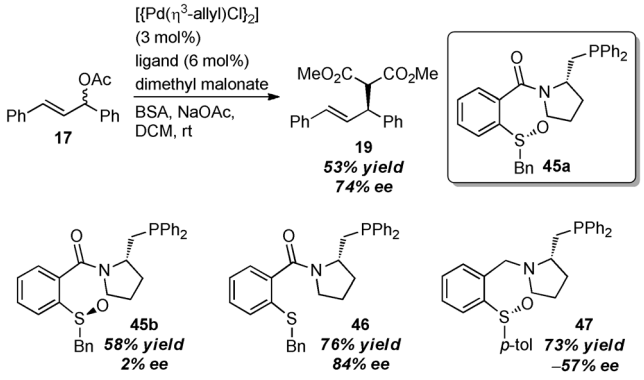
Scheme 11. Oxazolidinone-sulfoxide ligand developed for oxidative biaryl couplings by Itami and co-workers.

me 11).[24b] Efforts to improve the enantioselectivity of the process through changes in solvent, temperature, and ligand loading proved unsuccessful. Although the oxidative coupling was demonstrated with a range of substrates using chiral sulfoxide ligand **20a**, the enantioselectivities of these reactions were not discussed.

5. S,P Ligands

5.1. Palladium-Catalyzed Asymmetric Allylic Alkylation

Hiroi et al. have had a long-standing interest in the development of sulfoxide-containing S,P ligands for use in the Pd-catalyzed asymmetric allylic alkylation. The earliest example was disclosed in 1999 and involved the construction of proline-derived ligands.[26] As with the S,N ligands, 1,3-diphenylpropenyl acetate (**17**) was employed as the standard electrophile. Use of benzyl sulfoxide ligand **45a** was able to furnish alkylation product **19** in 53% yield and 74% *ee* (Scheme 12, top).[26c] A clear matched/mismatched effect was

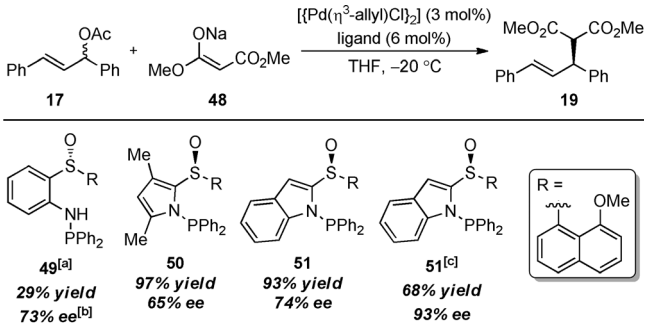


Scheme 12. Hiroi's first-generation sulfoxide-phosphine ligands derived from proline.

observed in this reaction, as use of diastereomeric ligand **45b** furnished **19** in a diminished 2% *ee*.

Interestingly, replacement of the sulfoxide with the corresponding sulfide (**46**) led to a more efficient and selective reaction, providing **19** in 76% yield and 84% *ee*. These combined data indicate that complexation of the sulfide to the Pd catalyst is likely to be diastereoselective. The enhanced reactivity and enantioselectivity observed with the use of sulfide **46** can likely be attributed to stronger binding of the ligand to the metal. Finally, removal of the carbonyl group of the amide (**47**) furnished the opposite enantiomer of the product, indicating that the ligand likely switches from being sulfur-bound to nitrogen-bound when the nitrogen atom is sufficiently Lewis basic.

Hiroi and co-workers also examined a series of aminophosphine-sulfoxide ligands in the same Pd-catalyzed asymmetric allylic alkylation.[27,28] These ligands were the first S,P ligand structures developed for asymmetric catalysis featuring only sulfur chirality. Aniline-containing ligand **49** provided



Scheme 13. Hiroi's second-generation aminophosphine-sulfoxide ligands. [a] Reaction run at 0°C. [b] The opposite enantiomer of **19** was formed. [c] Reaction run at −78°C.

product **19** in a promising 73% *ee*, but the reaction was quite slow (Scheme 13).[27] Tying up the nitrogen atom in a heterocycle resulted in much improved levels of reactivity, perhaps owing to better binding of the phosphine through enhanced π-backbonding interactions.[28] Use of the more active ligands allowed for a lower reaction temperature, and the alkylation product could be obtained in 68% yield and 93% *ee* with ligand **51** when the temperature was reduced to −78°C.

The success of these aminophosphine ligands belies their complexity, as they can theoretically bind the metal at four possible sites (P or N at the aminophosphine and S or O at the sulfoxide). Crystallographic analysis of the complex provided by reaction of ligand **51** with $[Pd(MeCN)_2Cl_2]$, however, revealed that for a Pd^{II} complex, ligand binding occurs through the phosphorus and sulfur atoms. An analogous Pd^0 complex was not synthesized. Furthermore, the Pd–Cl bond *trans* to the phosphorus ligand was found to be longer than the Pd–Cl bond *trans* to the sulfoxide. This finding suggests that alkylation likely occurs at the carbon atom *trans* to the phosphorus ligand (Figure 3).

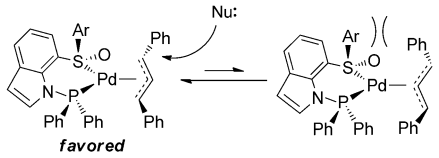
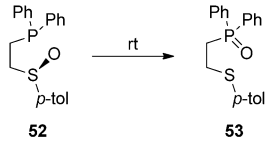


Figure 3. Stereochemical model for the AAA with Hiroi's aminophosphorane ligands. Nu = nucleophile.

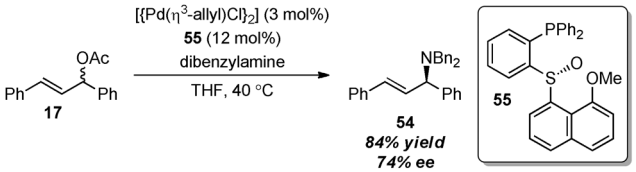
Hiroi et al. next sought to increase the reactivity and enantioselectivity of the reaction further by removal of the nitrogen linker to form five-membered S,P-chelates.[29] β-Phosphino-sulfoxide **52** was initially tested, but this species was found to lose its optical activity through an intramolecular redox event whereby the oxygen atom was transferred from the sulfur to the phosphorus atom (Scheme 14).

Replacement of the alkyl tether with an *ortho*-phenylene linker successfully raised the oxidation potential of the phosphine group, allowing for the synthesis of a series of phosphine-sulfoxide ligands that were stable at room temperature. These ligands indeed proved to be more active and



Scheme 14. An internal redox reaction occurs when (diarylphosphino)alkylsulfoxides are used.

selective than their aminophosphine counterparts, and the Pd-catalyzed asymmetric allylic alkylation of dimethyl malonate using ligand **55** at an increased temperature of −20 °C furnished adduct **19** in 71 % yield and 82 % *ee*. This system was also extended to the alkylation of dibenzylamine, providing tertiary amine **54** in 84 % yield and 74 % *ee* (Scheme 15).



Scheme 15. Use of Hiroi's third-generation sulfoxide-phosphine ligands.

Building upon the extensive work from the Hiroi group, Toru et al. developed a series of non-planar-chiral ferrocene-linked S,P ligands containing chirality only at the sulfur atom (Figure 4).[30] Again, these ligands were tested in the Pd-

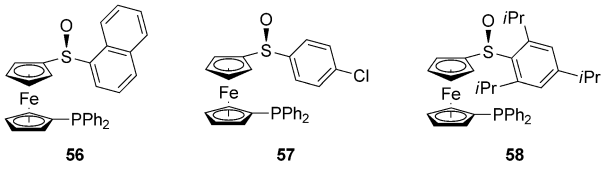
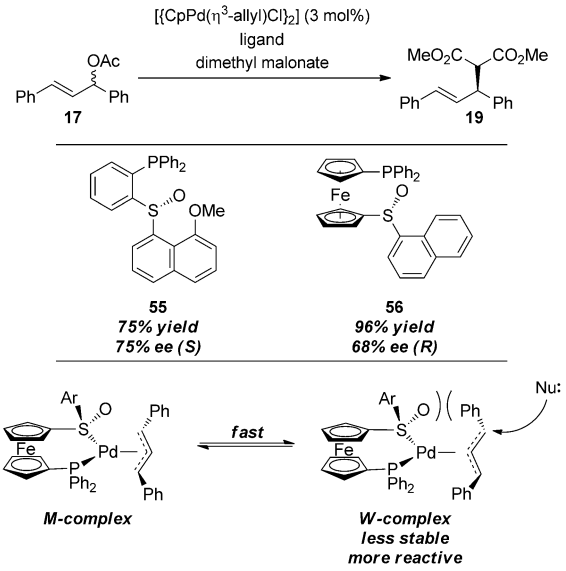


Figure 4. Toru's ferrocene-linked sulfoxide ligands contain a chiral center only at the sulfur atom.

catalyzed asymmetric allylic alkylation between 1,3-diphenylpropenyl acetate (**17**) and dimethyl malonate. The enantioselectivities were lower than those obtained by Hiroi et al. using the phenylene-linked phosphine-sulfoxide ligands, and product **19** could be obtained in 96 % yield and 68 % *ee* using ligand **56**. The introduction of an electron-withdrawing group at the sulfoxide (**57**) resulted in a sluggish reaction, whereas the presence of a bulky substituent (**58**) shut down the desired transformation completely, presumably by precluding binding of the sulfur atom to the palladium center.

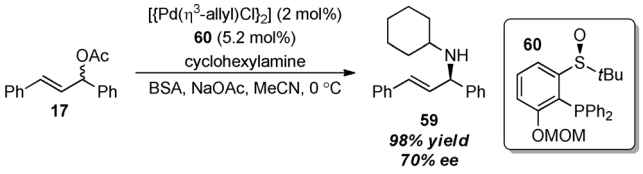
Interestingly, product (*R*)-**19** is favored using Toru ligand **56**, whereas (*S*)-**19** is favored using Hiroi ligand **55**, even though both sets of ligands feature the same configuration at the sulfoxide. This observed discrepancy prompted Toru et al. to conclude that the use of the ferrocene-based ligands favors a Curtin–Hammett scenario with a fast equilibration of the



Scheme 16. Proposed Curtin-Hammett scenario to explain a reversal in selectivity.

diastereomeric Pd allyl complexes; the less stable W complex reacts faster than the more stable M complex (Scheme 16).

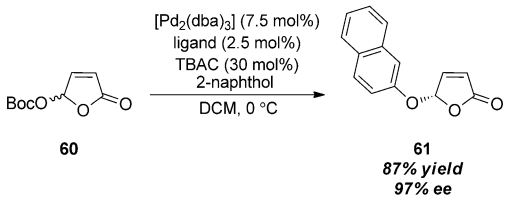
In 2009, the Liao group developed a series of phenylene-linked phosphine-sulfoxide ligands that were very similar to the Hiroi scaffold, but contained a *tert*-butylsulfinyl group.[31] These ligands incorporating a bulky alkyl sulfoxide substituent represent the most effective S,P ligands to date for the Pd-catalyzed allylic alkylation. Use of ligand **60** in acetonitrile as the solvent for the reaction of 1,3-diphenylpropenyl acetate (**17**) and dimethyl malonate provided malonate product **19** in quantitative yield and 89 % *ee*. This system could also be extended to the allylic alkylation of primary amines, providing cyclohexylamine product **59** in 98 % yield and 70 % *ee* (Scheme 17). Unlike in the Hiroi system, the presence of the



Scheme 17. Use of *tert*-butylsulfinyl-phosphine ligands in AAA reactions by Liao et al. MOM = methoxymethyl.

electron-donating substituent on the phenylene linker was found to have a significant positive effect on the enantioselectivity.

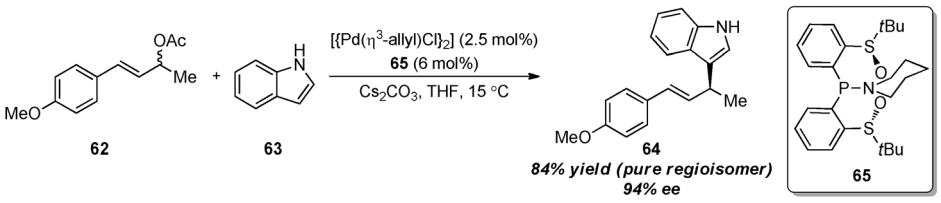
Most recently, Liao et al. disclosed a series of S,P ligands containing an additional pendant sulfoxide for the Pd-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of unsymmetric allyl electrophiles with indole nucleophiles.[32] The use of unsymmetric allyl electrophiles in a DYKAT process with high levels of regio- and enantiose-



Scheme 18. Ligands previously used in the DYKAT AAA of unsymmetric electrophiles. Ligand = Trost standard ligand; Boc = *tert*-butoxycarbonyl, dba = dibenzylidene acetone, TBAC = tetrabutylammonium chloride.

lectivity had previously only been demonstrated using BINAP and the Trost standard ligand.[33] For example, 2-naphthol could be alkylated with racemic Boc-protected γ-acyloxybutenolide **60** using the Trost standard ligand in 87% yield and 97% *ee* (Scheme 18).[33a]

Liao's hypothesis, inspired by the role of the *tert*-butylsulfinyl group in Jacobsen's chiral urea catalysts, was that the pendant sulfoxide could activate the indole nucleophile through a hydrogen-bonding interaction.[34] Indeed, treatment of unsymmetric allyl acetate **62** and indole with [{Pd(η^3-allyl)Cl}$_2$] and ligand **65** provided adduct **64** with 96% regioselectivity and 94% *ee* (Scheme 19).[32] The mechanism

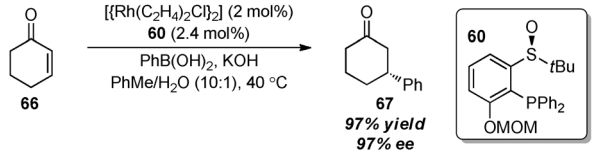


Scheme 19. Pd-catalyzed AAA of unsymmetric electrophiles described by Liao and co-workers.

of substrate racemization is proposed to be a relatively fast intermolecular Pd–Pd substitution, though a substitution mechanism involving the pendant sulfoxide on the ligand could also be feasible. Use of bisphosphine ligands (*R*)-BINAP and the *S*,*S*-configured Trost standard ligand resulted in severely reduced levels of reactivity (< 12% yield). The hydrogen-bond-accepting role of the pendant sulfoxide was evaluated through a series of experiments using N-protected indole nucleophiles. As anticipated, when the *N*-Me-, *N*-Bn-, and *N*-Boc-protected indoles were employed, no reactions were observed.

5.2. Rhodium-Catalyzed Conjugate Additions

Liao and co-workers have also extensively used the *tert*-butylsulfinyl-phosphine scaffold in various Rh-catalyzed conjugate addition reactions.[35] In 2010, they first reported the exceptional performance of **60** in the addition of phenylboronic acid to cyclohexenone, providing adduct **67** in 97% yield and 97% *ee* (Scheme 20).[35a] A similar ligand lacking



Scheme 20. Use of Liao's *tert*-butylsulfinyl ligand in a Hayashi–Miyaura reaction.

the electron-donating alkoxy group on the backbone was not catalytically active.

A stereochemical model for this reaction was developed that involves migratory insertion of the enone as the enantiodetermining step. In the case of the *S*-sulfoxide ligand, coordination through the *re* face of the enone minimizes steric interactions between the carbon atoms of the ring and the bulky *tert*-butyl group (Figure 5).

In 2011, Liao et al. reported that ligand **60** was also uniquely reactive and selective in the conjugate addition of aryl boronic acids to 2-nitrostyrenes.[35b] As in the case of cyclohexenone as the electrophile, the presence of an electron-donating group on the linker was found to be essential to reactivity. The use of BINAP was again found to result in a sluggish reaction with low levels of enantioselectivity (10% *ee*). The utility of this reaction was demonstrated by a short, high-yielding synthesis of (*R*)-cherylline, with the key step providing nitroalkane **70** in quantitative yield and 98% *ee* (Scheme 21). Ligand **60** could also be used in the Rh-catalyzed conjugate addition of aryl boronic acids to unprotected 3-indolylnitroalkenes and chalcones with exceptional yields and enantioselectivities.[35c,d] As

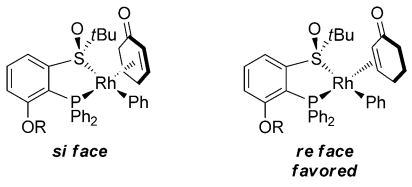
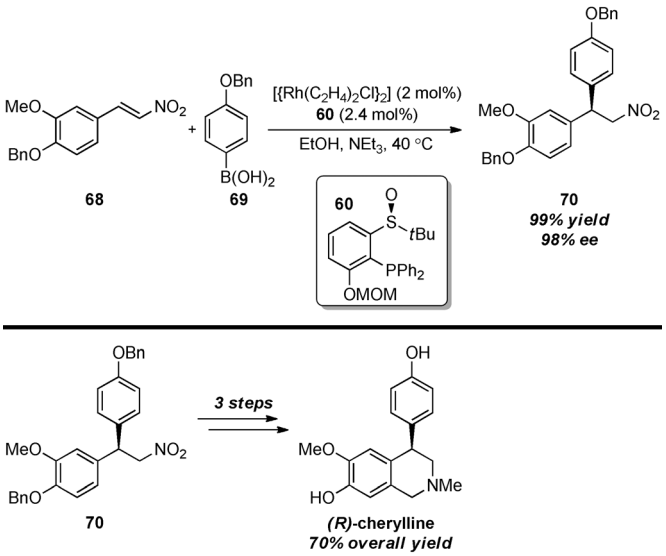


Figure 5. Stereochemical model for the Hayashi–Miyaura reaction using ligand **60**.

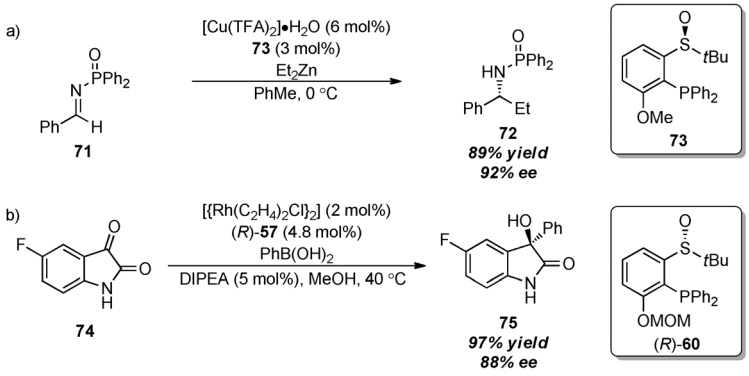
in the other conjugate additions, use of BINAP resulted in much lower levels of reactivity, as did ligands lacking the electron-donating alkoxy group on the phenylene linker.

5.3. Carbonyl Additions

Liao et al. have also been able to successfully utilize their phenylene-linked *tert*-butylsulfinyl-phosphine ligands for asymmetric 1,2-carbonyl additions. The first report involved Cu-catalyzed ethyl additions to phosphoryl-protected



Scheme 21. Use of chiral sulfoxide ligands for the total synthesis of (*R*)-cherylline.



Scheme 22. Application of chiral sulfoxide-phosphine ligands in carbonyl addition reactions by Liao et al. DIPEA = diisopropylethylamine, TFA = trifluoroacetate.

imines.[36] As such, $ZnEt_2$ could be added to imine **71** to furnish phosphinamide **72** in 89% yield and 92% *ee* with **73** as the ligand (Scheme 22a). The use of a hard Lewis acid catalyst such as copper suggests that the sulfoxide likely coordinates to the metal through the oxygen atom. The slightly modified ligand (*R*)-**60** was subsequently used by Liao in the Rh-catalyzed addition of aryl boronic acids to isatins (Scheme 22b).[37] Interestingly, unprotected isatins, which could not be used in the original reaction using bisphosphine ligands as reported by Hayashi et al., were competent acceptors when Liao's phosphine-sulfoxide ligands were employed.[38]

6. S,S Ligands

6.1. Palladium-Catalyzed Asymmetric Allylic Alkylation

The first report on using sulfoxide ligands with chirality only at the sulfur atom in the Pd-catalyzed asymmetric allylic alkylation was disclosed by Shibasaki et al. in 1995.[39]

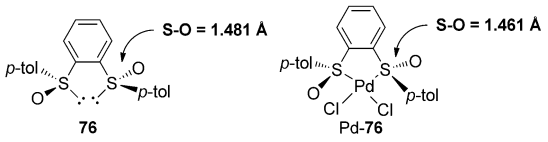
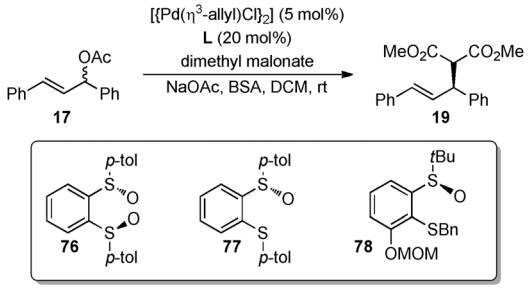


Figure 6. Analysis of the S–O bond length in Shibasaki's bis(sulfoxide) ligand and a complex thereof.

Crystallographic analyses of ligand **76** and its Pd complex were performed, and the S–O bond lengths were compared with those of a Pd DMSO complex (Figure 6). Analysis of the Pd DMSO complex revealed that the S–O bond length was reduced by 0.055 Å upon complexation.[40] This bond shortening was attributed to a change in electron localization from oxygen to sulfur, thus increasing the double-bond character of the sulfoxide and thereby enhancing the donor properties of the sulfur atom. The S–O bond of ligand **76** was only shortened by 0.02 Å upon complexation, suggesting that more electron density resides at the oxygen atom in the Pd-**76** complex than in the corresponding Pd DMSO complex, which leads to a decrease in the donor properties.

Bis(sulfoxide) **76** could be used as a ligand in the allylic alkylation of acetate **17** and dimethyl malonate, though the reaction was sluggish and the enantioselectivity moderate (40% yield, 64% *ee*; Table 4). Use of the corresponding sulfoxide-sulfide ligand **77** resulted in higher levels of reactivity, but a reduced enantioselectivity of 49% *ee*. A subsequent report from Liao et al. demonstrated that replacement of the aryl thioether with an alkyl substituent, modification of the phenylene linker, and use of a *tert*-butylsulfinyl group on the ligand (**78**) resulted in the formation of adduct **19** in 98% yield and 80% *ee*.[41] Strangely, the use of sulfoxides with opposite configurations resulted in the formation of the same product enantiomer, though neither of the authors commented on this discrepancy.

Table 4: Shibasaki's bis(sulfoxide) ligands feature a stereogenic center only at the sulfur atom.

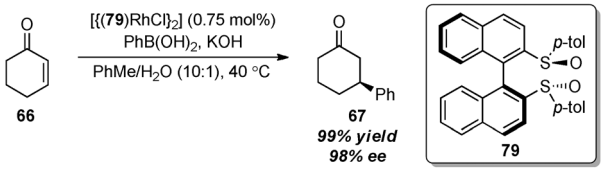


Entry	Ligand (**L**)	Yield [%]	*ee* [%]
1	**76**	40	64 (*R*)
2	**77**	82	49 (*R*)
3[a]	**78**	98	80 (*R*)

[a] [{Pd(η³-allyl)Cl}$_2$] (2.5 mol%) and **78** (5 mol%) with LiOAc in MeCN.

6.2. Rhodium-Catalyzed Conjugate Additions

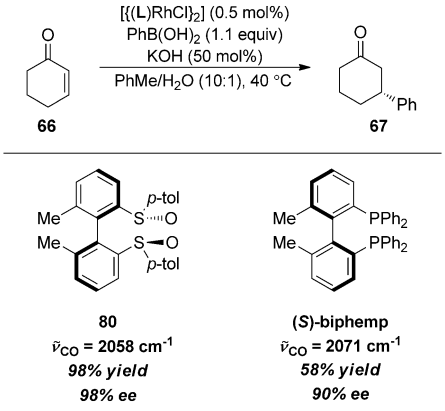
A major breakthrough in the development of chiral sulfoxide ligands was achieved in 2008 by Dorta et al.; binaphthyl-linked bis(sulfoxide) ligand **79** was successfully utilized in the Rh-catalyzed conjugate addition of aryl boronic acids to electron-deficient olefins.[42] For example, treatment of cyclohexenone and $PhB(OH)_2$ with a rhodium precatalyst and ligand **79** furnished ketone **67** in quantitative yield and 98% *ee* (Scheme 23). This report provides the first example of



Scheme 23. High yields and selectivities can be obtained with Dorta's sulfoxide ligand.

the ability of chiral sulfoxide ligands to furnish products in excellent yields and enantioselectivities. Dorta's catalyst system could also be used with a variety of aryl boronic acid nucleophiles, but changing the acceptor to cycloheptenone resulted in a significantly lower enantioselectivity (66% *ee*).

Alternative axially chiral backbones were later examined by the groups of Dorta and Li (Scheme 24), and ligand **80** was found to be even more efficient than **79**, allowing the catalyst loading to be lowered to 0.5 mol%.[43,44] A comparison of bis(sulfoxide) ligand **80** with its bis(diphenylphosphino) counterpart [(*S*)-biphemp] revealed that the sulfoxide complex is significantly more reactive than the phosphine complex (98% and 58% yield of **67** with ligands **80** and biphemp, respectively). An analysis of the carbonyl stretching frequencies of Rh–CO complexes containing a BINAP ligand (2071 cm^{-1}) or bis(sulfoxide) ligand **79** (2056 cm^{-1}) revealed that the bis(aryl sulfoxide) ligands are more σ-donating than their phosphine counterparts. This finding could serve as an explanation for the enhanced reactivity of the sulfoxide complexes, either owing to better binding of the acceptor or

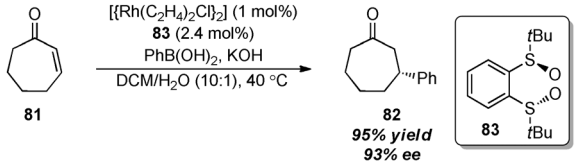


Scheme 24. Comparison of (*S*)-biphemp and Dorta's analogous sulfoxide ligand.

faster migratory insertion. From a series of computational studies performed on this system, Cavallo, Dorta et al. concluded that whereas phosphine ligands with backbone chirality (e.g., BINAP) control the selectivity through steric effects, electronic effects dominate when the analogous sulfoxide ligands are employed.[43c,d]

In all of the above cases, however, distinguishing the specific role of the sulfoxide chirality with respect to enantioselectivity proved impossible, as the use of the opposite ligand diastereomer resulted in no observed reaction. This conundrum was resolved by Liao et al. in 2010, marking a significant advance in the field of chiral sulfoxide ligands for asymmetric catalysis. In this report, Liao disclosed the ability of bis(sulfoxide) ligand **83**, only chiral at the sulfur atom, to participate in the Rh-catalyzed conjugate addition of aryl boron species to enones.[45]

As with Dorta's system, excellent yields and enantioselectivities could be obtained with very low catalyst loadings. Using ligand **83**, even the addition of phenylboronic acid to cycloheptenone, a problematic electrophile in the Dorta reaction, could be achieved to provide adduct **82** in 95% yield and 93% *ee* (Scheme 25). Use of the *R*,*R*-sulfoxide of **79**

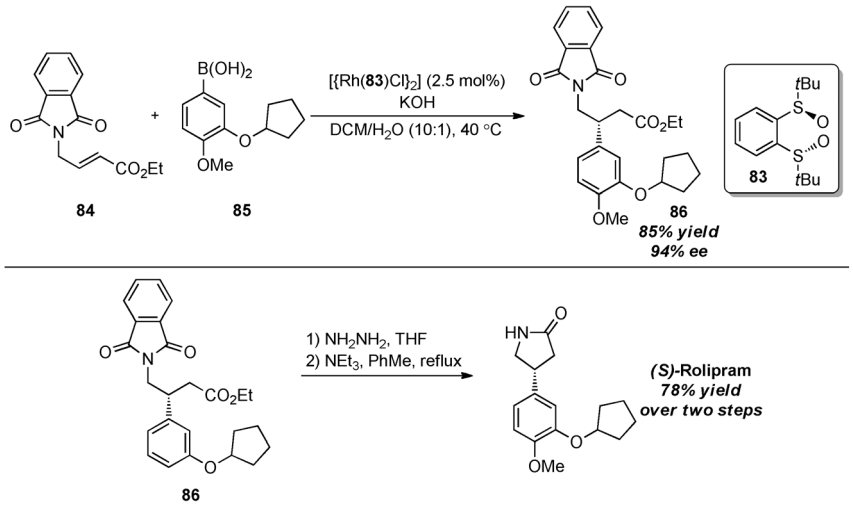


Scheme 25. Liao's ligand, which only features a stereogenic center at the sulfur atom, provides excellent selectivities.

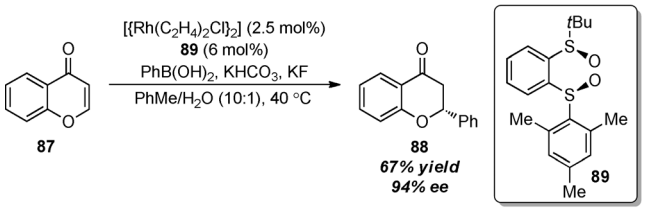
provided the opposite product enantiomer as use of the *R*,*R*-sulfoxide of **83**, which could be interpreted as evidence that the axial chirality of the linker, as opposed to the chirality of the sulfur atom, is the more dominant structural element for selectivity.

Liao et al. were able to extend the use of ligand **83** to highly enantioselective conjugate addition reactions with 2,3-dihydro-4-pyridones and γ-phthalimido enoates.[46] The latter reaction is the first example of the use of sulfoxide ligands for asymmetric additions to acyclic acceptors, and the reaction was applied to the synthesis of the antidepressant (*R*)-rolipram.[46b] To this end, aryl boronic acid **85** could be added to enoate **84** to provide **86** in 85% yield and 94% *ee* (Scheme 26). Removal of the phthalimide protecting group, followed by lactam formation, furnished the desired pharmaceutical compound.

Liao et al. also attempted to extend the use of *tert*-butylsulfinyl ligand **83** to the Rh-catalyzed conjugate addition of aryl boronic acids to chromenones.[47] However, low levels of reactivity were observed using either (*R*)-BINAP or **83** as the ligand (31 and 32% yield, respectively). Hoping to improve the reactivity through the use of the opposite diastereomer while maintaining the excellent levels of enantioselectivity imparted by the *tert*-butylsulfinyl group, non-C_2-symmetric bis(sulfoxide) ligands were examined in this reaction. Gratifyingly, use of ligand **89** furnished adduct



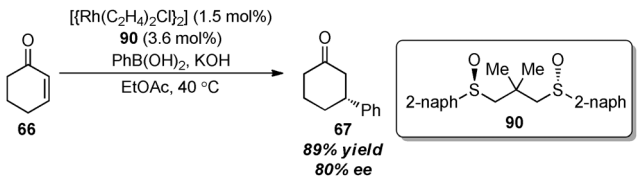
Scheme 26. Use of chiral sulfoxide ligands for the synthesis of (*R*)-rolipram.



Scheme 27. Liao's non-C_2-symmetric chiral sulfoxide ligand is employed in chromenone addition reactions.

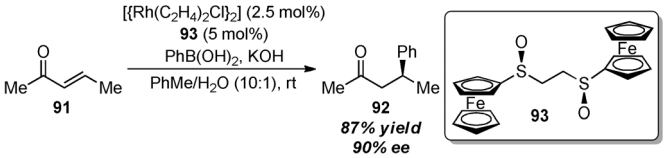
88 in 67% yield and 94% *ee*, but the reaction conditions also had to be significantly modified (Scheme 27). Control experiments indicated that the modification of the ligand alone accounted for a 20% increase in yield.

Similar bis(sulfoxide) ligands containing saturated alkyl tethers rather than phenylene linkers have also been explored in Rh-catalyzed conjugate addition reactions. In 2011, Dong et al. reported that the use of 2-naphthyl-substituted sulfoxide ligand **90** successfully provided adduct **67** in 89% yield and 80% *ee* (Scheme 28).[48] Interestingly, removal of the *gem*-dimethyl group on the linker resulted in formation of the opposite enantiomer of the product (−20% *ee*) using the same sulfoxide configuration. This observation illustrates the importance of the Thorpe–Ingold effect in allowing **90** to function as a suitable bidentate ligand, suggesting that six-membered-ring rhodium–sulfoxide chelates are not optimal catalysts for this reaction.



Scheme 28. Dong's neopentyl-linked bis(sulfoxide) ligand.

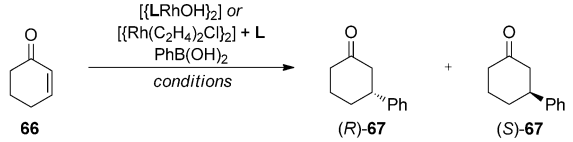
Finally, Fernández, Khiar, and co-workers reported the use of a series of two-carbon-tethered bis(sulfoxide) ligands in a Hayashi–Miyaura reaction.[49] Bis(ferrocenyl) ligand **93** was found to be optimal in terms of reactivity and enantioselectivity. Unlike the additions employing Liao's phenylene-tethered ligands, the scope of the reaction with ligand **93** was demonstrated to include both cyclic and acyclic enones (Scheme 29).



Scheme 29. Acyclic enones can be used as electrophiles with Khiar's ferrocenyl ligand.

7. S,Olefin Ligands

The most recently developed class of chiral sulfoxide ligands contain a tethered olefin as a second coordinating group, inspired by the chiral diene ligands developed by the groups of Hayashi and Carreira.[50] Remarkably, in 2011, four different laboratories independently disclosed the development of sulfoxide-olefin ligands for use in asymmetric catalysis.[51] All four groups used the Hayashi–Miyaura reaction of cyclohexenone and phenylboronic acid to test the effectiveness of their ligands (Scheme 30).



Scheme 30. The Hayashi–Miyaura reaction was used to evaluate sulfoxide-olefin ligands.

The first two reports, submitted within days of each other, were disclosed by the groups of Knochel and Xu.[52,53] The ligands developed by Knochel were based on a norbornene scaffold, in direct analogy to the phosphine-olefin ligands previously developed by Hayashi and co-workers (Figure 7, **94a**, **94b**, and **95**).[54] In the case of diastereomeric ligands **94a** and **94b**, the sense of enantioselectivity switched completely upon switching the configuration of the norbornene without affecting the reactivity, indicating that the central chirality of

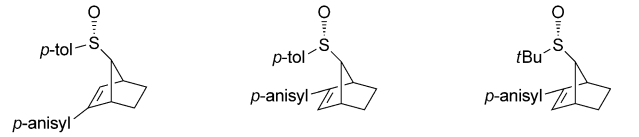


Figure 7. Performance of Knochel's norbornene-based chiral sulfoxide ligands.

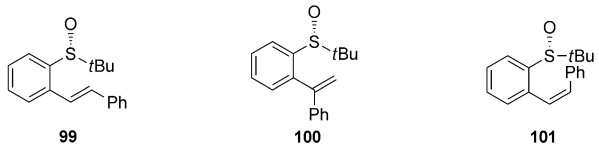


Figure 9. Liao's sulfoxide-olefin ligands allow for a switch in stereoselectivity.

the sulfur atom does not play a major role in determining the selectivity. However, replacement of the *para*-tolyl substituent on the sulfoxide with a *tert*-butyl substituent (**95**) completely shut down the reaction, indicating that binding of the sulfoxide is vital to the reactivity.

As opposed to the chiral diene scaffold of the Knochel ligands, Xu's ligands contained chirality only at the sulfur atom and incorporated a phenylene linker in analogy to the chiral sulfoxide ligands previously developed by Liao and co-workers.[53,45] Interestingly, these ligands were found to tolerate a bulky *tert*-butyl group on the sulfoxide, presumably owing to the decreased steric bulk of the phenylene linker compared with the norbornene scaffold. In the case of the Xu system, however, trisubstitution on the olefin (**96**) shut down the transformation, demonstrating the importance of olefin coordination for reactivity (Figure 8). Even though adduct **67**

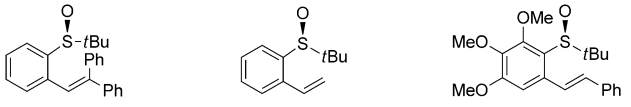


Figure 8. Performance of Xu's *tert*-butylsulfinyl-olefin ligands.

could be obtained in 98% yield using α-olefin ligand **97**, a low enantioselectivity of 8% *ee* was observed. Use of disubstituted olefin ligand **98** proved to be optimal, providing (*R*)-**67** in 99% yield and 95% *ee*.

Shortly after the reports from the Knochel and Xu groups, Liao et al. independently disclosed the use of sulfoxide-olefin ligands in the Hayashi–Miyaura reaction.[55,56] As with the Xu ligands, the use of olefins with 1,2-disubstitution in conjunction with the (*R*)-*tert*-butylsulfinyl group (**99**) furnished a highly enantioselective ligand, providing (*S*)-**67** in 97% yield and 97% *ee* (Figure 9). Remarkably, however, the sense of enantioselectivity could be completely reversed by simply switching the position of the olefin substituent. As such, (*R*)-**67** could be obtained in 98% yield and 95% *ee* with ligand **100**. Changing the stereochemistry of the olefin from *E* to *Z* (**101**) was also found to switch the sense of the enantioselectivity, furnishing (*R*)-**67** in 98% yield and 35% *ee*.[56]

Most recently, Wan and co-workers examined the effect of varying the sulfoxide component of olefin-sulfoxide ligands on the Rh-catalyzed conjugate addition reaction (Figure 10).[57] Use of a bulky *tert*-butylsulfinyl substituent

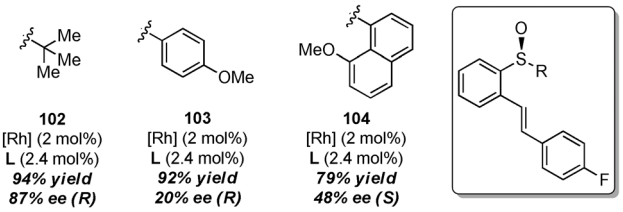


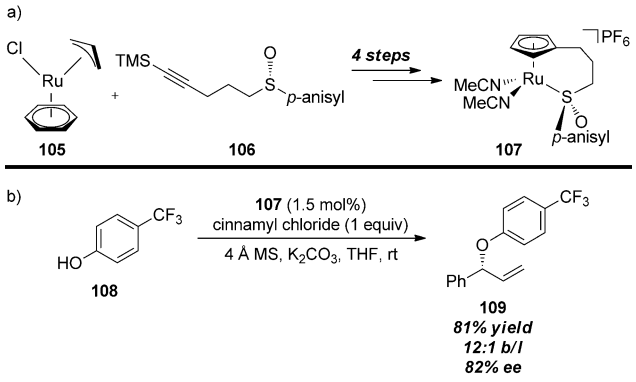
Figure 10. Wan's examination of the role of the sulfoxide substituent in olefin-sulfoxide ligands.

was found to be essential to obtain high levels of enantioselectivity. Surprisingly, incorporation of a 2-methoxy-1-naphthyl substituent (**104**) was reported to switch the sense of enantioselectivity, but no explanation was provided by the authors. Further optimization of the phenylene linker and the sulfonyl substituent allowed for the use of acyclic electrophiles, providing 3-aryl dihydrocinnamates in up to 92% yield and 91% *ee*.[58]

8. S,Cp Ligands

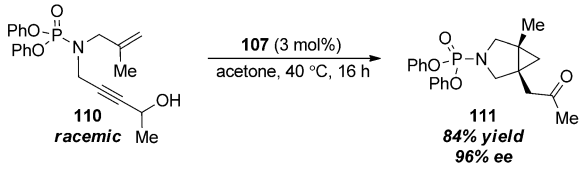
Cyclopentadienyl (Cp)-ligated metal complexes are well established as an important class of transition-metal catalysts.[59] In 2013, Trost et al. developed a novel class of Cp-sulfoxide ligands for ruthenium as a chiral analogue of $[CpRu(MeCN)_3]PF_6$. The tethered Cp/Ru complexes were synthesized in four steps from the corresponding alkyne-tethered sulfoxide (**106**), utilizing an oxidative [3+2] cycloaddition to form the cyclopentadienyl ligand (Scheme 31 a).[60a] This oxidative cyclization represents an atom-economic alternative to the traditional method of installing Cp ligands through the use of a Cp metal alkylating reagent (usually the highly toxic thallium salt). The resulting complexes were then utilized as catalysts in the branched-selective AAA of oxygen nucleophiles. As a representative example of this method, aryl ether **109** could be obtained in 81% yield and 82% *ee* with a 12:1 branched-to-linear ratio, which constitutes a formal synthesis of the antidepressant (−)-fluoxetine (Scheme 31 b).[61]

Very recently, ruthenium sulfoxide complex **107** was utilized as a catalyst in the enantioselective redox bicycloisomerization of propargyl alcohols with olefin tethers to



Scheme 31. Trost's sulfoxide-ligated CpRu catalyst for branched-selective AAA reactions. b = branched, l = linear, TMS = trimethylsilyl.

generate highly substituted bicyclic pyrrolidines. For example, racemic enyne **110** could be isomerized to bicycle **111** in 84% yield and 96% *ee* (Scheme 32). Notably, the use of chiral



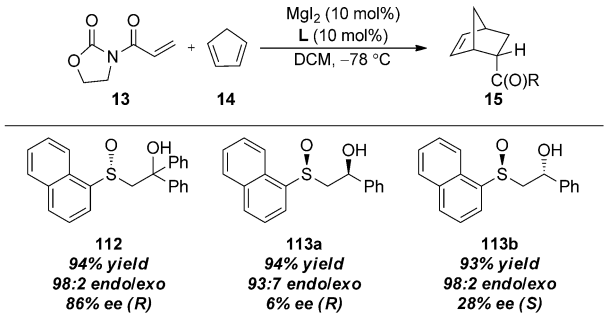
Scheme 32. Trost's CpRu sulfoxide catalyst enabled the first enantioselective Ru-catalyzed enyne cycloisomerization.

phosphine ligands such as BINAP and Feringa's ligand led to inhibition of the desired reaction. This cyclization is the first enantioselective Ru-catalyzed enyne cycloisomerization, highlighting that the use of chiral sulfoxide ligands can enable transformations previously inaccessible through the use of traditional chiral ligands.[60b]

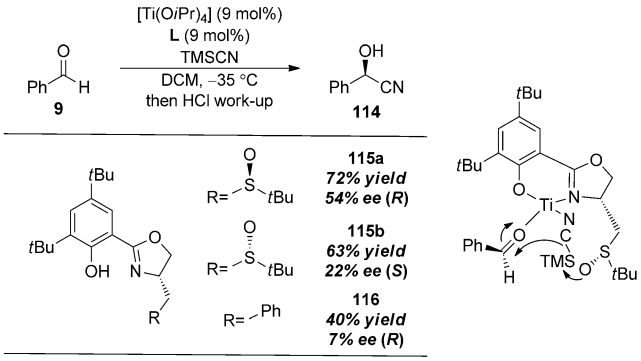
9. Other Ligands

Building on early work by Khiar et al. on asymmetric Diels–Alder reactions (see Section 3), Llera et al. showed that a series of β-hydroxysulfoxides (Scheme 33) could be used as chiral ligands in the same reaction using MgI_2 as the Lewis acid.[13,62] Interestingly, incorporation of both phenyl groups at the carbinol position is important for the enantioselectivity, as use of diastereomers **113a** and **113b** resulted in much lower selectivity in both cases.

In 2003, Rowlands developed a series of oxazolidine-sulfoxide ligands containing a pendant phenol for the Ti-catalyzed asymmetric addition of cyanide to benzaldehyde (Scheme 34).[63] Treatment of benzaldehyde with TMSCN in the presence of $Ti(OiPr)_4$ and the chiral ligand afforded cyanohydrin **114** in a 72% yield with a modest 54% *ee*. In this reaction, the sulfoxide was not anticipated to coordinate the catalyst, but rather to act as a Lewis base to desilylate the nucleophile. Despite not serving as a ligand, the stereochemistry of the sulfoxide was found to have a dramatic effect on



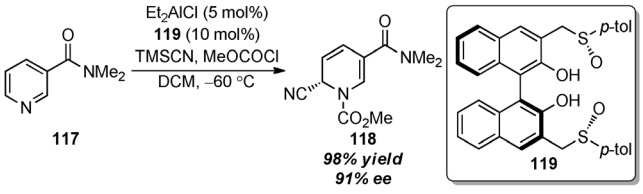
Scheme 33. Sulfoxide-alcohol ligands for a Lewis acid catalyzed Diels–Alder reaction.



Scheme 34. A pendant sulfoxide serves as a chiral Lewis base for cyanohydrin synthesis.

the enantioselectivity of the process, as opposite enantiomers of cyanohydrin **114** were formed using diastereomeric ligands **115a** and **115b**. Use of ligand **116**, which lacks the sulfoxide moiety, provided the desired product with a reduced yield as an almost racemic mixture (7% *ee*). This result indicates that an uncatalyzed reaction likely operates in the absence of the Lewis basic sulfoxide.

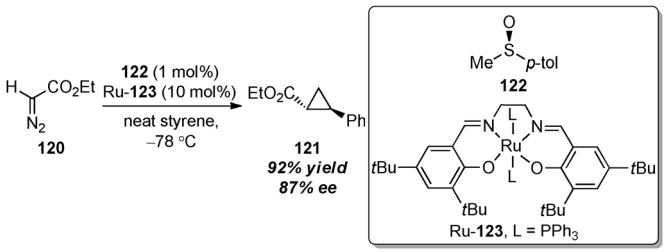
A similar system was later developed by Shibasaki et al. in 2004, whereby ligand **119** was utilized in an Al-catalyzed enantioselective Reissert reaction of pyridines.[64] Addition of cyanide to pyridine **117** using Et_2AlCl and ligand **119** furnished adduct **118** in 98% yield and 91% *ee* (Scheme 35). Use of diastereomeric complexes containing the (*S*)-BINOL backbone and both the *R*,*S*- and *S*,*R*-sulfoxide pairs resulted in severely diminished enantioselectivities (< 15% *ee*), illustrating the importance of the sulfur stereogenicity on the selectivity. As with the Rowlands system, the ligand is believed to coordinate to the Lewis acid through the



Scheme 35. Asymmetric Reissert reaction using a sulfoxide-BINOL ligand described by Shibasaki et al.

BINOL oxygen atoms, allowing the pendant sulfoxides to serve as Lewis basic sites for desilylation and delivery of the nucleophile. The use of alternative Lewis basic groups, such as phosphine oxides or phosphine sulfides, resulted in low regio- and enantioselectivities, serving as a testament to the unique nature of the sulfoxide moiety.

Finally, in 2005, Nguyen and co-workers disclosed the only use of a monodentate sulfoxide ligand for asymmetric catalysis since James' original chiral sulfoxide ligand was reported in 1976.[65] The report featured a chiral amplification strategy, in which chiral sulfoxide additives were used in conjunction with achiral salen ruthenium complexes to enable an asymmetric cyclopropanation reaction.[66] Indeed, use of sulfoxide **122** with achiral complex Ru-**123** furnished *trans*-cyclopropane **121** in 92% yield and 87% *ee* (Scheme 36).



Scheme 36. Nguyen's chiral amplification strategy using monodentate chiral sulfoxides.

Use of the sulfoxide additive is believed to induce a conformational change in the backbone of ligand **123**, pushing one end of the backbone (C1) up and the other end (C2) down (Figure 11). This induces asymmetry into the

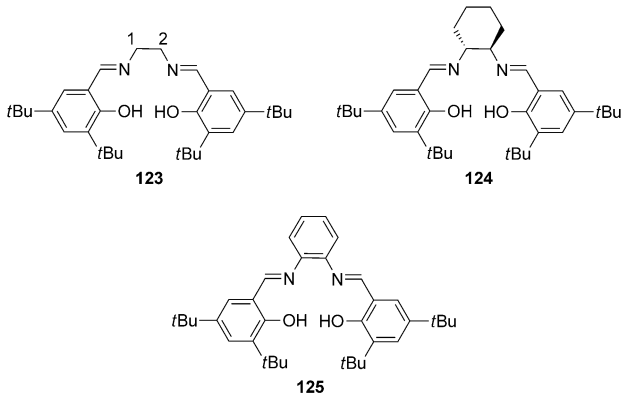


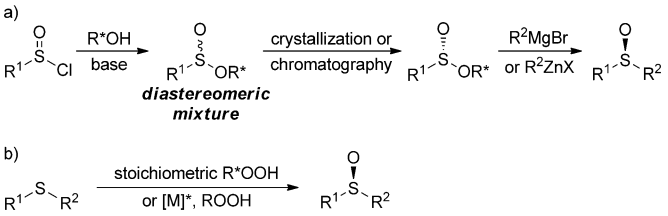
Figure 11. Chiral and achiral salen ligands.

achiral ligand backbone, allowing it to more closely resemble chiral salen-type ligands (**124**). Use of an analogous Ru complex containing a rigid phenylene diamine backbone (**125**) with sulfoxide **122** resulted in a non-selective reaction, which is consistent with the chiral amplification hypothesis.

10. Synthesis of Chiral Sulfoxides

The continued exploration and use of chiral sulfoxide ligands depends heavily on reliable methods to access chiral sulfoxides. The synthesis of enantiomerically pure sulfoxides is a growing field, in large part because of the biological significance of pharmaceutical agents containing chiral sulfoxide elements. Methods for the asymmetric synthesis of chiral sulfoxides have been reviewed several times in recent years.[67] As such, they will be discussed only briefly.

Two general strategies exist for the synthesis of enantiopure sulfoxides (Scheme 37). The first method involves the



Scheme 37. Two general methods for the synthesis of enantiopure sulfoxides.

synthesis of a chiral oxysulfinyl intermediate, followed by the stereospecific addition of an organometallic reagent (Scheme 37a). The second strategy involves the enantioselective oxidation of prochiral sulfides, either using chiral transition-metal catalysts or stoichiometric amounts of chiral oxidants (Scheme 37b).

10.1. The Andersen Method

The most established method for preparing chiral sulfoxides was pioneered by Andersen in 1962 (Scheme 37a).[68] In this procedure, a sulfinate ester containing a menthyl auxiliary is prepared from the corresponding sulfinyl chloride.[69] The resulting diastereomers are then separated by either crystallization or chromatography.[70] Finally, treatment with an organometallic reagent results in alkylation with inversion of configuration at the sulfur atom. Since Andersen's original report using (−)-menthol, a variety of auxiliary alcohols originating from the chiral pool have been examined (Figure 12), including diols and amino alcohols to prepare cyclic sulfite and sulfinamide intermediates.[71]

10.2. Enantioselective Sulfide Oxidation

Even though it is arguably the most robust method to access enantiomerically pure sulfoxides (the vast majority of the ligands discussed above were synthesized by alkylation of chiral sulfinates), the Andersen method requires the separation of the intermediary sulfinate diastereomers, through either crystallization or chromatography. An alternative approach, originally examined by Takata and Ando, involves the use of chiral hydroperoxides for the enantioselective

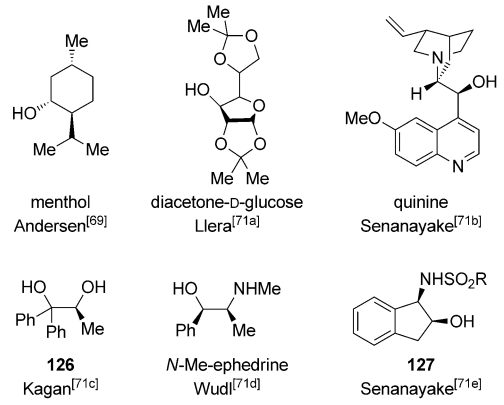


Figure 12. Chiral auxiliaries utilized for the synthesis of diastereomerically pure sulfinate ester intermediates.

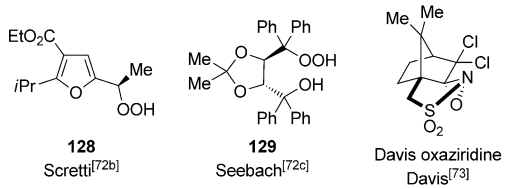
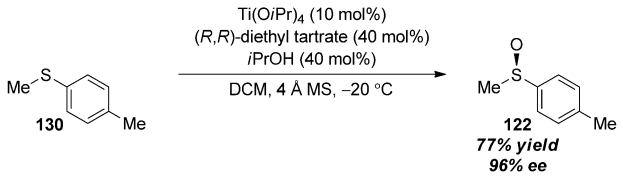


Figure 13. Chiral oxidants used for enantioselective sulfide oxidation.

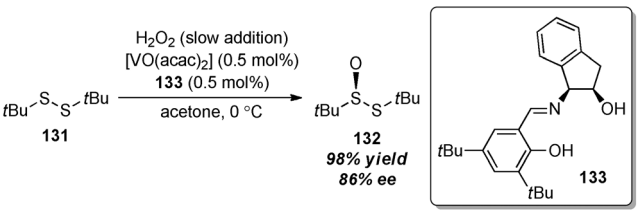
oxidation of sulfides to sulfoxides (Figure 13; **128** and **129**).[72a] Chiral oxaziridines derived from camphor have also been successfully used in enantioselective sulfide oxidations.[73]

Both the use of chiral sulfinate auxiliaries and chiral oxidants suffers from the waste of a stoichiometric amount of chiral material.[74] To address this, many groups have explored transition-metal-catalyzed enantioselective sulfide oxidation to access chiral sulfoxides.[75] The first reports on this approach were disclosed by the groups of Kagan and Modena, both using a modification of the Sharpless asymmetric epoxidation reaction.[76] For example, use of $Ti(OiPr)_4$ and cumene hydroperoxide with a diethyl tartrate ligand afforded sulfoxide **122** in 77% yield and 96% *ee* (Scheme 38).[76b] Since then, a variety of coordination complexes have been tested as catalysts for enantioselective sulfide oxidation.[77] Even though this avenue of sulfoxide preparation is perhaps most promising owing to its inherent atom economy and independence from the chiral pool, it suffers from a rather limited substrate scope and can therefore only be used in very specific circumstances.

Notably, Ellman and Weix have been able to utilize enantioselective oxidation with ligand **133** to prepare *tert*-butyl-*tert*-butanethiosulfinate (**132**), which they utilized as an



Scheme 38. Kagan's enantioselective Ti-catalyzed sulfoxidation.



Scheme 39. Enantioselective oxidation for the preparation of a chiral sulfinylation reagent as described by Ellman and Weix. acac = acetylacetonate.

intermediate towards the synthesis of *tert*-butanesulfinamide (Scheme 39).[78] Thiosulfinate **132**, however, can also be alkylated with organometallic reagents in a stereospecific fashion with inversion of configuration (as in the Andersen method) to prepare *tert*-butyl-substituted chiral sulfoxides.

11. Summary and Outlook

The use of chiral sulfoxides as ligands for asymmetric catalysis has experienced enormous growth since the original idea was explored by James in 1976. Building upon fundamental work from Hiroi and others, major breakthroughs have recently been achieved, which allow for the synthesis of optically active products with exceptionally high yields and enantioselectivities. The recent development of chiral sulfoxide-olefin ligands that allow for chirality switching is particularly promising.

New reports disclosing the development of chiral sulfoxide ligands, however, still reside in the proof-of-concept stage. As such, the scope of reactions explored using such ligands remains severely limited. In fact, the vast majority of the work covered in this Review centers on only two reactions: the palladium-catalyzed asymmetric allylic alkylation of symmetric electrophiles and the rhodium-catalyzed conjugate addition of aryl boronic acids to cyclic enones. New reactions with broader substrate scopes must be explored in the future if chiral sulfoxides are to move beyond being a novel ligand class.

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