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# The Emergence of Sulfoxides as Efficient Ligands in Transition Metal Catalysis

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Sulfoxides are capable of forming stable complexes with transition metals and there have been many comprehensive studies into their binding properties. However, the use of sulfoxides, particularly chiral sulfoxides, as ligands in transition metal catalysis is rather less well developed. This review aims to describe these catalytic studies and covers new developments that are showing very promising results and  
<sup>10</sup> that have led to a renewed interest in this field.

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## Introduction

Since the middle of the last century there has been an academic interest regarding the stereochemical properties of sulfoxides, their synthesis and their stability. This has more recently stimulated research into using sulfoxides as chiral auxiliaries in organic reactions.<sup>1</sup> The chirality in sulfoxides arises from their approximately pyramidal structure (Figure 1).<sup>2</sup> When the R groups are different from each other two possible enantiomers exist.

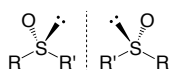


Fig. 1 Two enantiomeric forms of a sulfoxide

In the 1960's, enantiopure sulfoxides were made readily available when Andersen adapted a reaction first observed by Gilman,<sup>3</sup> by reacting enantiomerically pure menthyl *p*-toluene sulfinate with organometallic reagents in a classical S<sub>N</sub>2-type reaction.<sup>4</sup> Alternatively, enantiopure sulfoxides can be obtained either by:

- ) Resolution techniques; these involve making a salt, which is only possible if there is an acidic or basic group in the sulfoxide.<sup>5</sup>
- ) Or by enantioselective oxidation of sulfides.<sup>6</sup>

Although methods to enantioselectively oxidise sulfides have improved considerably since the 1960's, they still suffer from a lack of generality.<sup>7</sup> Therefore, Andersen's method remains the preferred method for generating enantiopure sulfoxides, because it is a relatively straightforward reaction which can be used to generate either enantiomer.<sup>8</sup> Andersen's method was later adapted by Kagan and coworkers to make a wide variety of chiral sulfoxides from chiral sulfites.<sup>9</sup> Cyclic sulfites were prepared with chirality at S, and one chiral -OR group. These could be reacted with an organometallic species, R<sup>1</sup>M, to give an enantiopure sulfinate. Reaction of the sulfinate with a second organometallic species, R<sup>2</sup>M, gave the enantiopure, chiral sulfoxide (Figure 2).

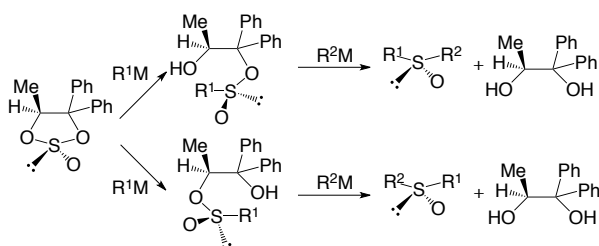


Fig. 2 Kagan's method for the synthesis of enantiopure sulfoxides

Fernandez *et al.* also extended the variety of chiral sulfoxides obtainable by making new enantiomerically pure sulfinate with diacetone-D-glucose as the -OR group.<sup>10</sup>

An advantage of using sulfoxides as chiral species in enantioselective organic transformations lies in their high optical stability. For the majority of sulfoxides, racemisation only occurs in appreciable amounts at around 200°C.<sup>11</sup> Exceptions to these being allyl and benzyl sulfoxides, where rearrangement reactions occur before pyramidal inversion at temperatures of 50-70°C and 130-150°C respectively.<sup>12</sup> Also, sulfoxides with a proton in the β-

position may undergo elimination to generate olefins at temperatures of around 80°C.<sup>13</sup>

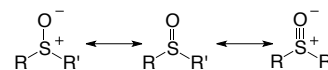


Fig. 3 The three canonical forms of sulfoxides

The S-O bond of a free sulfoxide molecule is polarised and can be thought of as existing in three canonical forms (Figure 3), with the first two being the main components. Owing to the polarised nature of the S-O bond, with a net positive charge on sulfur, sulfoxides are able to interact with both Lewis acids and transition metals.<sup>14</sup> The coordination of sulfoxides to metals has been comparatively well studied and many metal-sulfoxide complexes are known.<sup>14</sup> The use of these complexes in catalysis is, however, rather less well established and this review aims at covering the catalytic aspects in detail.<sup>15,16</sup>

## Metal Sulfoxide Complexes

Sulfoxides are able to bind to metals in two ways, either through the sulfur or through the oxygen. As a general rule, the 'hardness' or 'softness' of the metal centre determines how the sulfoxide will bind to it, with hard metal centres preferentially binding through O, and soft metal centres binding through S. An analysis by Calligaris<sup>14</sup> of all the X-ray crystal structures of sulfoxide complexes known to that date showed that across the periodic table there is a clear preference for O-bound complexes. This might appear somewhat unexpected but is at least in part due to the high degree of polarisation of the S-O bond (Figure 3), which favours O-bonding over S-bonding. However, groups 8-10 of the periodic table show a preference for S-bound sulfoxides. Sometimes, the same metal can bind through S or O, depending on the oxidation state of the metal and the other ligands surrounding the complex and there can be S- and O-bound sulfoxides within the same complex.<sup>17</sup> To determine whether a sulfoxide is S- or O-bound, an X-ray crystal structure is the surest way, but IR data can also be indicative and useful. It is widely accepted that binding of a sulfoxide through S causes a decrease in the S-O bond length, whereas binding through O leads to an increase.<sup>17</sup> These changes in bond length can be seen as a variation in the stretching frequency of the bond.

In an important contribution by Calligaris, Alessio and coworkers, steric profiling of common, monodentate sulfoxide ligands has been reported.<sup>18</sup> Using the concept of solid cone angles ( $\Omega$ ),<sup>19</sup> the circular cone apertures representing Tolman's cone angles ( $\Theta$ ) were derived. The authors fixed the bond distances for S-bound and O-bound metal complexes [M-(SORR') = 2.28 Å and M-(OSRR') = 2.10 Å]. Table 1 gives a small overview on sulfoxide ligands and values for the corresponding phosphines as reported by Tolman.<sup>20</sup> As can be expected, moving from the corresponding tertiary phosphines to S-bound sulfoxides leads to a decrease in steric of the ligand (due to the substitution of an R group with the sulfinyl moiety). More significantly, moving from an S-bound to an O-bound sulfoxide ligand generates another decrease in cone angle by approximately another 10°. This may, in case of relatively bulky sulfoxide ligands, favour the O-bound over the S-bound ligand even in

situations where the latter arrangement is electronically more likely, or lead to cases where O-bound and S-bound ligands are in equilibrium.<sup>21</sup>

**Table 1** Tolman's cone angles ( $\Theta$ ) for representative sulfoxides and phosphines

R	$\Theta$ (degrees) <sup>a</sup>		
	SOR <sub>2</sub>	OSR <sub>2</sub>	PR <sub>3</sub>
Me	112	100	118
Et	127	119	132
<sup>i</sup> Pr	141	122	160
Ph	124	107	145

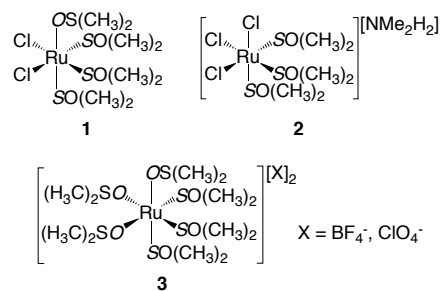
<sup>a</sup> The cone angles were calculated using the following metal-to-ligand bond lengths: M-S = 2.28 Å, M-O = 2.10 Å, M-P = 2.28 Å

In the following sections, some metal complexes with DMSO (dimethylsulfoxide) and other sulfoxides will be discussed, along with some (non-catalytic) applications of these metal complexes. The metal complexes with DMSO and other small sulfoxides have been studied since the 1960's and there are already several exhaustive review articles on the subject,<sup>14,22,23,24</sup> so herein these types of complexes will be covered only briefly, concentrating on metals relevant to the subsequent section on catalytic applications (Ru, Rh, Ir, Pd, Pt, Cu). It should be noted that sulfoxide-containing complexes are often used as precursors to make other coordination compounds and that DMSO-metal complexes were of interest early on for their potential activity in homogeneous catalysis.<sup>25,26,27</sup>

### Ruthenium DMSO Complexes

The first reported complex of ruthenium with DMSO was dichlorotetrakis(dimethylsulfoxide)ruthenium(II) **1**, synthesised in 1971 by James *et al.*<sup>28</sup> The synthesis was achieved by refluxing hydrated ruthenium trichloride in DMSO under an atmosphere of hydrogen. Wilkinson later showed that the hydrogen atmosphere was unnecessary,<sup>29</sup> and suggested that the complex contained both S- and O-bound sulfoxides. This was confirmed by an X-ray crystal structure determination of the complex. The complex has one O-bound ( $OS(CH_3)_2$ ) and three S-bound ( $SO(CH_3)_2$ ) DMSO ligands, with the chlorides in a *cis* arrangement (Figure 4).<sup>30</sup> Interestingly, the analogous bromo complex of **1** contains the bromides in a *trans* arrangement. The *cis*-chloro complex can be converted to the *trans*-chloro complex by photoisomerisation at room temperature in DMSO<sup>31</sup> and a method to obtain the *trans*-isomer directly was described later.<sup>32</sup>

It is also possible to synthesise complex **2**, where the O-bound DMSO ligand in **1** is replaced by a chloride (Figure 4)<sup>33</sup> by refluxing hydrated ruthenium trichloride with a stoichiometric amount of DMSO in *N,N*-dimethylacetamide. Wilkinson and Trotter observed that dissolving complexes **1** and **2** in an aqueous solution of silver nitrate abstracted the chlorides and replaced them in the complex by H<sub>2</sub>O ligands.<sup>29,33</sup>

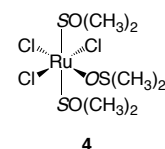


$SO(CH_3)_2$  = S-bound sulfoxide

$OS(CH_3)_2$  = O-bound sulfoxide

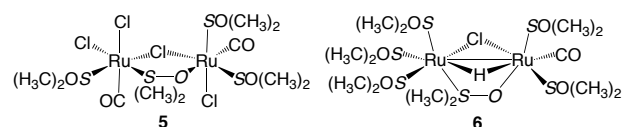
**Fig. 4** Ru(II) DMSO complexes

Abstraction of the chloride ligands using silver salts was also used to access complex **3** from complex **1** in a solution of DMSO;<sup>17,29</sup> this complex has three S-bound and three O-bound DMSO ligands, with each S-bound ligand *trans* to an O-bound ligand. It was not until the early 1990's that a Ru(III) DMSO complex was unequivocally made (Figure 5).<sup>34</sup>



**Fig. 5** Ru(III) DMSO complex

The development of ruthenium sulfoxide complexes continued with the discovery that DMSO can act as a bridging S,O-bidentate ligand (Figure 6).<sup>35,36</sup> The length of the S-O bond of the bridging sulfoxide is between the lengths of the S-O bonds in the solely S-bound and solely O-bound sulfoxides.



**Fig. 6** Ruthenium complexes with bridging DMSO ligands

### Rhodium and Iridium DMSO Complexes

The first Rh(I) and Ir(I) complexes containing only DMSO as a dative ligand were reported by Milstein *et al.* (Figure 7).<sup>37,38,39</sup> S-bound  $Rh(DMSO)_3Cl$  (**7**) and  $Ir(DMSO)_3Cl$  (**8**) were synthesised by treating a toluene slurry of  $[M(COE)_2Cl]_2$  (M = Rh, Ir; COE = cyclooctene) with an excess of DMSO. When the same reaction was repeated (M = Rh) with only 2-4 equivalents of DMSO, complex **9** with a bridging sulfoxide was obtained. Addition of diethyl ether to a  $CH_2Cl_2$  solution of complex **8** gave dimeric  $[Ir(DMSO)_2Cl]_2$  (**10**). Treating **8** or **10** in acetone with H<sub>2</sub>O led to complex **11** by formal oxidative addition of a water molecule.

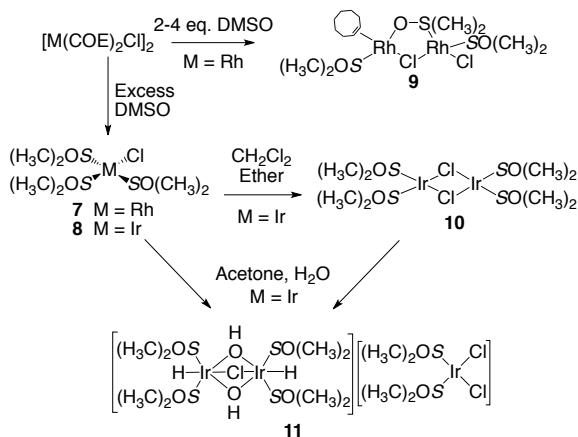


Fig. 7 Rh(I) and Ir(I) DMSO complexes

Cationic DMSO complexes **13** and **14** were synthesised by substituting the acetone and COE ligands in **12** with DMSO. These homoleptic complexes contain two S-bound and two O-bound ligands. The iridium complex **14** oxidatively added H<sub>2</sub>O to form complex **15** (Figure 8).

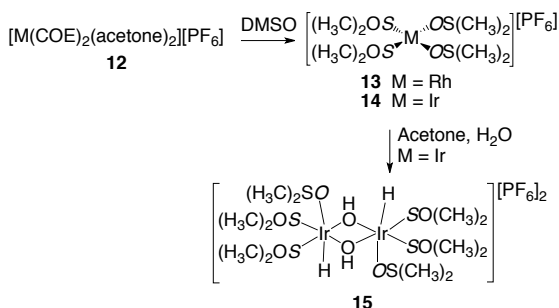


Fig. 8 Cationic Rh(I) and Ir(I) DMSO complexes

As seen in the complexes above, there seems to be a subtle balance between S- or O-binding of the DMSO ligands with the 'softer', neutral metal centres coordinating solely through the sulfur atom and cationic complexes resulting in mixed S- and O-bound DMSO. More recent work describing the structures of even 'harder', di- and tricationic rhodium(III) complexes [Rh(OS(CH<sub>3</sub>)<sub>2</sub>)<sub>5</sub>(SO(CH<sub>3</sub>)<sub>2</sub>)](CF<sub>3</sub>SO<sub>3</sub>)<sub>3</sub> and [Rh(OS(CH<sub>3</sub>)<sub>2</sub>)<sub>3</sub>(SO(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>Cl](CF<sub>3</sub>SO<sub>3</sub>)<sub>2</sub> have appeared.<sup>40</sup>

### Palladium and Platinum DMSO Complexes

Palladium and platinum complexes with DMSO of the general formula M(DMSO)<sub>2</sub>Cl<sub>2</sub> were synthesised and characterised in the 1970s. Both DMSO ligands were found to bind through sulfur.<sup>41</sup> Crystal structures of these compounds revealed that in the platinum case, the DMSO ligands were *cis* to one another,<sup>42</sup> but in the palladium case they were *trans*.<sup>43</sup> Subsequently, dicationic Pd and Pt complexes with four bound DMSO ligands were prepared.<sup>41b</sup> As discussed above for rhodium and iridium, these harder, cationic complexes were comprised of two S-bound and two O-bound DMSO ligands and their structure confirmed by X-ray crystallographic analyses.<sup>44,45</sup> In both complexes the similarly bound ligands were *cis* to each other.

### Copper DMSO Complexes

From available literature data, copper clearly prefers binding DMSO and other sulfoxide ligands through their oxygen atom, which originates from its harder nature as well as the fact that the sulfinyl unit is highly polarised.<sup>1</sup> For example, complexes of Cu(II) of general formula Cu(DMSO)<sub>2</sub>X<sub>2</sub> (DMSO ligands *trans*

to one another) and their dicationic counterpart [Cu(DMSO)<sub>4</sub>](ClO<sub>4</sub>)<sub>2</sub> show exclusive O-binding of the DMSO ligands.<sup>46</sup> Nevertheless, two crystallographically characterised examples where a DMSO moiety binds through its sulfur atom to polymeric copper compounds have been reported recently, although they show rather long Cu-S distances.<sup>47</sup>

### Bissulfoxide Metal Complexes

Bissulfoxide compounds with a methylene<sup>48</sup> or ethylene<sup>49</sup> bridge were first made in 1912 (Figure 9). The *meso* (*R,S*) form of **16a** was not separated from the racemate (*R,R* and *S,S*), and was not characterised until much later.<sup>50</sup> The crystal structure of *meso* **17a** was reported in 1976.<sup>51</sup>

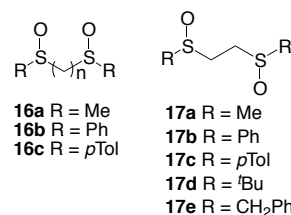
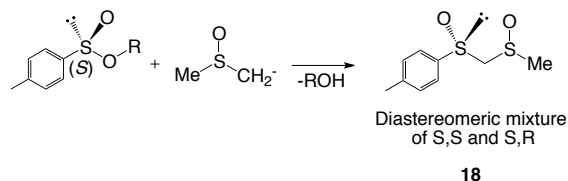


Fig. 9 Methylene and ethylene bridged bissulfoxides

A similar, enantiomerically pure bissulfoxide, **18**, was prepared by reacting the methylsulfinylcarbanion (made by treating DMSO with a strong base *e.g.* NaH) with (-)-menthyl-*(S)*-*p*-tolyl sulfinate (Figure 10). A mixture of the *meso* form and the enantiomerically pure bissulfoxide was obtained, which could be separated by crystallisation.<sup>52</sup>

Fig. 10 Preparation of **18** from methylsulfinylcarbanion and (-)-menthyl-*(S)*-*p*-tolyl sulfinate

This method was extended to produce other bissulfoxides by varying the substituents on the sulfinylcarbanion and sulfinate.<sup>53</sup> The sulfinylcarbanion was also used in the synthesis of **17c**. Two equivalents of the optically pure *p*-tolyl-sulfinylcarbanion were joined by a CuCl<sub>2</sub> mediated oxidative coupling to give the bissulfoxide (Figure 11).<sup>54</sup>

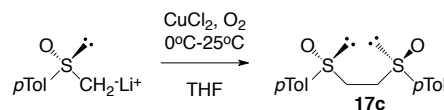


Fig. 11 Oxidative coupling method affording bissulfoxides

Ligand **17a** was used in complexation studies with several transition metals.<sup>55</sup> It was found that with the first row metals and Cd(II), complexes with the formula [M(ligand)<sub>3</sub>]<sup>2+</sup> are formed, where M = Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II). Furthermore, the IR spectra were indicative of binding through oxygen. However, with Pd(II) and Pt(II), the complexes incorporated only one bissulfoxide [M(ligand)Cl<sub>2</sub>], and exclusive S-binding of the sulfoxides was observed by IR spectroscopy. A platinum complex was also made with **17b**, and a crystal structure of this compound was obtained,<sup>56</sup> showing coordination through sulfur.

The complexation of **17c** was studied with several late transition metals, namely Pd(II), Pt(II), Rh(I) and Ir(I) by Evans

and coworkers.<sup>57</sup> The authors noted that these complexes were sterically and electronically dissymmetric. For example, in [Ir(COD)**17c**]BF<sub>4</sub> (COD = cyclooctadiene) the Ir-C bonds *syn* to the *p*-tolyl groups were considerably longer than those *anti* to the *p*-tolyl groups. Evans also made Rh- and Ir-dimers with this ligand of the form [M( $\mu$ -Cl)**17e**]<sub>2</sub> (M = Rh, Ir).

Analogous structures to these were synthesised with **17d**, leading to the isolation of [M( $\mu$ -Cl)**17d**]<sub>2</sub> (M = Rh, Ir), and reactivity studies were reported with these complexes.<sup>58</sup> Some interesting compounds were made by stoichiometric addition of pyridine derivatives to these Rh- and Ir-dimers to give monomeric structures (Figure 12). In most cases, pyridine derivatives with substituents in the 2-position (-CH<sub>3</sub>, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>OH) simply cleaved the chloride bridge, binding to the metal through the nitrogen in the ring only. When a sterically demanding alcohol was incorporated in the benzylic 2-position of the pyridine, oxidative addition of the O-H bond was observed resulting in complex **19**. Oxidative addition of the N-H bond in the analogous amine derivative was not observed, but addition of AgPF<sub>6</sub> gave the isolable cationic complex **20**. Analogous structures to [M(DMSO)<sub>4</sub>]PF<sub>6</sub> (where M = Rh, Ir) described earlier<sup>39</sup> were also made, containing S-bound and O-bound bisulfonide ligands respectively (**21**).

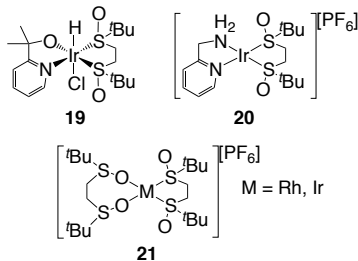


Fig. 12 Monomeric Ir-bisulfonide complexes with **17d**

Recently, platinum dichloride complexes were reported of the methylene bridged bisulfonides with substituents on the bridge (Figure 13).<sup>59</sup> Ligand **22** was first synthesised by Khair *et al.* and was used in asymmetric Diels-Alder reactions (see later discussion).<sup>60</sup>

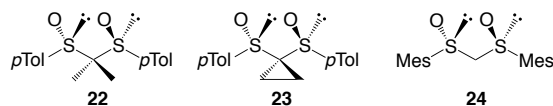


Fig. 13 Methylene bridged bisulfonide ligands

Inspired by earlier work,<sup>10,61</sup> Malacria *et al.* recently reported the syntheses of **23** and **24**. The formation of platinum dichloride complexes with ligands **16a** (Figure 9), **22**, **23** and **24** were attempted, but the only isolated complexes were those incorporating **22** and **23**. The *gem*-substituents are apparently very important for forcing the correct orientation of the sulfonides, so that they coordinate with platinum in 4-membered S-bound metallacycles.

Pettinari and Crucianelli made ethylene bridged bisulfonide ligands with additional ethyl substituents on the backbone, **25**.<sup>62</sup> The synthesis was achieved using the same oxidative coupling method shown in Figure 11, by preparing and reacting the lithiated derivative of *n*-propyl *p*-tolyl sulfoxide. This gave a diastereomeric mixture of bisulfonide ligands, which were separated by column chromatography. The three diastereomers were then reacted with Pd(CH<sub>3</sub>CN)<sub>2</sub>CIX (where X = Cl or NO<sub>2</sub>) as shown in Figure 14, providing **26** in good yield. The cationic rhodium complex, **27**, was also obtained with the *meso* ligand, by abstracting the chlorides from [Rh(COD)Cl]<sub>2</sub> with silver salt in a

solution containing the ligand.

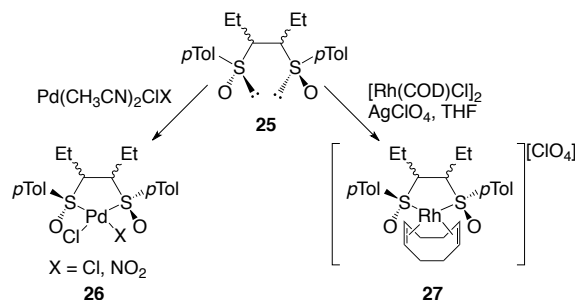


Fig. 14 Diastereoisomers of **25** and their Pd and Rh complexes

Another bisulfonide ligand reported by Poli *et al.* was generated from two units of benzothiophene, which were first oxidised to give enantiopure benzothiophene oxide and then coupled to give the bisulfonide.<sup>63</sup> The synthesis of the ligand produced a mixture of diastereoisomers, but only one of them had the correct geometry to bind to PdCl<sub>2</sub> to give enantiomerically pure palladium complex **28** (Figure 15). No crystal structure was obtained of this complex, but IR spectroscopy indicated that the ligand was S-bound.

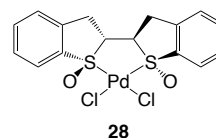


Fig. 15 Enantiomerically pure palladium complex of a benzothiophene oxide derived bisulfonide ligand

In the last twenty years, there have been sporadic examples of bisulfonide ligands with C<sub>2</sub>-symmetry and aromatic backbones, the first example being (*S,S*)-1,2-bis(*p*-tolylsulfonyl)benzene (BTSSB), **29**.<sup>64</sup> The ligand was successfully used by Shibasaki *et al.* to make compounds with Ru(II), **30**, Rh(I), **31**, and Pd(II), **32**, (Figure 16). A crystal structure of the palladium complex, **32**, revealed the ligand to be S-bound. The palladium complex with BTSSB will be discussed later as a catalyst for allylic alkylation reactions.

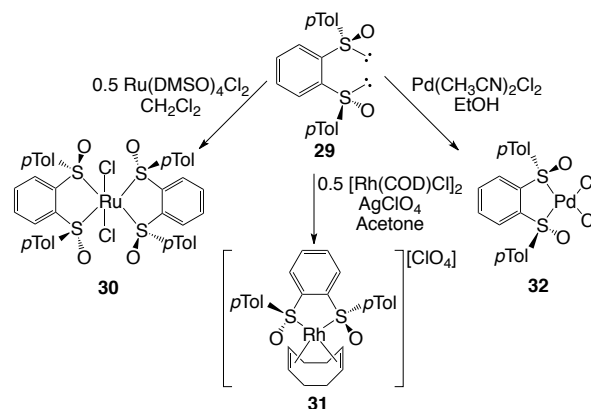


Fig. 16 Complexes made with BTSSB, **29**

Palladium and platinum complexes of the bisulfonide ligand *p*-tolyl-binaso (see also later discussions) was synthesised in the Dorta group.<sup>65</sup> It was found that in the cationic complex, **33**, the ligand was coordinated in a *cis*-κ<sup>2</sup>-S,O fashion (Figure 17). These studies also revealed that the *trans* effect of other ligands in Pt-binaso complexes determine the lability of the metal-sulfonide bond.

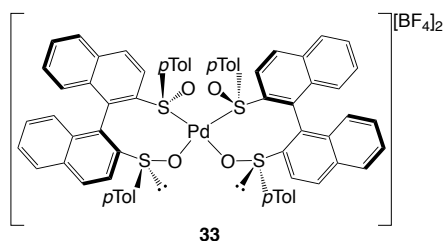


Fig. 17 Dicationic palladium *p*-tolyl binas complex

### Sulfoxide-containing Chelate Complexes

Given the above-mentioned studies on sulfoxide binding to LTM, it is not surprising that numerous reports exist that incorporate the sulfinyl group in chelates where other metal-binding moieties are present. In many cases, the sulfoxide is used as a possible replacement of a phosphine or nitrogen-based binding unit and selected examples with such structures are covered very briefly below. Catalytic applications of some of these and other mixed ligands will be presented and discussed in later sections.

An interesting bisulfoxide-pincer ligand, prepared as a diastereomeric *rac/meso* mixture, was studied through its complexation with palladium to give **34** (Figure 18).<sup>66</sup> The authors were able to separate the *rac* from the *meso* form in complex **34**, and both were found to be S-bound with *rac*-**34** showing higher stability. ESI-MS analysis of *rac*-**34** in methanol revealed that the major cationic species present had a mass corresponding to  $[(2,6-(i\text{-PrS(O)CH}_2)_2\text{C}_6\text{H}_3\text{Pd}]_2-\mu^2\text{-Cl}^+$ . As was previously observed with Pd(NCN) pincer complexes,<sup>67</sup> it seems that dimerisation is also possible with bisulfoxide-pincer palladium complexes.

Pyridine-based pincer complexes of Rh(I) and Ir(I) with an S-bound sulfinyl and a diethylamine coordination were reported by Milstein *et al.* and a series of cationic (Rh, Ir) and neutral (Rh) complexes were described.<sup>68</sup> The authors also showed that for cationic carbonyl-containing complexes **35**, deprotonation of the  $\alpha$ -carbon of the sulfoxide-bridge with a strong base was facile and lead to the dearomatised version of the pincer ligand complexes, **36**.<sup>69</sup> Dissolving the rhodium complex in acetic acid regenerated the cationic starting complex **35**.

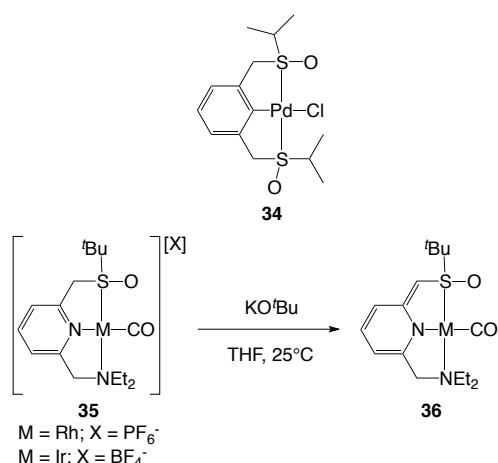


Fig. 18 Complexes of pincer ligands containing sulfoxides

Recently, a related pincer-type tridentate diphosphinosulfinyl ligand was described.<sup>70</sup> Binding properties of the ligand were studied in detail for a variety of LTMs (Rh, Ir, Ni, Pd and Pt) and stoichiometric reactivities were reported. In all cases, the ligand is binding in a  $\kappa^3$ -PS(O)P fashion and supports tetrahedral, square planar (**37**, Figure 19), trigonal-bipyramidal and octahedral geometries.

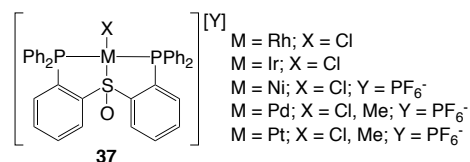


Fig. 19 Late transition metal S(O)P<sub>2</sub> pincer-type complexes

Mixed bidentate sulfoxide-phosphine ligands as well as representative examples of other sulfoxide containing chelates are abundant in the literature and a selection of structures, which are relevant for the catalytic discussion that follows include crystallographically characterised complexes **38**,<sup>71</sup> **39**,<sup>72</sup> **40**,<sup>62</sup> **41**,<sup>73</sup> **42**,<sup>74</sup> **43**,<sup>75</sup> and **44**,<sup>76</sup> **45**,<sup>77</sup> and **46**,<sup>78</sup> (Figure 20). A special mention deserves complex **46**, which shows non-bonding interactions between the apical sulfoxide moieties and the palladium metal centre (absent in the related platinum complex), as it might help explain some of the catalytic findings with palladium sulfoxide catalysts described below.

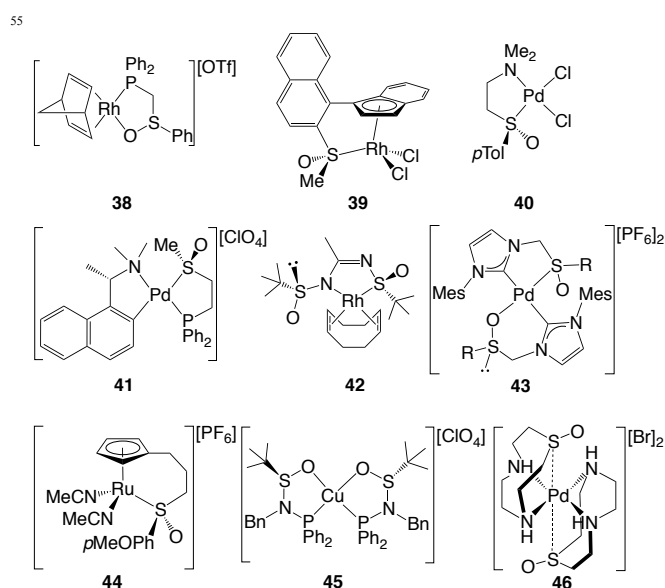


Fig. 20 Examples of complexes with mixed chelate ligands containing sulfoxide binding

Finally, we would like to mention some of the work of Riera and Verdager *et al.*,<sup>79</sup> who used sulfinyl containing ligands as chiral promoters in cobalt-mediated stoichiometric asymmetric Pauson-Khand reactions. The PNSO<sup>79a</sup> and PCSO<sup>79b</sup> ligands were bound to the two cobalt centers in a bridging fashion through ligation at the phosphorus and sulfur atoms as shown in Figure 21. While the PNSO-cobalt complexes gave excellent results in the Pauson-Khand reaction, the yields and *ee*'s were lower when PCSO ligands were applied.

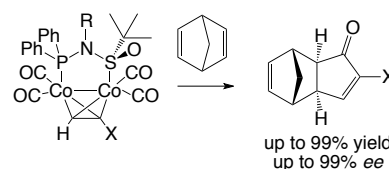


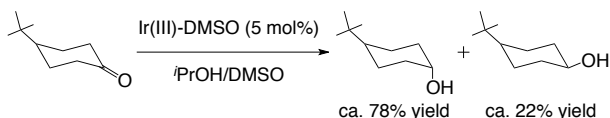
Fig. 21 Pauson-Khand reaction with PNSO ligands

## Non-enantioselective Catalysis with Sulfoxide Ligands

### Early Developments

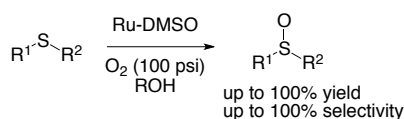
Iridium complexes with DMSO ligands first became of interest

when Henbest and co-workers demonstrated their catalytic activity in the reduction of cyclohexanones to alcohols (Figure 22).<sup>80</sup> Most systems performing the same transformation known until that time gave predominantly the equatorial alcohol, but the



**Fig. 22** Reduction of cyclohexanones by iridium DMSO complexes

The Ir complexes used for this reaction were  $\text{Ir}(\text{DMSO})_3\text{Cl}_3$  and the iridium acid  $[\text{HDMSO}_2][\text{Ir}(\text{DMSO})_2\text{Cl}_4]$ , giving an axial:equatorial ratio of 78:22 for the above reaction. The mechanism of the reaction was investigated, but it appeared to be quite complex.<sup>26,81</sup> An iridium hydride intermediate,  $\text{HIr}(\text{DMSO})_3\text{Cl}_2$  was isolated and an X-ray crystal structure analysis performed.<sup>82</sup> This revealed that the DMSO *trans* to the hydride was weakly bound and labile, suggesting it dissociates during catalysis. Following this, James reported that the same system can be used to selectively reduce the carbonyl bond of an  $\alpha,\beta$ -unsaturated aldehyde, with very little, if any, reduction of the olefin.<sup>83</sup> This success was however limited to aldehydes, as in the case of using  $\alpha,\beta$ -unsaturated ketones, indiscriminate reduction of both the carbonyl and the olefin was observed.



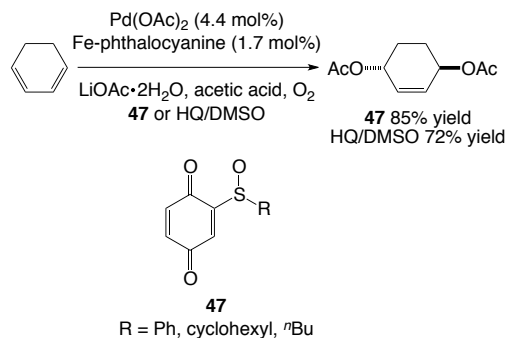
**Fig. 23** Oxidation of sulfides to sulfoxides catalysed by ruthenium DMSO complexes

On the other hand, ruthenium DMSO complexes have been shown to be successful catalysts for the molecular oxidation of sulfides to sulfoxides.<sup>84,85</sup> *cis*- $\text{Ru}(\text{DMSO})_4\text{Cl}_2$ , *trans*- $\text{Ru}(\text{DMSO})_4\text{Cl}_2$  and *mer*- $\text{Ru}(\text{DMSO})_3\text{Cl}_3$  all displayed good activity, and no over-oxidation to the sulfone was detected (Figure 23).

## Palladium Catalysed Reactions

### Palladium DMSO systems in catalysis

It was noticed by Bäckvall and co-workers that the use of catalytic amounts of sulfoxide in combination with  $\text{Pd}(\text{OAc})_2$  in the 1,4-diacetoxylation of 1,3-dienes improved both the conversion and regioselectivity of the reaction.<sup>86</sup> The group first attempted the reaction with a sulfinylbenzoquinone, **47**, (benzoquinone is normally employed in the reaction as an oxidant), but they later observed that the catalytic mixture of 1,4-hydroquinine (HQ) and DMSO gave the same selectivity (Figure 24). It was reasoned that binding of a sulfoxide to palladium encourages formation of a ( $\sigma$ -allyl)-palladium complex with the 1,3-diene, which facilitates internal migration of the acetate. Speckamp and co-workers later used a similar catalytic system comprised of  $\text{Pd}(\text{OAc})_2$ , DMSO and  $\text{Cu}(\text{OAc})_2$  to carry out oxidative cyclisations, in good yield and excellent selectivity for the 5-exo cyclisation product.<sup>87</sup>

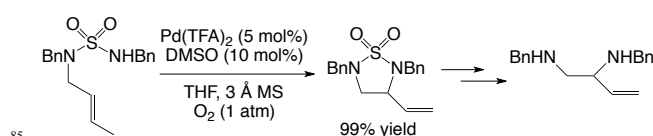


**Fig. 24** Palladium catalysed 1,4-diacetoxylation of 1,3-dienes with sulfoxides as co-catalysts

The reactions mentioned above require the use of iron phthalocyanine or  $\text{Cu}(\text{OAc})_2$  as an external oxidant to recycle the palladium catalyst by reoxidising it from  $\text{Pd}(0)$  to  $\text{Pd}(II)$ . Speckamp *et al.* subsequently discovered that the metal co-oxidant could be replaced by an atmosphere of molecular oxygen, if DMSO was used as the solvent. These conditions provide the added advantages of requiring less catalyst and giving higher yields, in shorter reaction times for the palladium catalysed oxidative cyclisation of allylic amines.<sup>88</sup> The groups of Bäckvall and Larock further explored the scope of this catalytic system, finding it could be successfully applied to other oxidative cyclisations<sup>89</sup> and the conversion of enol silanes to enones and enals.<sup>90</sup> The reason this catalytic system was successful was still unclear at that point, although it had been speculated that Pd clusters were responsible for the catalysis. To investigate this theory, Speckamp and co-workers performed TEM imaging on typical reaction solutions and observed that Pd clusters were indeed present.<sup>91</sup> They proposed that these clusters enable catalysis and reoxidation of  $\text{Pd}(0)$  to  $\text{Pd}(II)$  by molecular oxygen, and that they are stabilised by ligation of DMSO to palladium.

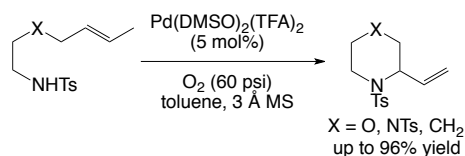
Later Stahl and co-workers explored the mechanistics of the  $\text{Pd}(\text{OAc})_2/\text{DMSO}$  catalytic system in aerobic alcohol oxidation and found the turnover-limiting step to be the aerobic oxidation of  $\text{Pd}(0)$  to  $\text{Pd}(II)$ .<sup>92</sup> However, further studies revealed that this is due to the low solubility of molecular oxygen in DMSO.<sup>93</sup> For similar reactions in other solvents, the  $\text{Pd}(II)$ -mediated oxidation of the alcohol was shown to be the turnover-limiting step in the catalytic cycle.

The same group more recently used a  $\text{Pd}(\text{TFA})_2/\text{DMSO}$  (TFA = trifluoroacetate) catalyst system for the aerobic oxidative cyclisation of allylic sulfamides, the products of which could easily be converted to diamines (Figure 25).<sup>94</sup>



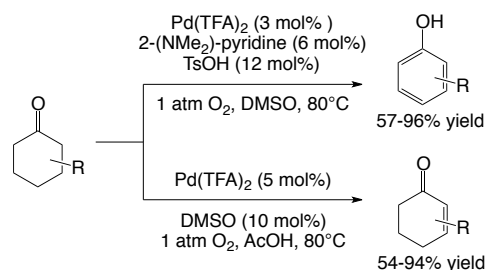
**Fig. 25** Aerobic oxidation of allylic sulfamides using the  $\text{Pd}(\text{TFA})_2/\text{DMSO}$  catalyst system

Isolated  $\text{Pd}(\text{DMSO})_2(\text{TFA})_2$  was also used as a catalyst in the oxidative amination of alkenes to form 6- and 7-membered nitrogen heterocycles in good yields (Figure 26).<sup>95</sup> These types of cyclic structures are abundant in natural products, so a simple way of forming them is very useful. Based on mechanistic studies, the authors suggested that the reaction proceeded by an aminopalladation of the alkene rather than a C-H activation pathway.



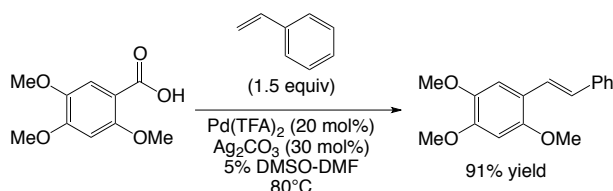
**Fig. 26** Intramolecular oxidative amination catalysed by  $\text{Pd}(\text{DMSO})_2(\text{TFA})_2$

The  $\text{Pd}(\text{TFA})_2/\text{DMSO}$  system was also used in the dehydrogenation of substituted cyclohexanones to yield phenols.<sup>96</sup> However, in this example DMSO was used as the solvent rather than in catalytic amounts and the addition of 6 mol% 2-(*N,N*-dimethylamino)pyridine and 12 mol% *p*-toluenesulfonic acid were also required to obtain the product in good yield (Figure 27 top). Stahl *et al.* subsequently discovered that a slightly different catalyst system efficiently dehydrogenated the same substrate only partially, giving the cyclic  $\alpha,\beta$ -unsaturated enone rather than the phenol as the product (Figure 27 bottom).<sup>97</sup> Investigations into the mode of coordination of DMSO to Pd(II) in solution in the  $\text{Pd}(\text{TFA})_2/\text{DMSO}$  system led to the conclusions that two molecules of DMSO interact with the Pd centre, one through O and one through S and that both of these bound DMSO ligands facilitated catalysis.<sup>98</sup> The O-bound DMSO is labile and allows the substrate to access the coordination sphere, whereas the S-bound DMSO stabilises Pd(0), meaning that it can be oxidised back to Pd(II) rather than precipitating out as Pd black. Very recently, further studies revealed that DMSO had minimal kinetic influence on the rate of dehydrogenation of cyclohexanone to cyclohexenone, but that it strongly inhibited the conversion of cyclohexenone to phenol.<sup>99</sup> The latter step becomes feasible under conditions that enable the conversion to Pd nanoparticles.<sup>100</sup>



**Fig. 27** Palladium catalysed aerobic dehydrogenation of cyclohexanones

Decarboxylative Heck-type olefinations (Figure 28) and protodecarboxylations were catalysed by  $\text{Pd}(\text{TFA})_2$  in a mixture of 5% DMSO in DMF or toluene.<sup>101</sup> Detailed experimental and theoretical studies showed the role of DMSO as a ligand,<sup>102</sup> and intermediates with bound DMSO ligands were characterised by X-ray crystallographic analyses.<sup>102b</sup>

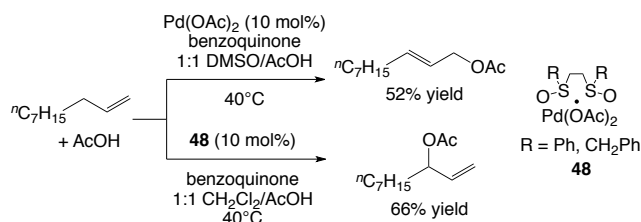


**Fig. 28** Decarboxylative Heck-type olefination

Related examples where DMSO has been used as an additive in palladium catalysed reactions have appeared and while we do not intend to cover these cases due to the unclear role DMSO is playing in these reactions, selected examples can be found in the reference section.<sup>103,104</sup>

#### 45 Palladium bissulfoxide systems in catalysis

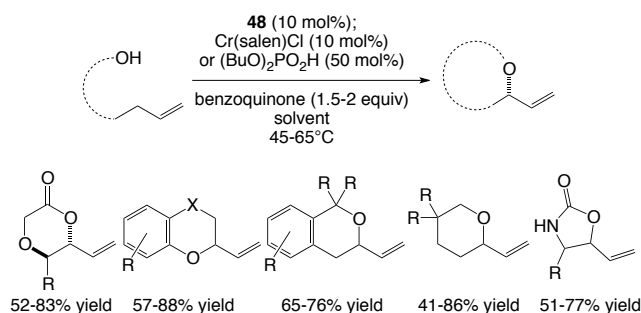
In initial work, White and co-workers showed that a catalyst system comprised of  $\text{Pd}(\text{OAc})_2$ , DMSO and 2 equivalents of benzoquinone was able to selectively catalyse an allylic C-H oxidation reaction of a monosubstituted olefin (Figure 29 top).<sup>105,106</sup> The authors noticed that the reaction without DMSO gave a mixture of addition products and therefore developed and tested compounds **48**, which comprise ethylene-bridged bissulfoxides ligands **17b** and **17e** and  $\text{Pd}(\text{OAc})_2$ , in these reactions. Whereas DMSO gave the linear product, the bissulfoxide system **48** gave the branched product (Figure 29 bottom). Sometimes, better selectivities for either the branched or the linear product can be obtained using slightly different catalyst systems.<sup>107</sup>



**Fig. 29** Selectivity of Pd/DMSO system and catalyst **48**

Since this initial discovery, White *et al.* as well as others have thoroughly investigated catalyst **48** in a series of allylic C-H functionalisations, and the catalyst system was more recently incorporated in key steps for the syntheses of natural products.<sup>108</sup>

In a first broadening of the scope, the C-H oxidation was carried out with tethered carboxylic acid nucleophiles to form small rings, such as *anti*-1,4-dioxan-2-ones (Figure 30, bottom left), which can be envisioned as versatile intermediates for the synthesis of natural products.<sup>109</sup> More recently, tethering alcohols into similar starting materials lead to the synthesis of chromans, isochromans, pyrans,<sup>110</sup> flavonoids,<sup>111</sup> and oxazolidinones,<sup>112</sup> using this oxidative C-H functionalisation strategy (Figure 30).

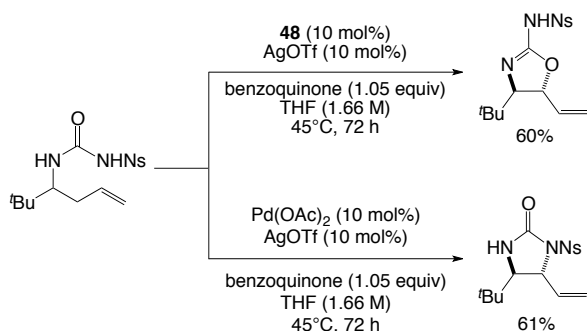


**Fig. 30** C-H oxidation for C-O bond formation catalysed by **48**

Carbon-nitrogen formation via such an allylic C-H functionalisation, where the carboxylic acid in the substrate is replaced by a carbamate, worked in good yield using **48** to give 5- and 6-membered rings.<sup>113</sup> Products from these reactions were then used in the preparation of *syn*-1,3-amino alcohol motifs, which are commonly present in pharmaceutically active molecules and natural products.

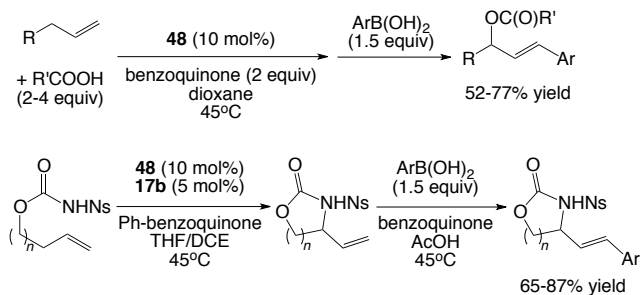
A catalyst-controlled allylic C-H functionalisation of urea derivatives was also developed.<sup>114</sup> Removing the bissulfoxide ligand resulted in a switch from C-O to C-N reactivity (Figure 31).





**Fig. 31** Catalyst-controlled C-O versus C-N selectivity in allylic functionalisation

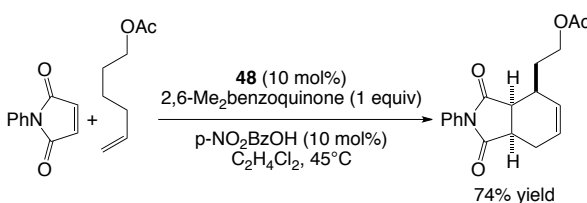
White and coworkers also developed a series of intermolecular carbon-carbon bond-forming reactions that rely on the same allylic C-H activation strategy. For example, they were able to follow the allylic C-H oxidation to give allylic esters with a subsequent vinylic C-H arylation using arylboronic acids as the coupling partner (Figure 32 top).<sup>115</sup> Likewise, allylic C-H aminations followed by vinylic C-H arylation reactions were efficiently catalysed by **48** (Figure 32 bottom),<sup>116</sup> resulting in the generation of interesting  $\alpha$ - and  $\beta$ -homophenylalanine precursors.



**Fig. 32** Tandem allylic C-H activation/vinylic C-C arylation reaction catalysed by **48**

The second step of the sequence in Figure 32, namely the oxidative vinylation, was developed separately to include not only arylboronic acids,<sup>117</sup> but also vinyl boronate esters that lead to the synthesis of dienes.<sup>118</sup> At the same time, more traditional carbon nucleophiles (nucleophiles with acidic  $\alpha$ -carbons) that result in allylic C-H alkylation were developed,<sup>119</sup> and most recently this reactivity was extended to the coupling of tertiary nucleophiles of that type.<sup>120</sup>

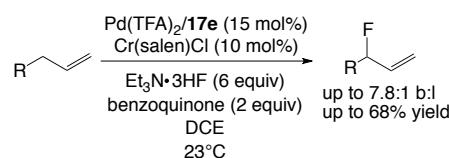
Another elegant application of this catalyst system to construct new C-C bonds in a dehydrogenative Diels-Alder reaction is shown in Figure 33. Here, palladium C-H activation is used to generate a reactive (*E*)-1,3-butadiene intermediate from a terminal alkene, which subsequently reacts with an electron-deficient olefin to give the product.<sup>121</sup>



**Fig. 33** Dehydrogenative Diels-Alder reaction catalysed by **48**

Finally, Doyle *et al.* have recently expanded this reaction scheme to include allylic C-H fluorination reactions.<sup>122</sup> Using Pd(TFA)<sub>2</sub> in combination with the bissulfoxide ligand **17e** under otherwise similar conditions as the ones developed earlier, branched fluorine-containing products were produced in moderate yields and high regioselectivity using a simple

nucleophilic fluoride reagent (Figure 34).

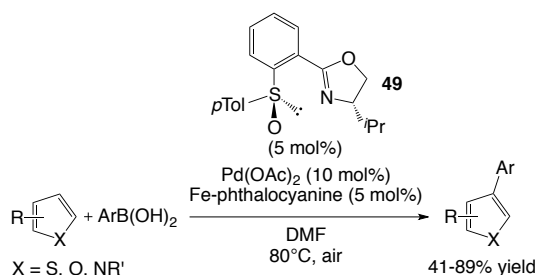


**Fig. 34** Catalytic fluorination reaction via allylic C-H functionalisation

The bissulfoxide-Pd complex **48** is represented, as shown in Figure 29, without proper bonds between the sulfoxide and the Pd because the nature of the binding is unclear. For example, when the <sup>1</sup>H NMR spectra of the free ligand and the 'complex' are compared, there is very little, if any, difference in the shifts. This suggests that the ligand interacts weakly with the metal. This relatively weak binding might be the reason why when the reaction was attempted with enantiomerically pure sulfoxides, no enantioselectivity was observed. Nevertheless, White *et al.* showed that by the use of chiral Cr(III)salen complexes as cocatalysts, the reaction would generate enantioenriched products.<sup>123</sup>

#### Palladium oxazoline-sulfoxide systems

More recently, Itami *et al.* reported that a chiral palladium(II)-sulfoxide-oxazoline (sox) catalyst system also effects the branch-selective allylic C-H carboxylation of terminal alkenes.<sup>124</sup> Whereas the branch-selectivity was high, the enantiomeric excess was negligible (5% *ee*). X-ray analysis of the complex showed that the ligand was bound to palladium through the sulfur and the nitrogen atoms.



**Fig. 35** Pd/sox catalysed C-H coupling reaction

The same authors reported that this catalyst (Pd(OAc)<sub>2</sub>/**49**), in combination with an iron-phthalocyanine cocatalyst, was successful in the C-H coupling of aromatic 5-membered heterocycles with arylboronic acids (Figure 35).<sup>125</sup> The presence of a stoichiometric co-oxidant was not needed. In these studies, the catalytic system enabled the synthesis of highly hindered heterobiaryls using such a C-H functionalisation protocol. Applications of enantioselective C-H biaryl couplings might be possible and the paper gives one example of such an atroposelective process (61% *ee*).

A new direction of research sees the application of the sulfinyl moiety as a directing group and/or chiral auxiliary in such C-H functionalisation chemistry. While these studies use sulfoxides to bind to the palladium catalyst during catalysis, recent reviews on the subject (sulfoxide auxiliaries) are available,<sup>1,3b,c</sup> and a list of most recent publications on these interesting studies can be found in the reference section.<sup>126</sup>

#### Ruthenium Catalysed Metathesis Reactions

Given the ample literature data on ruthenium-sulfoxide

complexes and the growing importance of catalytic metathesis reactions, it is rather surprising that only very few studies have tried to merge these two research fields.

In an interesting early study, Dixneuf *et al.* have used  $\text{Ru}(\text{DMSO})_4\text{Cl}_2$  as a precursor for the synthesis of neutral and cationic allenylidene-ruthenium systems that incorporate either one  $\{\text{Ru}(\text{C}=\text{C}=\text{C}=\text{Ar}_2)(\text{PCy}_3)_2(\text{DMSO})\text{Cl}_2$  respectively  $[\text{Ru}(\text{C}=\text{C}=\text{C}=\text{Ar}_2)(\text{PCy}_3)_2(\text{DMSO})\text{Cl}]\text{TfO}$  or two DMSO ligands  $\{\text{Ru}(\text{C}=\text{C}=\text{C}=\text{Ph}_2)\text{PCy}_3(\text{DMSO})_2\text{Cl}_2$  respectively  $[\text{Ru}(\text{C}=\text{C}=\text{C}=\text{Ph}_2)\text{PCy}_3(\text{DMSO})_2\text{Cl}]\text{TfO}$ .<sup>127</sup> These precatalysts were then tested in the ROMP reaction of strained norbornene and unstrained cyclooctene and were shown to be moderately active giving rise to varying degrees of polydispersities. While the role of the DMSO ligands is unclear during catalysis, the authors proposed a reaction pathway where the allenylidene ligand would behave as an ancillary ligand in these systems.

More recently, Grela *et al.* have incorporated a sulfoxide tether into Hoveyda-Grubbs type precatalysts **50** (Figure 36).<sup>128</sup> In order to be able to control the initiation speed of the precatalyst, different aryl- and alkyl-sulfinyl substitutions were tested. Careful analysis in representative ring-closing metathesis (RCM) reactions of dienes and enynes showed that the initiation rate of these complexes could be modulated and that the most active precatalysts were able to initiate simple RCM reactions at room temperature. Obviously and as outlined by the authors, the sulfoxide chelate will no longer be tethered to the precatalyst after the initiation event.

An example where sulfoxide ligands do seem to be an integral part of the catalyst system has been reported by Lima-Neto and coworkers.<sup>129</sup>  $\text{Ru}(\text{DMSO})_3(\text{DMSO})\text{Cl}_2$ , when activated with ethyldiazoacetate, is forming complex **51** (Figure 36) that was used in situ in the ROMP reaction of norbornene, resulting in high yields of polymer and rather narrow polydispersities (1.6-2.1).

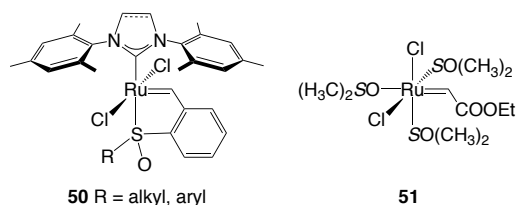


Fig. 36 Sulfoxide ruthenium complexes used in metathesis reactions

## Enantioselective Catalysis with Sulfoxide Ligands

### Hydrogenation/Hydrogen Transfer Reactions

The first example of enantioselective transition-metal catalysis with a chiral sulfoxide ligand (Figure 37) was reported by James.<sup>130</sup> The ligand, **52**, was tested in the ruthenium catalysed hydrogenation of olefins.

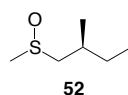


Fig. 37 First sulfoxide ligand used in enantioselective catalysis

The enantioselectivity, however, was quite low, ~12% *ee*, and in an attempt to increase it, attention was turned to chelating, chiral bisulfoxides as ligands. A series of bisulfoxides (ligands **53-55**) based on the known phosphine ligand diop,<sup>131</sup> were synthesised and tested in the same catalytic reaction (Figure 38).<sup>132</sup> Using  $\text{Ru}(\text{II})\text{Cl}_2(\text{diop})(\text{ddios})$ , the enantioselectivity of the reaction was increased to 25% *ee*.

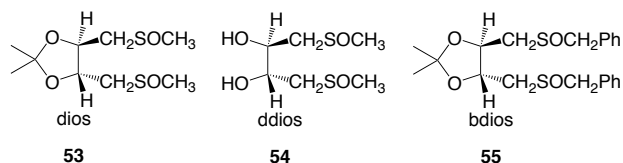


Fig. 38 Bisulfoxide ligands based on the phosphine ligand diop

A decade later, rhodium-catalysed transfer hydrogenation of aryl-alkyl ketones was attempted using *N*-acetyl-(*S*)-methionine (*R,S*)-sulfoxide (AMSO, **56**).<sup>133</sup> The ligand was synthesised by non-stereoselective oxidation of methionine, hence a mixture of the (*R*<sub>S</sub>)- and (*S*<sub>S</sub>)- diastereomers were obtained, and used as such in catalysis. AMSO was used in combination with  $[\text{Rh}(\text{hd})\text{Cl}]_2$  (*hd* = 1,5-hexadiene), in a 1:2 ratio of Rh/ligand. Only moderate yields were achieved, but in the hydrogenation of 4-methylacetophenone, an enantiomeric excess of 75% was measured, despite using a mixture of diastereomers (Figure 39). The reaction was only effective for the hydrogenation of aryl-alkyl ketones; alkyl-alkyl ketones could not be reduced by the same catalyst.

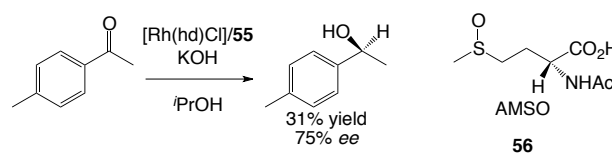


Fig. 39 AMSO and rhodium catalysed transfer hydrogenation

It was thought that the ligand binds to rhodium through the acyl group and through the sulfoxide, although there were no studies to confirm this. Aminosulfoxides were later also used in iridium catalysed asymmetric transfer hydrogenations (ATH) (Figure 40),<sup>134</sup> using formic acid as the hydrogen donor, instead of 2-propanol. The evolution of  $\text{CO}_2$  as a side product makes the reaction irreversible. In this class of amino-sulfoxide chelate ligands, it is believed that binding to the iridium is through the S and N atoms. The ligand was obtained enantiomerically pure by crystallisation, however it was first used in catalysis as a mixture. The mixture gave 35% *ee* of the (*S*)-product. When clean enantiomers were used, ligand (*S*<sub>S</sub>)-**57** gave the (*S*)- product in 65% *ee* and (*R*<sub>S</sub>)-**57** gave the (*R*)-product in 27% *ee*. Much more recently, the reaction was revisited using a sulfinyl-NH-pyridine ligand giving modest enantioselectivities of the product.<sup>135</sup>

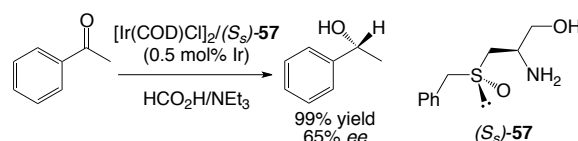
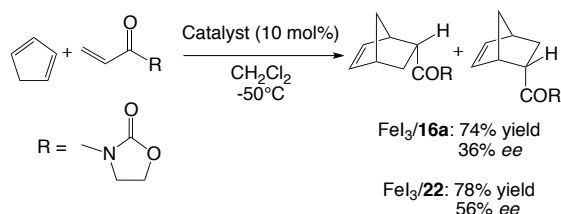


Fig. 40 *S*-benzyl-(*R*)-cysteinol-(*S*)-sulfoxide, **57**, and iridium catalysed transfer hydrogenation of acetophenone

### Sulfoxides in the Diels-Alder Reaction

As mentioned above, ligands **16a** and **22** were used in asymmetric Diels-Alder reactions.<sup>60</sup>  $\text{FeI}_3$  was mixed with the ligand and the resulting complex was used to catalyse the reaction shown below (Figure 41). The two ligands were both almost completely selective for the *endo* product, displaying moderate enantioselectivities.

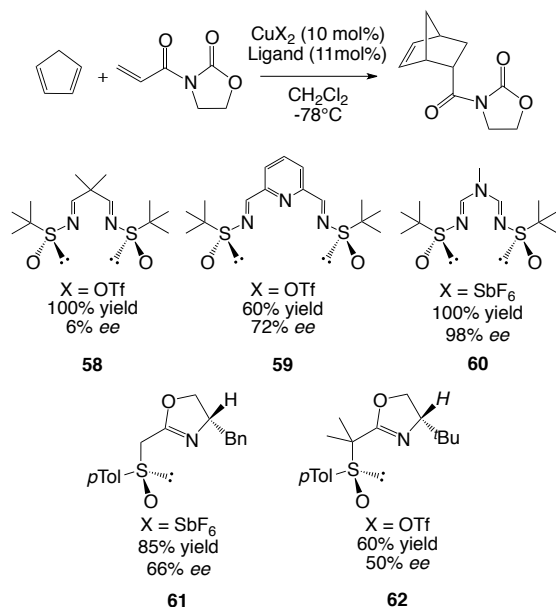


**Fig. 41** Iron catalysed Diels-Alder reaction with bissulfoxide ligands

N-Sulfinyl imine ligands, **58**, **59**, and **60**, inspired by bis-oxazoline ligands, which were previously found to be highly reactive and selective in various Lewis acid-catalysed reactions,<sup>136</sup> were synthesised by Ellman.<sup>137</sup> They were then tested in a copper catalysed Diels-Alder reaction, initially using Cu(OTf)<sub>2</sub> as the copper source. **58** displayed excellent reactivity, but almost no selectivity; **59** and **60** provided moderate selectivity and reactivity (Figure 42). Changing the copper source to Cu(SbF<sub>6</sub>)<sub>2</sub> and using ligand **60** gave complete conversion and an excellent enantioselectivity of 98% *ee* for the reaction shown. The authors originally thought that the ligands would bind through nitrogen, but a crystal structure of ligand **60** bound to Cu(II) showed that it actually bound through the oxygen atoms of the sulfoxides, in a M<sub>2</sub>L<sub>4</sub> quadruple stranded helicate. The authors investigated the scope of this catalytic system, and found that it also provided good results with less reactive acyclic diene substrates (up to 96% yield and 92% *ee*).<sup>138</sup> This was not the case when bis-oxazolines were used as ligands, where poor selectivities were measured. However, lower selectivities were obtained when acyclic substrates with terminal substituents were tested.

Mixed oxazoline-sulfoxide chelates, in combination with in situ generated Cu(II) salts, were indeed and at around the same time tested by Hiroi *et al.* in this Diels-Alder reaction (Figure 42).<sup>139</sup> The reaction provided the product with relatively high endo selectivity and good yields, but enantioselectivity was moderate at best (up to 66% *ee*). The various ligands synthesised kept the sulfinyl group unchanged (*p*-tolyl group) and varied substituents at the chiral centres of the 1,3-oxazoline binding site, showing that the degree of asymmetric induction and absolute configuration of the product were dependent on the steric bulk of these substituents (Figure 42 shows the best ligands, **61** and **62**).

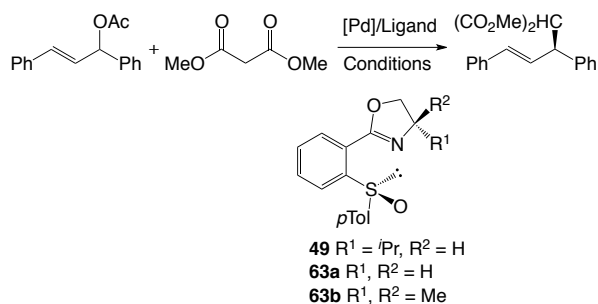
Finally, it should be noted that some Lewis-acid catalysed reactions of main group metals with sulfoxide ligands have appeared and while not part of this review, the reader is referred to the relevant literature.<sup>139,140</sup>



**Fig. 42** N-Sulfinyl imine ligands used in copper catalysed Diels-Alder reactions

### Asymmetric Allylic Substitution Reactions

Williams demonstrated that S,N ligands could be successfully applied in palladium catalysed asymmetric allylic substitution (AAS) reactions (Figure 43).<sup>141,142</sup> Ligands **49/63** contained a chiral sulfoxide and a chiral oxazoline moiety and provided enantioselectivities of up to 88% *ee* in the classical alkylation reaction of *rac*-(*E*)-1,3-diphenylallyl acetate with dimethylmalonate (Table 2, Entry 1). The ligand was also synthesised without a chiral centre on the oxazoline moiety; when the <sup>*i*</sup>Pr group was replaced by a hydrogen atom, the enantioselectivity dropped to 56% *ee* (Table 2, Entry 2). When replaced by two methyl groups, the selectivity decreased even further to 49% *ee* (Table 2, Entry 3). The authors therefore concluded that the combination of the chirality on the sulfoxide and the oxazoline backbone was important to achieve high enantioselectivity.

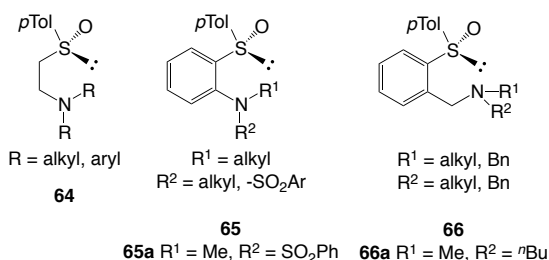


**Fig. 43** Palladium catalysed allylic alkylation reaction with **63** as ligand

A few years later, Hiroi *et al.* began to investigate the palladium catalysed AAS reaction with β-amino sulfoxides.<sup>143,144</sup> First attempts were carried out with ligand **64** (Figure 44), however low yields and enantiomeric excesses of only 39% *ee* were obtained in the model reaction of *t*-butyl-2-methylacetoacetate and allyl acetate. Additionally, a ligand/metal ratio of 4:1 had to be employed. In an effort to increase the enantioselectivity of the reaction, the authors rigidified the backbone of the ligand by introducing a phenyl ring. Ligand **65**, when applied in the same reaction, gave low yields but enantioselectivity was increased to 50% *ee*.

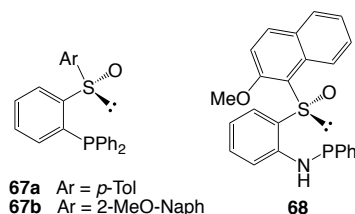
Another modification made to the ligand was the addition of a methylene spacer between the phenyl group and the amino group.

Ligand **66** would then form a 6-membered, rather than a 5-membered chelate ring with palladium. Ligands **65** and **66** were then compared in the reaction of *rac*-(*E*)-1,3-diphenylallyl acetate with dimethylmalonate (Table 2, Entry 4-5). Generally these ligands gave low yields of product with a maximum enantioselectivity of 58% *ee*.



**Fig. 44** Amino-sulfoxide ligands used in palladium catalysed allylic alkylation reaction

The same group later had more success with phosphino sulfoxide and phosphinoamido sulfoxide ligands. The amino group of ligand **65** was replaced by a phosphine, to give ligand **67** that was stable at room temperature.<sup>145</sup> The ligand was also synthesised with a 2-methoxy-1-naphthyl unit on the sulfoxide, the idea being that a larger aryl group would create more steric hindrance around the metal centre, and lead to better selectivity. Indeed, when tested in the AAS reaction, this bulkier ligand gave the best results with respectable yields and good enantioselectivity (82% *ee*). Changing the palladium source from [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> to Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> was found to be favourable for selectivity (Table 2, Entry 6-8).<sup>146</sup> Substitutions (alkyl and alkoxy groups) were also made on the phenyl backbone of ligand **67**, but these were found to have a detrimental effect on the selectivity of the reaction.



**Fig. 45** Phosphine-sulfoxide ligands for AAS reactions

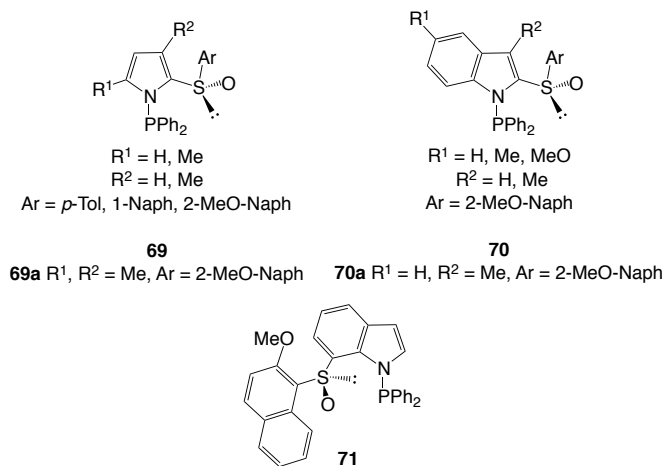
Subsequently, Hiroi and co-workers developed phosphinoamido sulfoxide ligands (Figure 45), by inserting a nitrogen atom between the phenyl and the phosphine.<sup>147</sup> Again, the 2-methoxy-1-naphthyl sulfoxide derivative was the best ligand, **68**, achieving an excellent enantioselectivity of 97% *ee* when the ratio of ligand to [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> was 8:1 (Table 2, Entry 9). However, the isolated yield was only moderate. The choice of solvent was found to be crucial for high selectivity, with THF giving the best results. In DMSO an enantioselectivity of only 11% *ee* was recorded (Table 2, Entry 10).

Hiroi presented a further class of *N*-phosphinosulfinyl ligands, *N*-phosphanopyrrolyl aryl sulfoxides, **69**, and *N*-phosphinoindolyl aryl sulfoxides, **70** and **71** (Figure 46).<sup>148</sup> These ligands were also successfully employed in the same AAS reaction described above (Table 2, Entry 11-13). Both the *N*-phosphanopyrrol and the *N*-phosphanoindolyl ligands were made with *p*-tolyl-, 1-naphthyl-, and 2-methoxy-1-naphthyl sulfoxide substituents. In all examples, the latter displayed the best enantioselectivity, giving 93% *ee* in the case of **70a**, when the reaction was carried out at -78°C (Table 2, Entry 12). It was suggested that repulsions between the methoxy and the S-O bond fix a conformation leading to the high selectivity observed by blocking access to the metal from one side. In addition, substituting electron-donating groups on the pyrrole or indole ring improved the reactivity considerably.

**Table 2** Palladium-catalysed asymmetric allylic alkylation of diphenylallyl acetate with dimethyl malonate

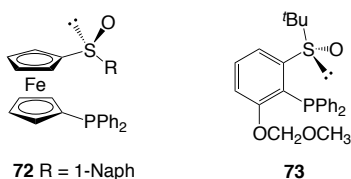
Entry	[Pd] (mol%)	Ligand (mol%)	Solvent	Additives	Yield (%)	<i>ee</i> (%)	ref
1	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.5)	<b>49</b> (10)	DCM	KOAc	96	88	141
2	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.5)	<b>63a</b> (10)	DCM	KOAc	92	56	141
3	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.5)	<b>63b</b> (10)	DCM	KOAc	60	49	141
4 <sup>a</sup>	Pd(dba) <sub>2</sub> (6.0)	<b>65a</b> (12)	THF		19	38	144
5 <sup>a</sup>	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (3.0)	<b>66a</b> (12)	THF		36	58	144
6 <sup>a</sup>	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (3.0)	<b>67b</b> (12)	THF		72	70	146
7 <sup>a</sup>	Pd(CH <sub>3</sub> CN) <sub>2</sub> Cl <sub>2</sub> (3.0)	<b>67b</b> (12)	THF		71	82	146
8 <sup>a</sup>	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (6.0)	<b>67a</b> (12)	DMSO		39	46	146
9 <sup>a</sup>	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (6.0)	<b>68</b> (48)	THF		49	97	147
10 <sup>a</sup>	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (6.0)	<b>68</b> (12)	DMSO		83	11	147
11 <sup>a</sup>	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (3.0)	<b>69a</b> (6)	THF		96	80	148
12 <sup>a</sup>	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (3.0)	<b>70a</b> (6)	THF		68	93	148
13 <sup>a</sup>	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (3.0)	<b>71</b> (6)	THF		93	32	148
14 <sup>b</sup>	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5.0)	<b>29</b> (20)	DCM	AcONa	70	62	64
15	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.6)	<b>72</b> (5.3)	DCM	BSA, KOAc	96	68	149
16	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.0)	<b>73</b> (5.2)	CH <sub>3</sub> CN	BSA, LiOAc	68	93	150
17	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (2.0)	<b>75</b> (4)	DCM	K <sub>2</sub> CO <sub>3</sub> , Cs <sub>2</sub> CO <sub>3</sub>	96	99	153

<sup>a</sup> *In situ* generated sodium salt of dimethyl malonate was used. <sup>b</sup> TMSO(MeO)C=CHCO<sub>2</sub>Me was used instead of dimethyl malonate.



**Fig. 46** *N*-phosphanopyrrole and *N*-phosphanoindolyl sulfoxides

The first promising results in AAS with measurable levels of enantioselectivity employing a bisulfonamide ligand were achieved by Shibasaki *et al.* with the previously mentioned ligand BTSB, **29**.<sup>64</sup> Using 10 mol% Pd and 20 mol% ligand, the system gave a moderate yield and selectivity in the model reaction (70% yield, 62% *ee*) (Table 2, Entry 14). Nevertheless, at the time and until our own first report (see below), this was the best enantioselectivity known in transition metal catalysis employing a chiral bisulfonamide ligand.

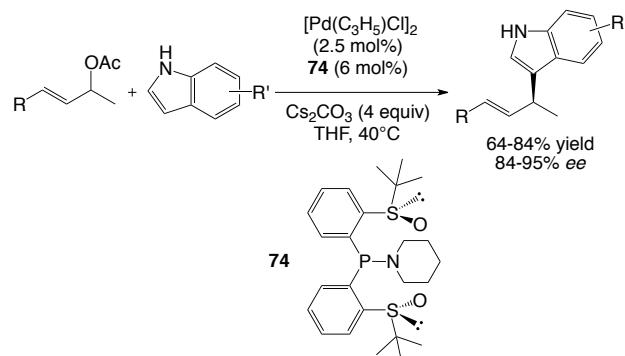


**Fig. 47** Sulfoxide-phosphine hybrid ligands for AAS

More recently, ferrocenyl ligands having chiral sulfinyl and phosphinyl groups (**72**) were evaluated in palladium catalysed AAS reaction.<sup>149</sup> Moderate results were achieved (up to 69% *ee*) during the substitution of dimethyl malonate with *rac*-(*E*)-1,3-diphenylallyl acetate (Table 2, Entry 15).

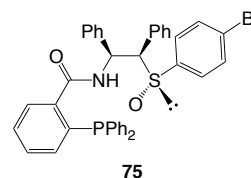
Ligand **73**, which is structurally very closely related to ligands **67** but features a *tert*-butyl substituent on the sulfinyl unit, proved to be successful in palladium catalysed allylic alkylation (Table 2, Entry 16) and allylic amination reactions, giving excellent yields and moderate to good enantioselectivities.<sup>150</sup>

An important new step into further establishing chiral sulfoxide-based ligands in late-transition metal AAS catalysis was made by the group of Liao *et al.*<sup>151</sup> The authors reported the use of a new bisulfonamide-phosphine ligand (**74**) in the palladium-catalysed alkylation of indoles with unsymmetrically substituted allyl acetates via a dynamic kinetic asymmetric transformation (Figure 48). A series of control experiments showed that the ligand served two purposes. Firstly, as a classical chiral phosphine-sulfoxide chelate, it creates a chiral environment around the palladium metal. Secondly, the additional, free sulfoxide moiety serves to activate and direct the indole nucleophile via the creation of a hydrogen bond between the sulfinyl group and the substrate.



**Fig. 48** Bisulfonamide-phosphine ligand for palladium-catalysed AAA reaction of unsymmetrical  $\pi$ -allyls with indoles

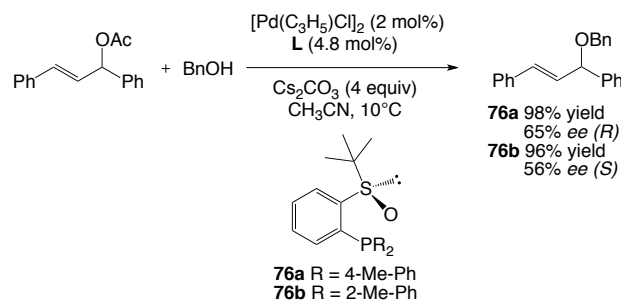
Another new class of sulfoxide-phosphine ligands was developed through condensation of a phosphine-benzaldehyde with a chiral sulfoxide amine (Figure 49).<sup>152,153</sup> The reaction of *rac*-(*E*)-1,3-diphenylallyl acetate and dimethyl malonate catalysed by [Pd(C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub>/**75** gave excellent yields (96%) and enantioselectivity (99%) (Table 2, Entry 17).



**Fig. 49** Sulfinyl-phosphine ligand from condensation between a phosphine benzaldehyde and a chiral sulfinyl amine

Chiral SO/P hybrid ligands, **76**, were applied in the palladium-catalysed asymmetric allylic etherification of *rac*-(*E*)-1,3-diphenylallyl acetate.<sup>154</sup> The *O*-benzylation of the substrate proceeded with good yields (up to 98%). Unfortunately, only moderate selectivity values (up to 67% *ee*) were achieved. The absolute configuration was controlled by changing the substituents' position on the *P*-aryl group (Figure 50).

Following the work shown in Figure 48, higher *ee*'s were achieved in asymmetric allylic etherification and amination using the *N*-pyrrolyl derivative of bisulfonamide-phosphine ligand **74**.<sup>155</sup> Improvement was also published for the same reaction (up to 98% *ee*) by the group of Xiao using the previously mentioned ligand **67** (Figure 49).<sup>156</sup>



**Fig. 50** Asymmetric allylic etherification

Recently, Trost *et al.* reported the first ruthenium catalysed AAS reaction using the mixed Cp/sulfoxide-containing complex **44**. The catalyst system was selective for the branched product of the AAS between cinnamyl chloride and carbon-, oxygen- and nitrogen-based nucleophiles.<sup>76</sup> Overall, very encouraging results were obtained, especially for oxygen nucleophiles where high regio- and enantioselectivities were observed (Figure 51).

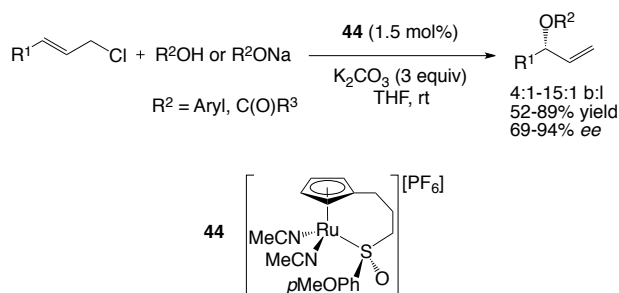
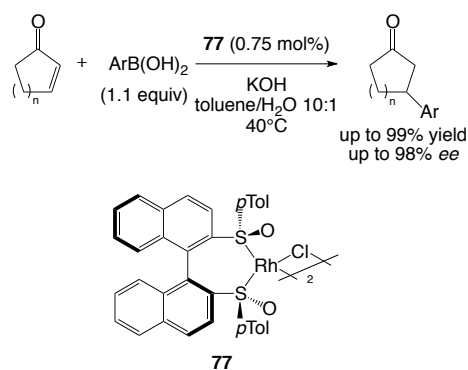


Fig. 51 Ruthenium catalyzed AAS

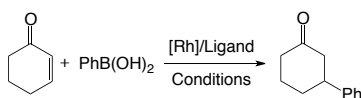
## Rhodium Catalysed 1,4-Addition Reactions

As mentioned above, early catalyst systems that rely exclusively on sulfoxide ligation were very rare and after Shibasaki's report in the nineties,<sup>64</sup> it wasn't until 2008 when the next asymmetric catalysis with a chiral bissulfoxide ligand was reported by Dorta *et al.*<sup>157</sup> The ligand described, named *p*-tolylbinaso, was the bissulfoxide analogue of the well-known phosphine ligand, binap, developed by Noyori in 1980.<sup>158</sup> The ligand was readily synthesised from commercially available starting materials.

Fig. 52 Rhodium catalyzed 1,4-addition of phenylboronic acid to cyclohexenone with **77**

This ligand was of interest because as well as the chirality on the sulfur, it also contains axial chirality in the backbone. When enantiomerically pure sulfinate, *S*- or *R*-, was used in the synthesis of the ligand, two diastereomers of the ligand were obtained, which were easily separated by column chromatography. The (*M,S<sub>S</sub>,S<sub>S</sub>*)- and the (*P,R<sub>S</sub>,R<sub>S</sub>*)-diastereoisomers of *p*-tolylbinaso formed a Rh(I) dimer, **77**, when reacted with  $[Rh(C_2H_4)_2Cl]_2$  (Figure 52). However, the (*M,R<sub>S</sub>,R<sub>S</sub>*)- and the (*P,S<sub>S</sub>,S<sub>S</sub>*)- diastereoisomers did not bind to Rh. The rhodium complex **77** was tested in the 1,4-addition of arylboronic acids to cyclic enones with toluene as the solvent, and found to give excellent yields and enantioselectivities, without the need for a large excess of expensive boronic acid (Table 3, Entry 1).

Table 3 Rhodium catalyzed 1,4-addition of phenylboronic acid to cyclohexenone



Entry	Catalyst	[Rh] (mol%)	PhB(OH) <sub>2</sub> (equiv)	Solvent	Base	Yield (%)	ee (%)	ref
1	<b>77</b>	1.5	1.1	Tol/H <sub>2</sub> O	KOH	99	98	157
2	<b>78</b>	0.5	1.1	Tol/H <sub>2</sub> O	KOH	98	99	160
3	$[Rh(C_2H_4)_2Cl]_2$ / <b>79a</b>	2	1.5	Tol/H <sub>2</sub> O	KOH	89	99	161
4	$[(\mathbf{81})RhCl]_2$	0.5	1.1	Tol/H <sub>2</sub> O	KOH	99	98	162
5	$\{[(M,S,S)\text{-}\mathbf{80a}\}RhCl]_2$	1.5	1.1	Tol/H <sub>2</sub> O	KOH	97	99	162
6	$[Rh(C_2H_4)_2Cl]_2$ / <b>82</b>	2	2	DCM/H <sub>2</sub> O	KOH	96	98	164
7	$[Rh(C_2H_4)_2Cl]_2$ / <b>84</b>	3	4	EtOAc/H <sub>2</sub> O	KOH	72	80	169
8	$[Rh(C_2H_4)_2Cl]_2$ / <b>85</b>	5	2	Tol/H <sub>2</sub> O	KOH	87	86	170
9	$[Rh(C_2H_4)_2Cl]_2$ / <b>86</b>	2	2	Tol/H <sub>2</sub> O	KOH	99	98	1723
10	$[(\mathbf{87})Rh(OH)]_2$	5	1.2	dioxane/H <sub>2</sub> O	CsF	98	92	176
11	$[(\mathbf{88})Rh(OH)]_2$	5	1.2	dioxane/H <sub>2</sub> O	CsF	87	92	176
12	$[Rh(C_2H_4)_2Cl]_2$ / <b>89</b>	3	2	THF/H <sub>2</sub> O	K <sub>2</sub> HPO <sub>4</sub>	99	97	181
13	$[Rh(C_2H_4)_2Cl]_2$ / <b>90</b>	3	2	dioxane/H <sub>2</sub> O	K <sub>3</sub> PO <sub>4</sub>	99	95	177
14	$[Rh(C_2H_4)_2Cl]_2$ / <b>91</b>	3	2	dioxane/H <sub>2</sub> O	K <sub>3</sub> PO <sub>4</sub>	99	97	182
15	$[Rh(C_2H_4)_2Cl]_2$ / <b>91</b>	5	2	MeOH/H <sub>2</sub> O	KOH	93	99	183
16	$[Rh(C_2H_4)_2Cl]_2$ / <b>92a</b>	2	2	MeOH/H <sub>2</sub> O	KOH	98	99 ( <i>R</i> )	185
17	$[Rh(C_2H_4)_2Cl]_2$ / <b>93a</b>	2	2	MeOH/H <sub>2</sub> O	KOH	93	98 ( <i>S</i> )	185
18	$[Rh(C_2H_4)_2Cl]_2$ / <b>92b</b>	2	2	MeOH/H <sub>2</sub> O	KOH	98	95 ( <i>R</i> )	185
19	$[Rh(C_2H_4)_2Cl]_2$ / <b>93b</b>	2	2	MeOH/H <sub>2</sub> O	KOH	97	97 ( <i>S</i> )	185
20	$[Rh(C_2H_4)_2Cl]_2$ / <b>94a</b>	5	1.5	dioxane/H <sub>2</sub> O	K <sub>3</sub> PO <sub>4</sub> ·3H <sub>2</sub> O	90	94	187
21	$[Rh(C_2H_4)_2Cl]_2$ / <b>94b</b>	5	1.5	dioxane/H <sub>2</sub> O	K <sub>3</sub> PO <sub>4</sub> ·3H <sub>2</sub> O	79	95	187
22	$[Rh(C_2H_4)_2Cl]_2$ / <b>95</b>	3	1.5	MeOH	K <sub>3</sub> PO <sub>4</sub> ·3H <sub>2</sub> O	90	96	189
23	$[Rh(C_2H_4)_2Cl]_2$ / <b>96</b>	2	1.5	Tol/H <sub>2</sub> O	KOH	94	92	191
24	$[Rh(C_2H_4)_2Cl]_2$ / <b>99</b>	1.5	2.5	dioxane/H <sub>2</sub> O	KOH	99	99	194

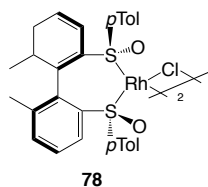


Fig. 53 Rhodium complex of (*M,S,S,S*)-*p*-tolyl-Me-bipheso, **78**

Even better results were subsequently obtained with another bisulfonate ligand based on the known phosphine ligand biphemp.<sup>159,160</sup> [*(M,S,S,S)*-*p*-tolyl-Me-bipheso]RhCl<sub>2</sub>, **78**, was made and tested in the same 1,4-addition reaction (Table 3, Entry 2). A lower catalyst loading of only 0.25 mol%, and a shorter reaction time of 30 minutes, was required. Yields up to 98% and enantioselectivities of >99% *ee* were recorded.

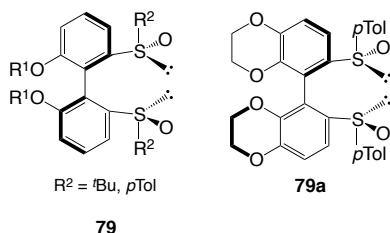


Fig. 54 Bisulfonate ligands **79** synthesised by Li *et al.*

Li *et al.* were then able to synthesise a series of ligands (**79**) based on the same structure as *p*-tolyl-bipheso (Figure 54).<sup>161</sup> These were also tested, in combination with a Rh precursor, in the 1,4-addition reaction (Table 3, Entry 3). The bisulfonate ligands with *p*-tolyl substituents on the sulfur displayed high activity and selectivity, while those with *tert*-butyl substituents on the sulfur gave no product.

A whole family of bisulfonate ligands (**80**, **81**) based on *p*-tolyl-binaso was later synthesised by making modifications to the original ligand (Figure 55).<sup>162</sup> The rhodium complex of the binaso derivative with the partially hydrogenated backbone **81** was comparable as a precatalyst in the 1,4-addition reaction (Table 3, Entry 4) to that of (*M,S,S,S*)-*p*-tolyl-bipheso. This suggests that the greater the steric bulk on the backbone of the ligand, the better the precatalyst for this reaction. The other binaso derivatives, with the exception of the 4-F-Ph derivative (Table 3, Entry 5), were less active and/or less selective.

The electron-donating properties of this bisulfonate ligand family were estimated and compared to the phosphine analogues from the IR stretching frequencies of the CO ligands in the respective [Rh(ligand)(CO)<sub>2</sub>][BF<sub>4</sub>] complexes.<sup>160,162</sup> Converse to what was expected, the bisulfonate ligands were more electron-donating to rhodium than their diphosphine counterparts.

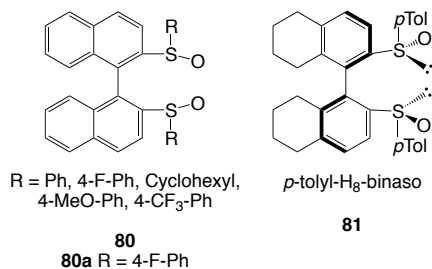


Fig. 55 Other ligands in the binaso family

X-ray crystal structures of the rhodium complexes, **77** and **78**, demonstrated that the ligands do not provide any significant steric bulk around the metal centre. The *p*-tolyl substituents are pointed away from the metal, and are arranged parallel to the backbone. The only moieties creating any steric hindrance around the metal

are the sulfonate oxygens.

This observation prompted studies into the origin of the enantioselectivity of the reaction. In-depth DFT studies were carried out with **78** to investigate how the nature of the transition state affected the enantioselectivity of the reaction.<sup>162</sup> After initial transmetalation of the phenylboronic acid to the catalytically active [Rh]-OH to give [Rh]-Ph, these studies revealed that coordination of the enone to the metal centre was not the enantiodiscriminating step, showing that the wrong approach of the enone was even slightly favoured (Figure 56, structure A). Selectivity arises in the subsequent C-C bond formation/insertion of the enone and the phenyl group (A-B). Here, the *pro-S* complex is higher in energy by 4.4 kcal mol<sup>-1</sup> and is disfavoured, explaining the very high selectivity for the *R* product. Details in the structure that would lead to the *S* product shows that the phenyl group and the C=O of the substrate form unfavourable steric and electronic interactions with the sulfonate groups, whereas in complex A-B ultimately leading to the *R* product, the phenyl and the C=O of the substrate are pointed towards the *p*-tolyl groups of the bisulfonate ligand, where there is an open space, and interaction with the sulfonate oxygens is minimised. Subsequent steps that close the catalytic cycle are all energetically downhill and include coordination of a molecule of water and subsequent proton transfer to the substrate that is liberated with regeneration of the catalytically active [Rh]-OH species.

Computational studies were also performed to compare the C-C bond formation step in bipheso and its diphosphine analogue biphemp.<sup>163</sup> This revealed that the enantiocontrol with the biphemp complex was almost entirely due to the steric hindrance from the appropriately oriented P-phenyl groups of the ligand, whereas the selectivity with the bipheso complex is mostly controlled by electrostatic interactions.

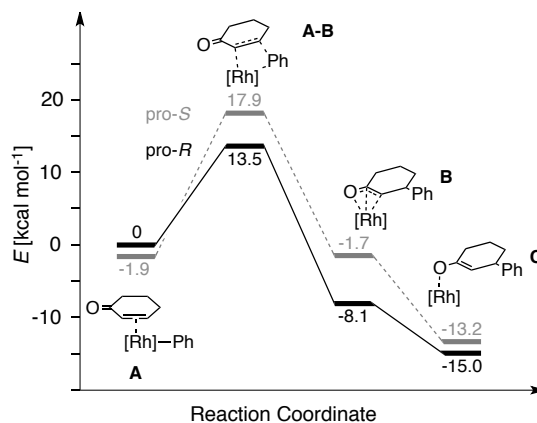
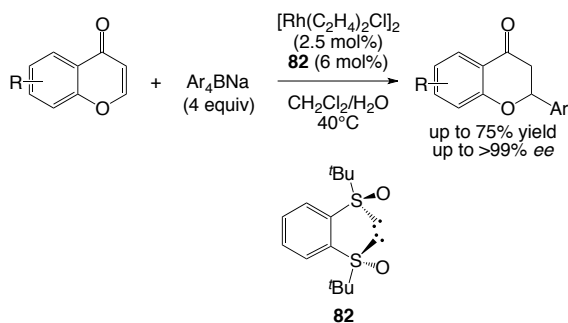


Fig. 56 Transition states for the formation of the C-C bond in the 1,4-addition reaction

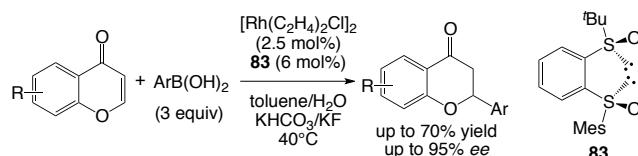
Liao subsequently presented promising results with a new ligand related to Shibasaki's ligand **29**, (*R,S,R,S*)-1,2-bis(*tert*-butylsulfanyl)benzene **82**, which was readily prepared in a two-step synthesis from bromobenzene and *tert*-butyl *tert*-butanethiosulfinate.<sup>164</sup> This ligand in combination with [Rh(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>Cl]<sub>2</sub> (2 mol% Rh) catalysed the 1,4-addition of arylboronic acid to cyclic and acyclic enones in excellent yield and enantioselectivity (Table 3, Entry 6).

The mode of action of catalyst **82**/Rh(I) with these enones was very recently investigated *in silico* by Kantchev *et al.*,<sup>165</sup> concluding that contrary to bipheso and its derivatives, the high steric pressure exerted by the two *t*-Bu groups in bisulfonate ligand **82** was the major factor that contributed to the high enantioselectivity of the system.

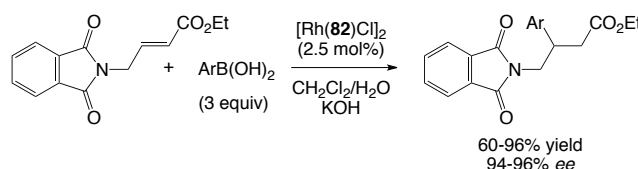
Fig. 57 Rhodium catalyzed 1,4-addition reactions with **82**

The authors were also able to carry out a transformation previously not achieved by late transition-metal catalysis. **82** and  $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$  were used to catalyze the 1,4-addition of sodium tetraaryl borates to chromenones,<sup>164</sup> 2,3-dihydro-4-pyridones and 4-quinolones,<sup>166</sup> in moderate to good yields and excellent enantioselectivities (Figure 57). The addition is challenging due to the more electron-rich nature of the double bond in chromenone compared to cyclohexen-2-one and related substrates.

In a further development by the same authors, the monosulfonamide analogue of **82**, *tert*-butylsulfinylbenzene, was reacted with different sulfonamides to generate a new family of  $C_1$ -symmetric heterobissulfonamide ligands (Figure 58). These were then applied to the 1,4-addition to chromenones employing the more convenient and atom-economical, but less reactive arylboronic acids.<sup>167</sup> The best ligand was discovered to be 1-((*R*)-*tert*-butylsulfinyl)-2-((*S*)-mesitylsulfinyl)benzene, **83**, which gave 20 yields of up to 70% while maintaining excellent enantioselectivity.

Fig. 58 Rhodium catalyzed 1,4-addition of arylboronic acids to chromenones with **83**

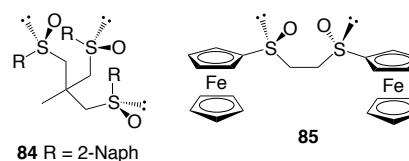
Another transformation achieved by the same group was the 1,4-addition of arylboronic acids to  $\gamma$ -phthalimidocrotonates with the isolated  $[\text{Rh}(\mathbf{82})\text{Cl}]_2$  complex (Figure 59).<sup>168</sup> Enantioselectivities of up to 96% *ee* were reached with this system, and could therefore potentially be used as the key step in preparing enantiopure molecules that represent synthetic precursors to pharmaceutically active entities.

Fig. 59 Rhodium catalyzed 1,4-addition of arylboronic acid to  $\gamma$ -phthalimidocrotonates

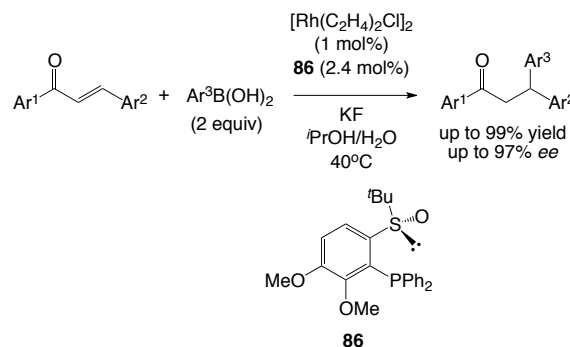
Another series of  $C_2$ - and  $C_3$ -symmetric bisulfonamide ligands (**84**) were prepared by Dong *et al.* (Figure 60, left).<sup>169</sup> When the ligands (in combination with  $[\text{Rh}(\text{NBD})_2\text{BF}_4]$ ) were applied in the hydroacylation reaction, no enantioenrichment of the product was observed, while low enantioselectivity was achieved in the rhodium catalyzed 1,4-addition to cyclohexenone (Table 3, Entry 7).

New, ethylene bridged bisulfonamides were prepared by the Khair and Fernandez groups.<sup>170</sup> Out of these, the most efficient

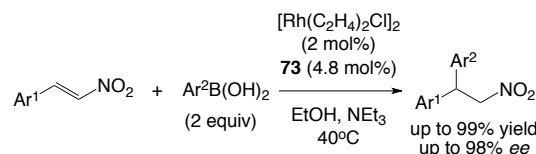
was the Ferbisox ligand (**85**), which incorporates two ferrocenyl groups on the sulfur atoms (Figure 60, right). Interestingly, lower *ee* values were measured during the addition of boronic acids to cyclic substrates than to open chained ones (Table 3, Entry 8).

Fig. 60 Newer  $C_2$ - and  $C_3$ -symmetric sulfonamide ligands

Prior to the bisulfonamide ligand **82**, Liao and co-workers developed sulfinyl phosphine ligands **73**, which they then used in asymmetric transition-metal catalysis.<sup>150,171</sup> This class of *tert*-butylsulfinylphosphines were later also tested in the rhodium-catalyzed 1,4-addition (Table 3, Entry 9).<sup>172</sup> At that time, the reaction was a rare example of a sulfinylphosphine ligand being used in rhodium catalysis and the results were promising. It was later found that **86** could be used for the efficient 1,4-addition of arylboronic acids to chalcones, a reaction that has proven to be challenging with other ligands, even with systems that had given 60 excellent results in the 1,4-addition to other cyclic and acyclic enones (Figure 61).<sup>173</sup>

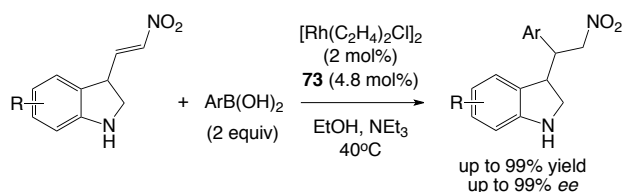
Fig. 61 Rhodium catalyzed 1,4-addition reaction of arylboronic acids to cyclic and acyclic enones with **86**

The scope of this reaction was expanded to include 1,4-addition reactions of arylboronic acids to 2-nitrostyrenes (Figure 62).<sup>174</sup> This was the first time nitrostyrenes could be used in this type of reaction. The sulfinylphosphine ligand **73** enabled yields as high as 99% and enantioselectivities of up to 98% *ee*. The methodology was applied to the synthesis of the pharmaceutically active (*R*)-cheryline, giving highly enantioenriched product.

Fig. 62 Rhodium catalyzed 1,4-addition reaction of arylboronic acids to 2-nitrostyrenes with **73**

Further developments by Liao *et al.* include the 1,4-addition of arylboronic acids to indolynitroalkenes, to form indolynitroethanes.<sup>175</sup> Normally, these compounds are synthesised by a Friedel-Crafts reaction between nitroalkenes and indolyls. The system presented by Liao offers a simple alternative, which has been demonstrated to be tolerant of various functional groups (Figure 63).

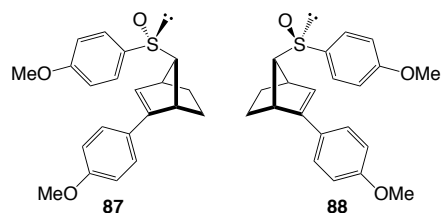




**Fig. 63** Rhodium catalysed 1,4-addition reaction of arylboronic acids to indolynitroalkenes with **73**

Another important contribution to the sulfoxide ligand family has seen the introduction of novel sulfoxide-alkene<sup>176</sup> and sulfonamide-alkene<sup>177</sup> ligands, both of which were applied to Rh-catalysed addition reactions. These types of ligands are inspired by chiral dienes of Hayashi<sup>178</sup> and Carreira,<sup>179</sup> and P/N-olefin hybrid ligands<sup>180</sup>, which have also displayed good activity in these types of 1,4-addition reactions.

Knochel and co-workers synthesised two diastereoisomers of a sulfoxide-alkene ligand, **87** and **88**.<sup>176</sup> The chirality on both ligands was the same at sulfur, but different with regards to the alkene. The ligands were tested in the rhodium catalysed 1,4-addition of arylboronic acids to enones, and were both found to give the product in equally high enantioselectivities (Table 3, Entries 10-11), but opposite configuration. This points to a mechanism where the chiral environment around the alkene determines the stereochemical outcome of the reaction.

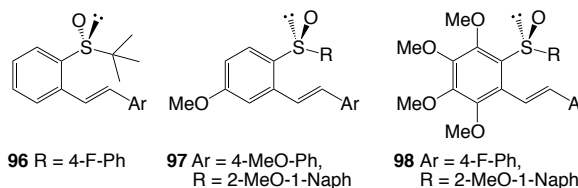
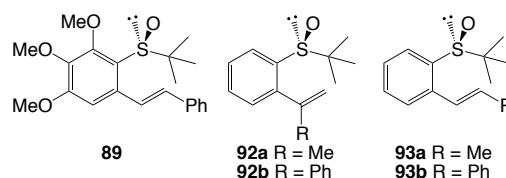


**Fig. 64** Sulfoxide-olefin ligands **87** and **88** for rhodium catalysed 1,4-addition of phenylboronic acid to cyclohexenone

Xu *et al.* presented a family of sulfoxide-alkene ligands, **89**, based on the bissulfoxide **82** where one sulfoxide was replaced by an olefin (Figure 65).<sup>181</sup> These ligands were highly active for the 1,4-addition of arylboronic acid to cyclic enones. It was observed that exchanging the *tert*-butyl on the sulfoxide with *p*-tolyl dramatically reduced the selectivity of the system. Introducing methoxy groups onto the backbone of the ligand increased the activity and selectivity of the catalyst (Table 3, Entry 12).

Xu also synthesised **90** (Figure 66), a sulfonamide-olefin ligand that enabled high yields and enantioselectivities to be reached in the 1,4-addition reaction (Table 3, Entry 13).<sup>177</sup> Interestingly, changing the chirality at the C-1 and C-2 backbone positions of the ligand had no effect on the selectivity of the reaction, indicating that it is controlled solely by the chiral sulfinyl moiety.

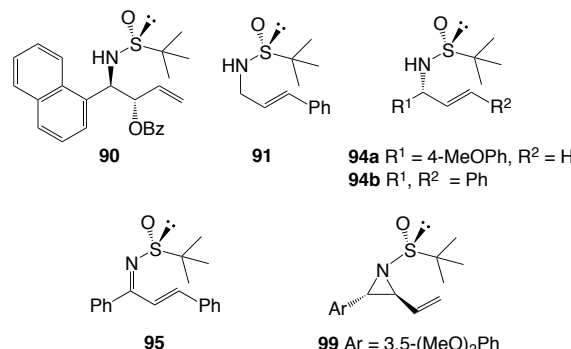
Later, the groups of Xu and Khair simultaneously published **91** (Figure 66) for use in rhodium catalysed additions of arylboronic acids to cyclic and acyclic enones (Table 3, Entries 14-15).<sup>182,183,184</sup> These publications show that an aryl group on the backbone of the ligand is not necessary for coordinating the sulfonamide and olefin units in a chelating fashion to the metal atom.



**Fig. 65** Sulfoxide-alkene hybrid ligands

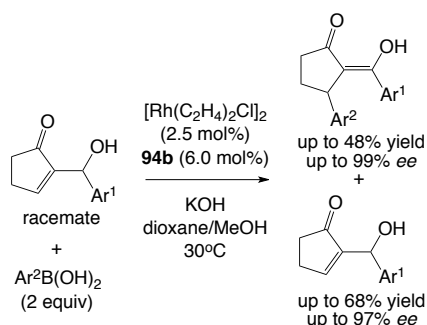
Recently, Liao reported sulfoxide-olefin hybrid ligands **92** and **93**, which were found to give excellent yields and enantioselectivities in the rhodium catalysed 1,4-addition (Table 3, Entries 16-19).<sup>185,186</sup> Interestingly, switching the position of the substituent on the olefin completely reversed the selectivity of the 1,4-addition reaction. **92** gave the *R* product in up to 99% *ee*, whereas **93** gave the *S* product in up to 98% *ee*.

A class of sulfonamide-olefin ligands (**94**) similar to **90** was developed by Du and co-workers (Figure 66).<sup>187</sup> It was established that the olefin and the sulfinyl group are bound to rhodium during catalysis. **94a** and **94b** were used in the reaction shown in Table 3 (Entries 20-21), giving good yields and excellent selectivities. **94b** also proved to be a good ligand for the addition of aryl boronic acids to *tert*-butyl cinnamate. This is important as often rhodium catalysed 1,4-addition reactions to acyclic substrates are difficult to achieve, even with systems that show excellent activity in the reactions with cyclic substrates. An easily accessible analogue of **94** (ligand **95**), which was first synthesised by Ellman *et al.*,<sup>188</sup> was also applied in the 1,4-addition reaction (Table 3, Entry 22).<sup>189</sup>



**Fig. 66** Sulfonamide-alkene hybrid ligands

Ligand **94** was employed by the group in two additional catalytic applications. Firstly, for the kinetic resolution of Morita-Baylis-Hillman adducts by 1,4-addition/ $\beta$ -hydroxy elimination.<sup>190</sup> While attempting to carry out 1,4-addition reactions with  $\alpha,\alpha,\beta$ -substituted enones, the authors observed that a kinetic resolution of the substrate was taking place, accompanied by moderate conversion to the desired product (Figure 67). Secondly, it was applied in 1,2-addition reactions, which will be discussed later.



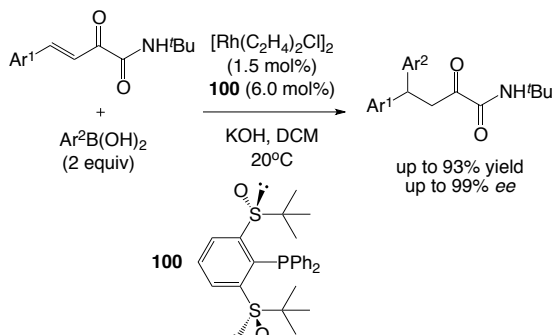
**Fig. 67** Kinetic resolution of Morita-Baylis-Hillman adducts *via* rhodium catalysed 1,4-addition/ $\beta$ -hydroxy elimination with **94b**

Another example of using sulfoxide-based ligands in such rhodium catalysed addition reactions (ligand **96**) was published by Wan *et al.* The system was found to effect the 1,4-addition of arylboronic acids to cyclic enones (Table 3, Entry 23) with up to 97% yield and 97% *ee*,<sup>191</sup> using similar conditions to the ones presented originally by Dorta *et al.*

Subsequently, the structure of these sulfoxide-olefin hybrids was further modified. Ligand **97** was successfully applied in the Rh-catalysed asymmetric conjugate addition to nitroalkenes,<sup>192</sup> while **98** proved to be efficient in the addition to unsaturated esters.<sup>193</sup> Interestingly, the 2-methoxy-1-naphthyl substituted sulfoxide unit provided better results than the normally used *tert*-butyl substituent.

*N*-*tert*-butylsulfinyl vinyl aziridine ligand **99** was synthesized and tested in the 1,4-addition reaction of phenylboronic acids to  $\alpha,\beta$ -unsaturated ketones.<sup>194</sup> Good yields and enantioselectivities (85-99% *ee*) were achieved when cyclohexenone was used as a substrate (Table 3, Entry 24). The addition to cyclopentenone resulted in significantly lower *ee* values (41-85%). Using the *cis* or *trans* configured olefin ligands gave the same absolute stereochemistry in the product.

In early 2014, Liao published the application of a new sulfanylphosphine ligand **100** in the rhodium catalysed asymmetric arylation of  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoamides.<sup>195</sup> The authors were able to carry out the reaction with excellent chemo-, regio- and enantioselectivities (up to 99% *ee*) in high yield (up to 93%) (Figure 68). The synthetic utility of the methodology was demonstrated in a formal synthesis of sertraline, which is a pharmaceutical agent for the treatment of depression. A similar approach was described for the arylation of  $\beta,\gamma$ -unsaturated  $\alpha$ -keto esters. However, only moderate to good 1,4-regioselectivities and enantioselectivities were achieved.<sup>196</sup>

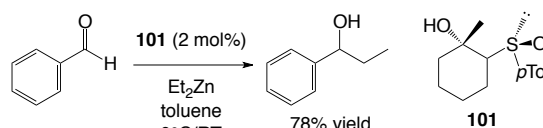


**Fig. 68** Rhodium catalysed 1,4-addition of arylboronic acids to  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoamides

## 1,2-Addition Reactions

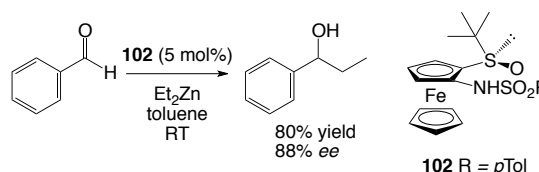
The enantioselective 1,2-addition of an alkyl group to benzaldehyde to give 1-phenyl-propanol has been developed using diethyl zinc as the alkylating agent in combination with a

catalytic amount of a chiral ligand. A first report employing chiral sulfoxides in this reaction was reported by Carreno and Ruano, who used enantiomerically pure  $\beta$ -hydroxysulfoxides such as **101** (Figure 69).<sup>197</sup> They were believed to coordinate to the zinc in a bidentate fashion. The results obtained were moderate; ligands containing a tertiary alcohol gave the highest enantioselectivities (up to 45% *ee* with **101**, compared to 23% *ee* with the best secondary alcohol). The addition reaction was in competition with a side reaction, namely the reduction of benzaldehyde to give benzyl alcohol. It was observed that as the enantioselectivity increased, the extent of the side reaction also increased.



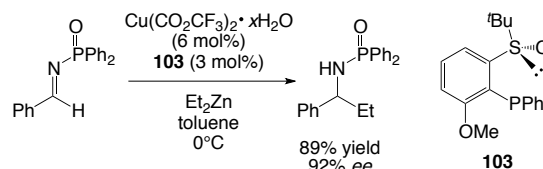
**Fig. 69**  $\beta$ -hydroxysulfoxide ligand, **101**, and 1,2-addition reaction of diethylzinc to benzaldehyde

Carretero achieved more success with 2-amino-1-*tert*-butylsulfinyl ferrocene ligands, **102** (Figure 70).<sup>198,199</sup> Good yields and enantioselectivities of up to 88% *ee* were observed for the 1,2-addition of diethyl zinc to benzaldehyde. When the *tert*-butyl group on the sulfoxide was replaced by a *p*-tolyl, the selectivity decreased dramatically to 32% *ee*, indicating that steric bulk around the sulfoxide is important. Interestingly, when the sulfoxide was reduced to a sulfide (or oxidised to a sulfone) and used in the same reaction, almost the same *ee* was reached. This demonstrates that the planar chirality of the ferrocene plays a major role in the selectivity observed.



**Fig. 70** 1,2-Addition of  $\text{Et}_2\text{Zn}$  to benzaldehyde with 2-amino-1-*tert*-butylsulfinyl ferrocene, **102**

In 2008, an asymmetric addition of diethyl zinc to diphenylphosphonyl imines was attempted using ligand **103** in combination with catalytic  $\text{Cu}(\text{CO}_2\text{CF}_3)_2 \cdot x\text{H}_2\text{O}$ , in a 1:2 ratio (Figure 71).<sup>200</sup> It was shown that an alkoxy group *ortho* to the phosphine in **103** was important to achieve good reactivity and enantioselectivity (89% yield, 92% *ee*).



**Fig. 71** Sulfanylphosphine ligand and copper catalysed addition of diethylzinc to diphenylphosphonyl imine

Very recently, a chiral sulfoxide-Schiff base hybrid ligand was used in the related copper catalysed asymmetric Henry reaction.<sup>201</sup> The addition of nitromethane to 4-nitrobenzaldehyde proceeded smoothly at 25°C with a  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\mathbf{104}$  system (Figure 72). The scope of the reaction was expanded to the enantioselective synthesis of tetrahydrofuran derivatives. The Henry reaction of  $\gamma,\delta$ -unsaturated aldehydes with nitromethane (or its derivatives) was followed by a iodocyclization to give the

product in good yield (up to 98%) and *ee* (up to 95%). Unfortunately, low *cis/trans*-selectivity was observed.

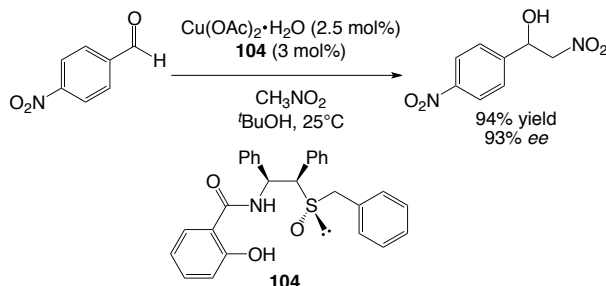


Fig. 72 Copper catalyzed asymmetric Henry reaction

Given the precedents employing the sulfinyl group as a ligand in rhodium catalyzed 1,4-addition reaction, **94** was used with  $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$  in 1,2-additions of arylboronic acids to  $\alpha$ -diketones to give the corresponding  $\alpha$ -hydroxyketone (Figure 73).<sup>202</sup> The catalyst loading could be reduced to as little as 0.1 mol% Rh, with little effect on the activity and selectivity at 50°C. The authors stated that this was the first example of an asymmetric, transition metal catalyzed version of this reaction.

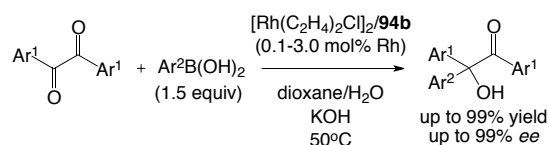


Fig. 73 Rhodium catalyzed 1,2-addition of arylboronic acids to  $\alpha$ -diketones with **94**

The previously mentioned ligand **91** proved to be useful in the 1,2-addition of boronic acids to  $\alpha$ -ketoesters and  $\alpha$ -diketones.<sup>184,203,204,205</sup> Xu's group found that using  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$  as a metal precursor gave superior results compared to  $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ .<sup>203</sup> A broad substrate scope was presented and good yields and excellent enantioselectivities were observed. The addition to  $\alpha$ -diketones gave somewhat better results, although the presence of aromatic substituents seems crucial. No diarylation was observed (this is generally true for the 1,2-addition reactions described herein). Following this work, a tandem one-pot synthesis leading to optically active 3-tetrasubstituted isochroman derivatives was developed by the same group.<sup>204</sup> Similarly, 3-hydroxyoxindole, 1,3-dihydroisobenzofuran and 3-isochromanone derivatives were prepared by an asymmetric arylation-cyclization sequence.<sup>206</sup>

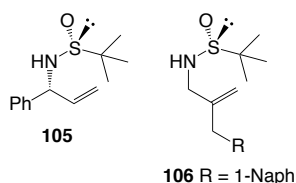


Fig. 74. Sulfinamide-alkene hybrid ligands used in rhodium catalyzed 1,2-addition reactions

A rare example of an intramolecular 1,2-addition was achieved by Lam *et al.*<sup>207</sup> Substrates containing an arylpinacolboronic ester tethered to a ketone via a nitrogen linkage were cyclized in the presence of  $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ /**105** to give 1,2,3,4-tetrahydroisoquinolines-4-ols in good yields and enantioselectivities (Figure 75).

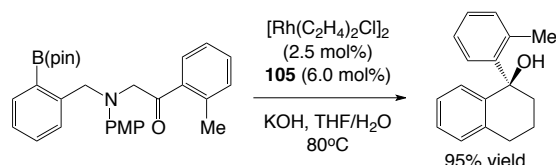


Fig. 75 Rhodium catalyzed enantioselective cyclisation

Based on observations in the 1,4-addition to nitroalkenes, Liao *et al.* were able to apply the sulfoxide-phosphine hybrid ligand **86** in the addition of boronic acids to isatins.<sup>208</sup> Various 3-aryl-3-hydroxy-2-oxindoles were obtained with excellent yields (93-99%) and good enantioselectivities (85-92% *ee*) (Figure 76). Lower *ee*'s were achieved in the same transformation with the sulfinamide-alkene ligand **94b**.<sup>209</sup> In this case, the outcome of the reaction was also highly dependent on the nature of the nitrogen protecting group.

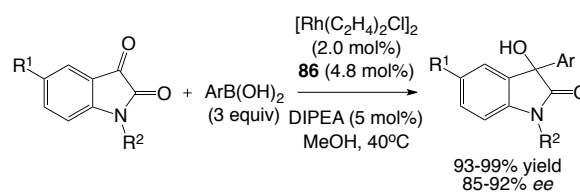


Fig. 76 Rhodium catalyzed asymmetric addition of arylboronic acids to isatins

A further application of ligand **91** led to the enantioselective rhodium catalyzed arylation of fluorinated ketones; the tertiary trifluoromethyl substituted alcohols were isolated with moderate *ee*'s (up to 78%).<sup>210</sup>

The branched olefin-sulfinamide ligand **106** was used by Xu *et al.* with  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$  in the asymmetric arylation of cyclic ketimines<sup>211</sup> and diketimines (Figure 77).<sup>212</sup> A broad variety of substrates were tested in these reactions. Carboxy-,  $\text{CF}_3$ - and H-substitutions on the iminic carbon in benzosultams and benzosulfamides were tolerated as substrates for these arylation. By changing reaction conditions, even aryl substituted benzosultams underwent arylation reactions to give products with chiral quaternary carbon centers.<sup>211a</sup> Finally, by a simple modification of the original conditions (changing from toluene to dichloromethane as the solvent), the addition to cyclic diketimines became feasible.<sup>212</sup> Although excellent *ee*'s were achieved, the diastereoselectivity of the reaction was low.

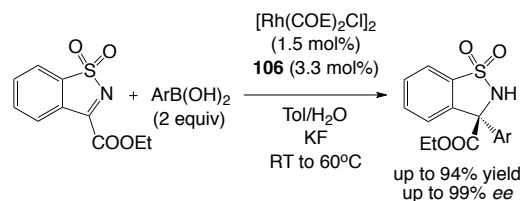
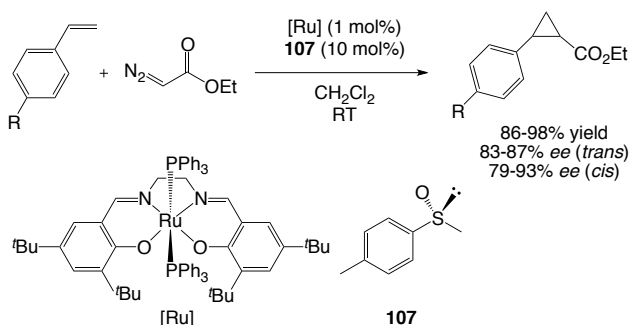


Fig. 77 Rhodium catalyzed asymmetric arylation of cyclic ketimines

## Miscellaneous Reactions

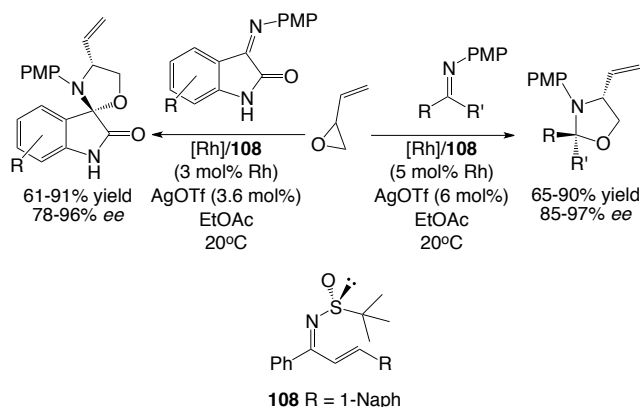
Nguyen and coworkers have reported on a non-chiral salen-ruthenium(II) complex that effects asymmetric olefin cyclopropanation reactions when a chiral, monodentate sulfoxide ligand is added in the apical position of the complex.<sup>213</sup> The idea was that the chiral Lewis base (sulfoxide **106**) would force the achiral salen ligand, more exactly its ethylene backbone linker, to adopt a twisted conformation reminiscent of the previously used chiral salen-type ligand backbones.<sup>214</sup> Indeed, the authors were able to observe high *ee*'s and high yield for the cyclopropanation of styrene with EDA, preferentially forming the *trans*-cyclopropane derivatives. Mechanistic studies showed that the

intermediate Ru-carbenoid species added the chiral sulfoxide ligand *trans* to it and as an O-bound species.



**Fig. 78** Ruthenium catalysed asymmetric cyclopropanation with a monodentate chiral sulfoxide ligand

A rhodium catalysed formal [3+2] cycloaddition of racemic butadiene monoxide and imines was carried out with the use of the chiral sulfonimide-alkene ligand **108** (Figure 76).<sup>215</sup> Highly enantioenriched spirooxindole oxazolidines or 1,3-oxazolidines were formed in high yield with good to excellent diastereoselectivities. The authors assume that both a dynamic kinetic resolution as well as a kinetic resolution are involved in the catalytic process. Interestingly, the reaction conditions ([Rh(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>Cl]<sub>2</sub>/**108**, AgOTf, EtOAc) are rather unusual compared to other Rh-sulfinyl catalysed additions (typically neutral Rh/ligand, non coordinating solvent, base).

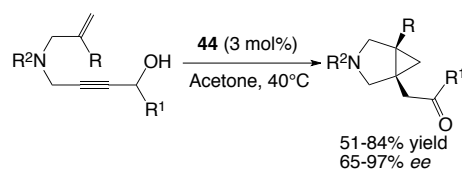


**Fig. 79** Rhodium catalysed asymmetric formal [3+2] cycloaddition of racemic butadiene monoxide and imines.

The last two examples covered in this review have been published after submission of this manuscript but are included because they clearly expand the reactivity of chiral sulfoxide ligands in transition metal catalysis.

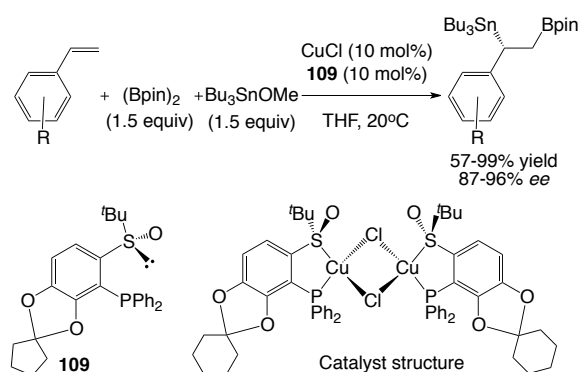
In an extension of their previous work, Trost and coworkers have applied complex **44** in an asymmetric redox bicycloisomerisation reaction (Figure 80).<sup>216</sup> The reaction, originally developed by the same authors using a non-chiral CpRu(PPh<sub>3</sub>)<sub>2</sub>Cl precatalyst activated in situ,<sup>217</sup> relies on the generation of a β-oxo carbenoid species from a propargyl alcohol. The species is subsequently trapped by a pendant olefin and leads to the creation of [3.1.0] and [4.1.0] bicycles that contain vicinal stereocenters. When employing sulfoxide-containing chiral catalyst **44**, [3.1.0] bicycles with vicinal quaternary stereocenters were obtained in moderate to good yields with good enantioselectivities. The choice of solvent was important as the authors noted that decreasing the polarity and ligating ability of the solvent (from acetone to THF) lead to a significant erosion of enantioselectivity. A careful study indeed revealed that when enantiomerically enriched propargyl alcohol (*R* and *S*) was used in THF, a pronounced matched/mismatched effect was observed

which was negligible in acetone. The authors concluded that coordination of acetone to the metal center during catalysis was important for observing high selectivities in this transformation.



**Fig. 80** Ruthenium catalysed asymmetric bicycloisomerisation reaction

Finally, a very interesting contribution by Liao *et al.* describes an asymmetric bis-metalation reaction of styrene substrates catalysed by CuCl and a chiral phosphino-sulfoxide ligand, **109**, derived from **86**.<sup>218</sup> In this reaction, they generate enantioenriched dimetalated alkanes with a primary C-B bond and a secondary C-Sn bond in high yields and excellent enantioselectivities (Figure 81). The authors also show how the products can be easily and selectively derivatised, highlighting the method's versatility. An X-ray structural determination of a close derivative of the catalyst was also reported which lead to the proposed stereochemical model for the reaction. While the paper does not discuss the structure in any detail, it seems to represent the first structure with this metal (copper) that contains both a phosphine and an S-bound sulfoxide. The S-bonding of the sulfoxide in this complex is just as unusual (see discussion above) and certainly plays a key role in providing the products with high enantioselectivity.



**Fig. 81** Copper catalyzed asymmetric bis-metalation of styrene

## Summary and Outlook

Sulfoxides and methods of making them have been known for many years now and syntheses of enantiopure sulfoxides are now quite well developed. Metal complexes with sulfoxides, especially DMSO, have also been well studied, and their binding properties are well understood.

Despite this large body of work, reports of metal catalysis with sulfoxide ligands have remained sporadic for several decades. Reports of the use of DMSO in combination with metals for non-enantioselective catalysis were (and still are) sometimes vague regarding the actual function of DMSO in the reaction and it is unclear whether the sulfoxide is bound to the metal throughout the catalytic cycle and to what degree its ambidentate nature plays a role. Nevertheless, catalytic developments over the last decade, especially from the careful approaches reported by the groups of White *et al.* and Stahl and coworkers, illustrate that palladium-sulfoxide systems are able to mediate a range of oxidative catalytic processes. These studies have uncovered unique reactivity patterns with these systems.

At the same time, the introduction of chiral, sulfur-bound bisulfoxide chelate ligands for rhodium-catalysed addition reactions has led to an impressive array of new ligand structures

being reported over the last years that rely on the use of the chiral sulfinyl moiety to promote these asymmetric transformations. There again and within a short time period, these ligands have been able to surpass and extend the reactivity profile when compared to their more classical ligand counterparts. A very important practical aspect for further developing these chiral sulfoxides lies in their generally very straightforward synthesis in enantiopure form.

Perhaps the most interesting inherent properties of sulfoxides, namely their ambidentate nature as well as their highly polarized sulfur-oxygen bond, might well represent the biggest potential for future applications. In some of the work involving oxidation catalysis with palladium sulfoxide systems, it appears at least plausible that switching between sulfur- and oxygen-bound metal-sulfoxide species determines the different catalytic outcome when compared to classical ligand systems. Electrostatic interactions direct the enantiocontrol when binaso-[Rh] systems are used as shown by Dorta, Cavallo and coworkers. Furthermore, Liao *et al.* have shown that a pendant (and free) sulfoxide unit serves as an activating group towards one of the reactants via the creation of a hydrogen bond, resulting in unprecedented reactivity in palladium catalysed AAS reactions.

Overall, these recent reports indicate that the sulfinyl moiety in these ligands can serve unique purposes when compared to more traditional ligand types, a fact that should help uncover novel and unconventional reactivities in the future. Extending the utility of sulfoxides by including transition metals other than palladium or rhodium, such as reported recently by Trost *et al.* (Ru) and Liao *et al.* (S-bound Cu), appears to be just as promising for exciting discoveries in this emerging and topical field of catalytic research.

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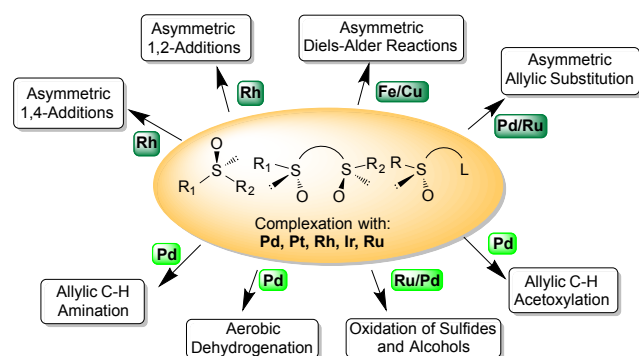


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**Graphical Abstract:**

**Text:** This review describes the use of sulfoxides as ancillary ligands in transition metal catalysis.

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