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Review

Application of mono- and bis-sulfonamides in asymmetric catalysis

Ratnasamy Somanathan*, Daniel Chávez, Felipe Antonio Servín, José Alfonso Romero and Gerardo Aguirre

Centro de Graduados e Investigación en Química, Instituto Tecnológico de Tijuana, Apartado Postal 1166, Tijuana, B. C. 22000, México.

ABSTRACT

Chiral enantiopure mono- and bis-sulfonamides have found wide application in asymmetric catalysis. They have been successfully applied in the alkylation of aldehydes, asymmetric transfer hydrogenation of aromatic ketones, aldol reactions, Diels-Alder reaction, Simmons-Smith cyclopropanation, α-oxidation, α-aminoxylation of carbonyl compounds and as organocatalysts in the asymmetric Michael addition. This review details the usefulness of these ligands and the mechanisms involved in inducing chirality.

KEYWORDS: asymmetric, organocatalysts, mono-sulfonamides, bis-sulfonamides

INTRODUCTION

Chiral enantiopure mono- and bis-sulfonamides have found wide application in asymmetric catalysis. They have been successfully applied in the alkylation of aldehydes, asymmetric transfer hydrogenation of aromatic ketones, aldol reactions, Diels-Alder reaction, Simmons-Smith cyclopropanation, α-oxidation and α-aminoxylation of carbonyl compounds; in majority of the reactions, mono- and bis-sulfonamides are used as metal complexes to catalyze the reaction. More recently, enantiopure mono-sulfonamides have found applications as organocatalysts in the asymmetric Michael addition of nucleophiles to α,β-unsaturated compounds.

*Corresponding author: rsomanathan@mail.sdsu.edu

1. Application of bis-sulfonamides in asymmetric addition of diethylzinc to prochiral aldehydes

Chiral secondary alcohols are an integral part of biologically active compounds and are versatile intermediates for the synthesis of complex natural and unnatural products. The most obvious way of synthesizing such alcohols from achiral starting materials involve enantioselective addition of organometallic reagents to the corresponding aldehyde. Highly reactive organomagnesium and organolithium reagents lead to very low enantioselectivity. In 1984, Oguni and Omi [1] discovered that chiral aminoalcohols catalyzed the addition of diethylzin to aldehydes with moderate yields and enantioselectivities. Following this work, Ohno and coworkers [2] showed that chiral bis-sulfonamide ligands also catalyzed the reaction giving the final alcohol with poor enantioselectivity and turnover numbers (TON). However, when titanium tetraisopropoxide was used as an additive, the reaction showed high enantioselectivity and turnover frequency (TOF) (Figure 1).

The mechanism involving bis-sulfonamide-titanium tetraisopropoxide and diethylzinc was resolved by Walsh and coworkers [3] as shown in the Figure 2. Both the isolated titanium complex and the mixture of bis-sulfonamide + $Ti(O^iPr)_4$ catalyzed the diethylzinc addition to benzaldehyde with similar enantioselectivity, thus establishing the titanium-bis-sulfonamide as the intermediate in the reaction. The authors suggested that the possible shift of the equilibrium to the right depends on the diethylzinc

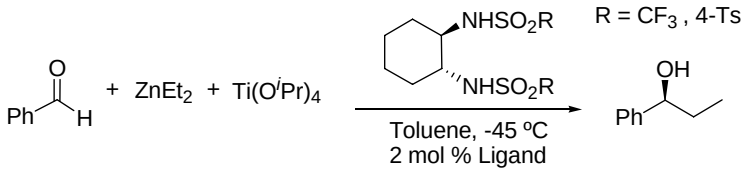


Figure 1. Bis-sulfonamide catalyst in the asymmetric addition of diethylzinc to benzaldehyde.

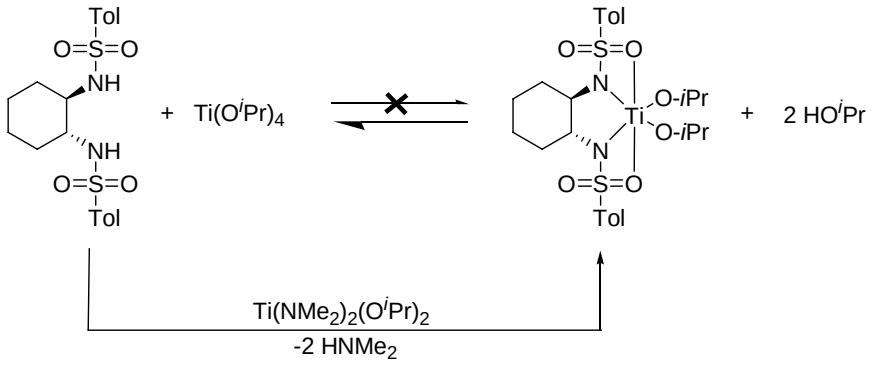


Figure 2. Titanium-bis-sulfonamide as the intermediate in the asymmetric addition of diethylzinc to aldehydes.

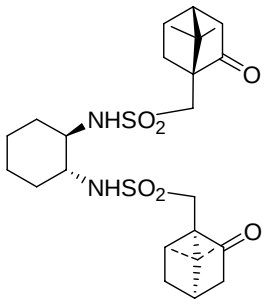


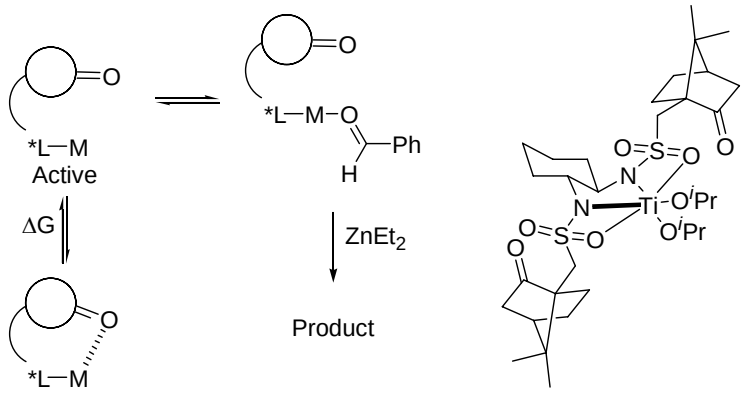
Figure 3. Bis-sulfonamide of camphor ligand catalyzes the diethylzinc addition to aromatic aldehydes in the presence of $Ti(O^iPr)_4$.

reacting with isopropanol. The complex intermediate then reacts with more diethylzinc and aldehyde followed by the transfer of the alkyl group to the aldehyde [4]. Literature on the application of various bis-sulfonamides/$Ti(O^iPr)_4$ catalysts in addition of diethylzinc to aromatic aldehydes have been reviewed [4, 5, 6].

Hwang and Uang [7] found that optically pure bis-sulfonamide of camphor ligand (Figure 3) 20 mol%/$Ti(O^iPr)_4$ catalyzed the diethylzinc addition to a variety or aromatic aldehydes giving the alcohols in 59-90% enantiomeric excess (ee).

Asymmetric amplification has been well studied in the case of diethylzinc addition to aldehydes catalyzed by aminoalcohols that are not enantiomerically pure [8]. A positive nonlinear effect in the asymmetric amplification is synthetically useful because a chiral catalyst of high enantiopurity is not needed to prepare a chiral product with high enantiomeric excess. However, very little is known of chiral amplification with enantiomerically impure bis-sulfonamides-catalyzed diethylzinc addition to aldehydes. Walsh and coworkers [9] discovered that the bis-sulfonamide of camphor ligand derived from a mixture of racemic *trans* and *meso cis* isomer of (1*S*)-(+)-10-camphorsulfonyl compound, catalyzed the diethylzinc addition to benzaldehyde in the presence of $Ti(O^iPr)_4$ with good enantioselectivity (80%). This high enantioselectivity was attributed to the positive nonlinear effect due to an intramolecular inhibition involving the coordination of the camphor carbonyl group to the titanium center. The less effective diasteromeric catalyst formed the more stable carbonyl-Ti-coordinated complex, thus, letting the more effective catalyst to control the reaction (Scheme 1) [10].

Most alkylation reactions using diethylzinc involve aromatic aldehydes. Paquette and Zhou [11] reported that a rigid bidentate sulfonamide **2** derived



Scheme 1. One of the isomers of the racemic camphor sulfonamide forms a stable catalytically inactive sulfonyl-Ti-coordinated complex in the diethylzinc addition to benzaldehyde.

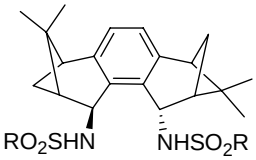


Figure 4. Rigid bidentate bis-sulfonamide-Ti(O^iPr)$_4$ as a catalyst for the addition of diethylzinc to aromatic and aliphatic aldehydes.

from a chiral 1,4-diamine ligand (Figure 4) in 1 mol%/Ti(O^iPr)$_4$ catalyzed the addition of diethylzinc to aromatic and aliphatic aldehydes, thus making the ligand a synthetically useful catalytic agent.

Following the same lines, Yus and coworkers [12] studied a camphordisulfonamide ligand which with Ti(O^iPr)$_4$ catalyzed the diethylzinc addition to aliphatic aldehydes in 92-96% ee (Figure 5).

Zhang, Walsh and coworkers [13] prepared a series of sulfonamide ligand bearing phenolic groups (Figure 6). The expectation was that the phenolic –OH would bind strongly with Ti(O^iPr)$_4$ leading to a stable catalytically active species. Ligands **1**- and **2**-Ti(O^iPr)$_4$ catalyzed the diethylzinc addition to benzaldehyde in good yields and enantioselectivity. Best results were obtained with ligand **1** with substituents R^1 = R^2 = F, Cl and Br giving the final alcohol in 91%, 99% and 92% ee, respectively. Ligand **2** bearing a 2'-acohol also catalyzed the diethylzinc addition to benzaldehyde with 92% ee in the presence of Ti(O^iPr)$_4$ [8].

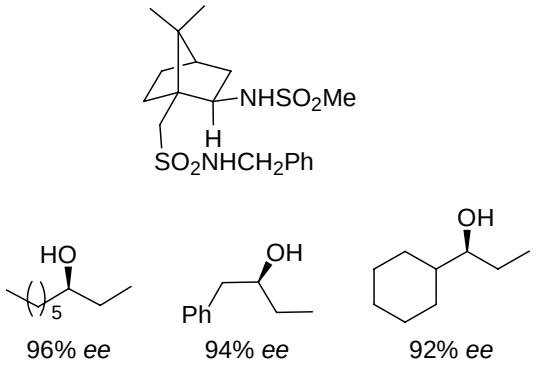


Figure 5. Enantioselective addition of diethylzinc to aliphatic aldehydes catalyzed by camphordisulfonamide-Ti(O^iPr)$_4$ complex.

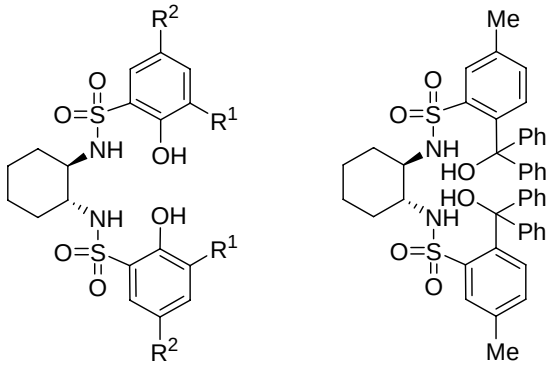


Figure 6. Sulfonamides with a phenolic group as the catalyst in the diethylzinc addition to benzaldehyde in the presence of Ti(O^iPr)$_4$.

Chiral tertiary alcohols are useful intermediates in the asymmetric synthesis of biologically active molecules. Alkylation of ketones using diethylzinc has been a challenge in the past. Ramon and Yus [14], using mono-sulfonamide-alcohol ligands derived from camphor alcohol, demonstrated for the first time the addition of diethylzinc to ketones in the presence of $Ti(O^iPr)_4$ (Figure 7).

In most diethylzinc reactions, bis-sulfonamides are used as ligands along with $Ti(O^iPr)_4$. Recently, Somanathan and coworkers [15] reported the use of tetrakis-sulfonamides with $Ti(O^iPr)_4$ to catalyze the diethylzinc addition to benzaldehyde (Figure 8). The alcohols were obtained in good yields (up to 98%) and moderate ee (up to 81%).

Chiral 1,2-diamines have found wide application in the synthesis of bis-sulfonamides. Lake and Moberg [6] reported that a series of bis-sulfonamides derived from 1,5-diamines (Figure 9) catalyzed the diethylzinc addition in the presence of $Ti(O^iPr)_4$ to benzaldehyde and gave good conversions up to 99% and moderate ee (up to 69%). The low ee can be attributed to the conformational flexibility of the ligands.

Anaya de Parrodi and coworkers [16] reported a series of more rigid bis-sulfonamides (Figure 10), which with $Ti(O^iPr)_4$ catalyzed the addition of diethylzinc to benzaldehyde in good yields (85%) and poor ee (52%). The rigid molecule with the two nitrogens far apart, probably leads to poor binding with the titanium and this explains the poor enantioselectivity observed.

2. Sulfonamides in the asymmetric transfer hydrogenation of aromatic ketones

Optically pure secondary alcohols are valuable intermediates in the synthesis of pharmacologically active molecules [17]. A direct approach in the synthesis of these molecules is by catalytic enantioselective reduction of the corresponding

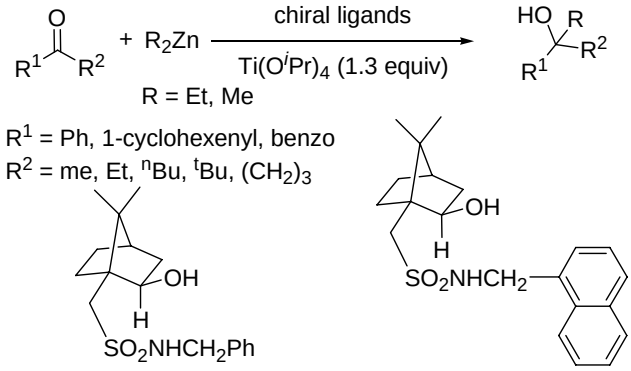
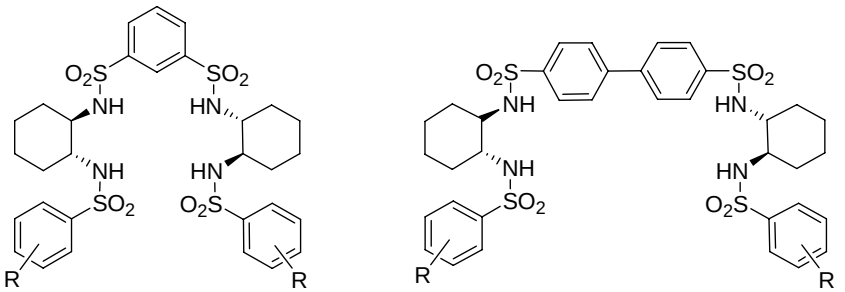


Figure 7. Mono-sulfonamide-alcohol-$Ti(O^iPr)$ catalysts in the addition of diethylzinc to ketones.



R: a = H, b = *p*-CH_3, c = CF_3, d = *p*-NO_2, e= 2,4,6-trimethyl, f = 2,4,6-tri*iso*propyl

Figure 8. Tetrakis-sulfonamides-$Ti(O^iPr)_4$ catalyst in the diethylzinc addition to benzaldehyde.

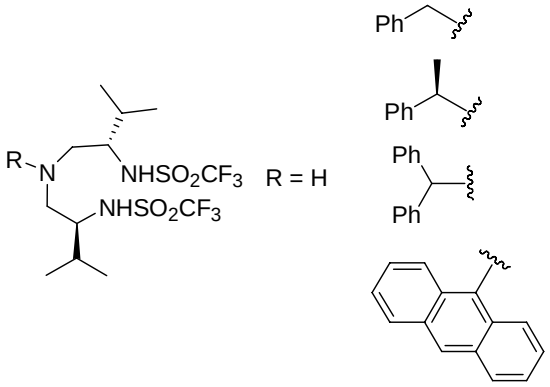


Figure 9. Bis-sulfonamides-Ti(O^iPr)$_4$ catalyst in the diethylzinc addition to benzaldehyde.

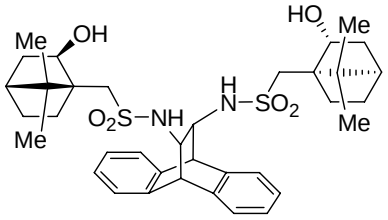


Figure 10. Rigid bis-sulfonamide-Ti(O^iPr)$_4$ as a catalyst in the addition of diethylzinc to benzaldehyde.

ketones, which have been extensively studied during the past decades [18]. A particularly useful method in the direct reduction of ketones by asymmetric transfer hydrogenation (ATH) is catalyzed by metal complexes associated with various chiral ligands using 2-propanol or HCOOH/NEt_3 as the hydrogen source. The metal complexes used are often derived from chiral mono-sulfonamides of 1,2-diamines coordinated to Ru(II), Rh(III), and Ir(I) metals (Figure 11) [19].

Noyori and coworkers [20], through extensive experimental and theoretical calculations established the mechanism shown in Scheme 2. They also showed that the enantioselectivity induced comes from the arene (CH_3 or H) δ^+ interaction with the π-electron cloud of the aromatic ketone [21], which is ~3-5 kcal/mol (Figure 12).

In most cases of ATH reactions, isopropanol was used as the source of hydride. Xiao and coworkers [22] showed that Ru(*R*,*R*)-Ts-dpen (Ts-dpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylendiamine) or its polymer supported analogues, catalyzed the

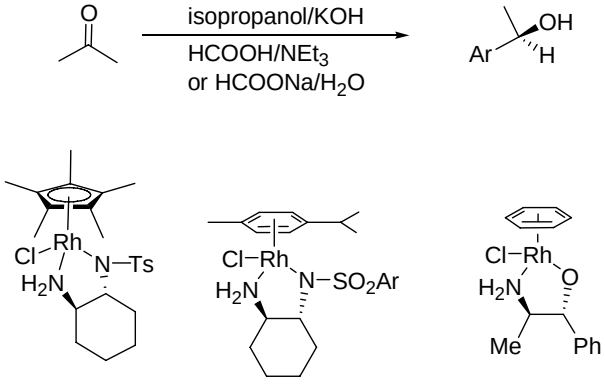


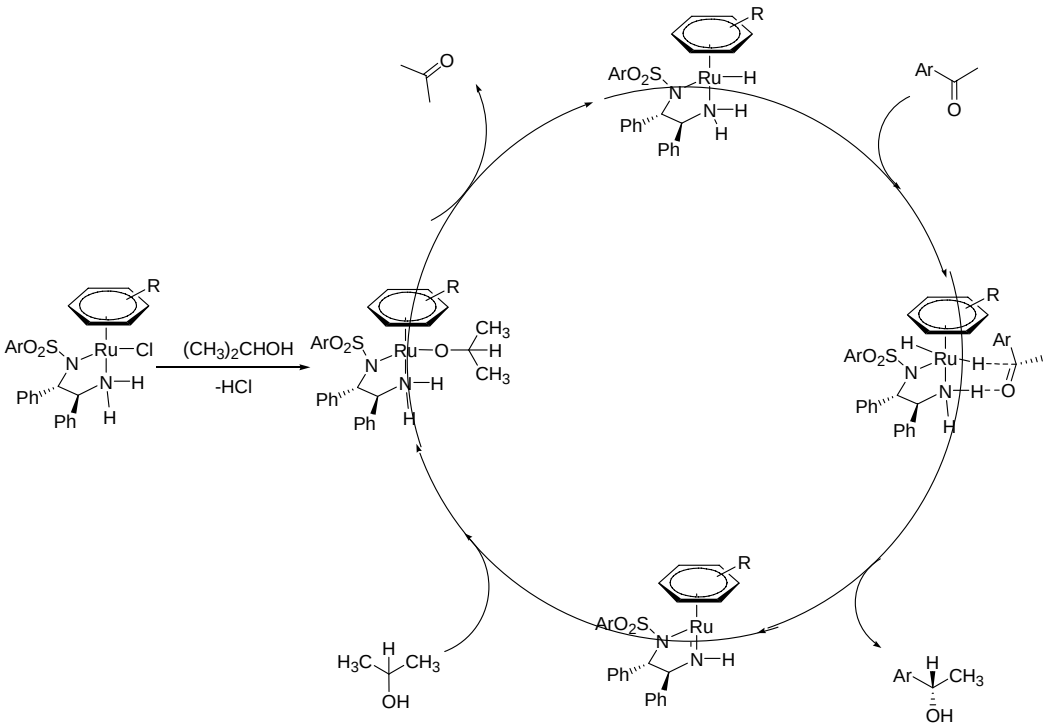
Figure 11. Mono-sulfonamides of 1,2-diamines coordinated to Ru(II), Rh(III), and Ir(I) metals catalyze the asymmetric transfer hydrogenation (ATH).

ATH of aromatic ketones using aqueous sodium formate as the hydride source (Figure 13). Results indicated a faster reaction rate and higher turnover numbers in conjunction with excellent ee. The mechanism of ATH using aqueous sodium formate is shown in Scheme 3. Furthermore, the same authors showed, through detailed kinetic and theoretical study, that the rate increase in the ATH of ketones under aqueous sodium formate is due to the participation of a water molecule in the transition state, lowering TS energy by about 4 kcal/mol [23].

Following the use of monosulfonamide-Ru complexes in the ATH of aromatic ketones, Somanathan and coworkers [19] reported several new bis-sulfonamide ligands (Figure 14) which gave excellent ee and yields in the ATH of aromatic ketones using aqueous sodium formate. The immobilized ligand **3** also gave a yield > 99% and 89% ee. The ligand was recycled 4-5 times with only a slight drop in the ee [19]. The same authors reported a library of mono-sulfonamides bearing heterocyclic or heteroatom sulfonamides (Figure 15), all showing excellent ee and yields when used with [Cp*$RhCl_2$]/HCOONa/water [17].

Wills and coworkers [24] reported a novel tethered Ru-sulfonamide ligand (Figure 16) which gave excellent yields (> 99%) and ee (> 98%) in the asymmetric reduction of aromatic ketones.

In a recent review, Somanathan and coworkers [25] reported the use of immobilized chiral metal catalysts for enantioselective hydrogenation of ketones (Figure 17).



Scheme 2. Mechanism for reduction of ketones by asymmetric transfer hydrogenation (ATH).

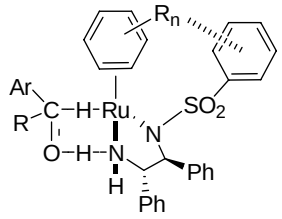


Figure 12. Enantioselectivity induced from arene in the reduction of ketones by asymmetric transfer hydrogenation (ATH).

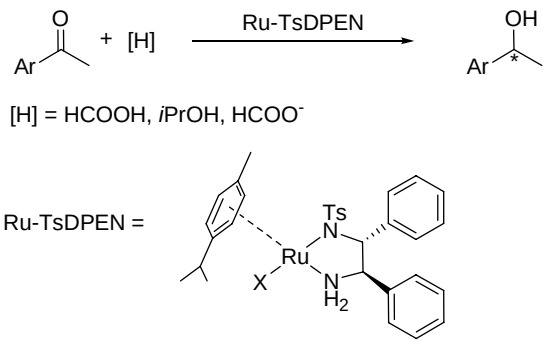


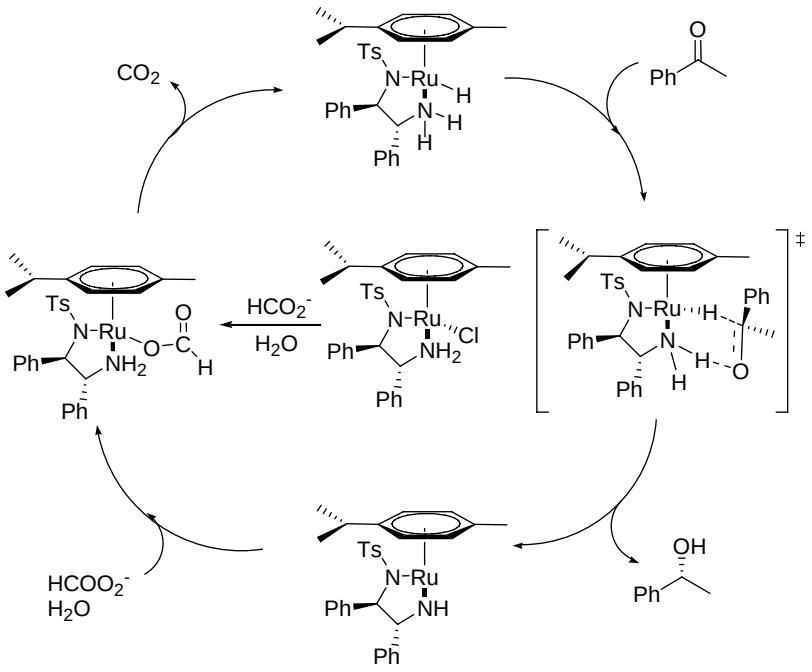
Figure 13. Reduction of ketones by ATH using aqueous sodium formate.

3. Use of sulfonamides in asymmetric Michael addition

The catalytic Michael reaction is an important and well-studied process for stereoselective carbon-carbon bond formation in organic synthesis [26]. In recent years, the field of asymmetric organocatalytic Michael reactions has received widespread attention [27]. Among the reactions studied, the conjugate addition of nitroalkanes to α,β-unsaturated systems and the addition involving carbonylic compounds to α,β-unsaturated nitroalkenes are of great interest (Scheme 4) [28, 29]. The products obtained are direct precursors to important structural moieties, such as γ-aminocarbonyls, 2-pyrrolidones, and 2-piperidones [28a].

Enantiomerically pure bifunctional mono-sulfonamides derived from (1*R*,2*R*)-cyclo-hexanediamine have been used as organocatalysts in the addition of carbonylic compounds to β-nitrostyrene as shown in Figure 18 [29a].

The sulfonamide organocatalyst acts as a weak hydrogen bond donor, and at the same time it contains a basic primary amino group that can activate the



Scheme 3. Mechanism of ATH using aqueous sodium formate.

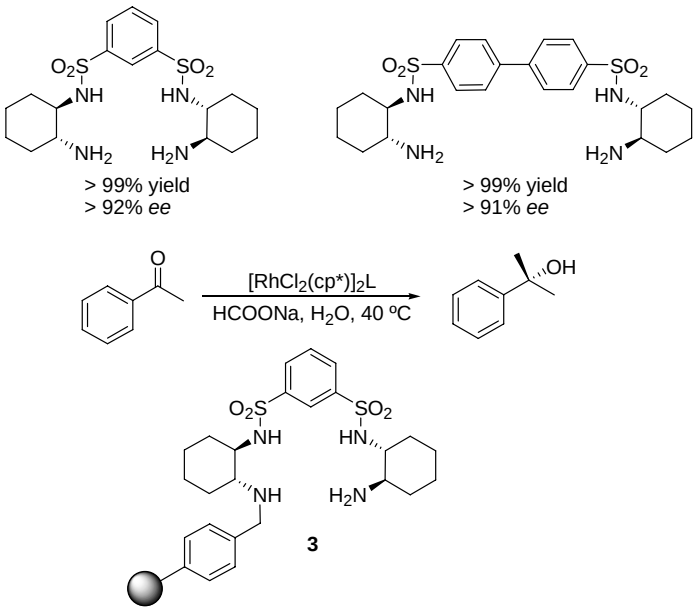


Figure 14. Bis-sulfonamide ligands in the ATH of aromatic ketones using aqueous sodium formate.

nucleophilic reaction partner (in this case, acetone) by the generation of an enamine. Thus, the catalyst is proposed to be bifunctional in the transition state of the reaction. Using this concept, Somanathan and coworkers [30] synthesized a series of ligands bearing the halogens Cl and Br and showed for the first time an O···Cl interaction in the transition state. These ligands gave good yields and moderate ee. The O···Cl interaction was supported by theoretical calculations (Figure 19).

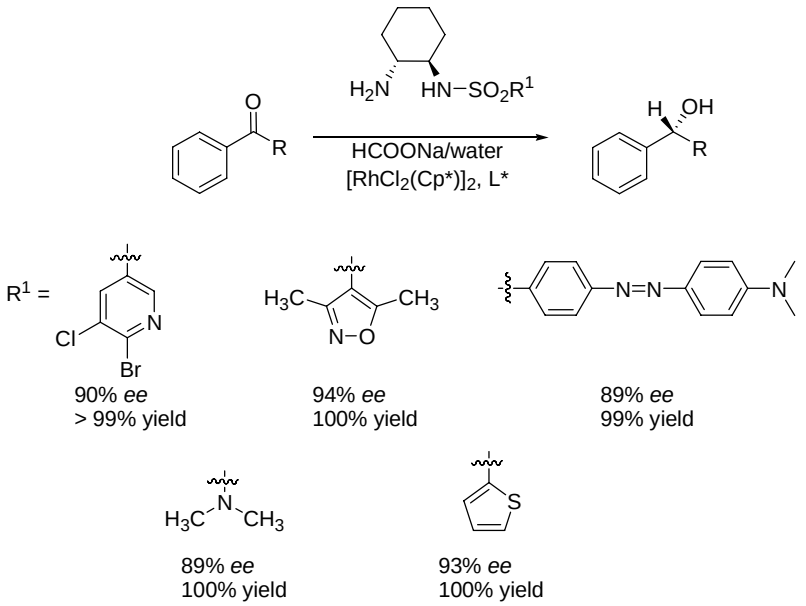


Figure 15. Mono-sulfonamides bearing heterocyclic or heteroatom sulfonamides in the ATH of aromatic ketones.

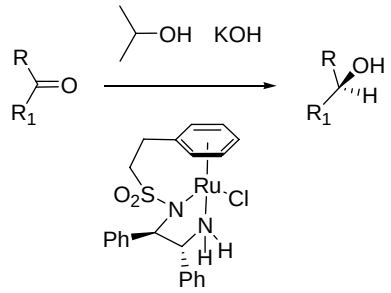


Figure 16. Tethered Ru-sulfonamide ligand in the ATH of aromatic ketones.

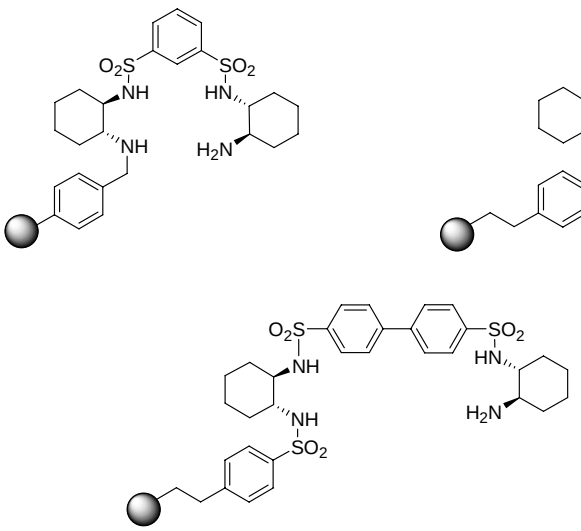
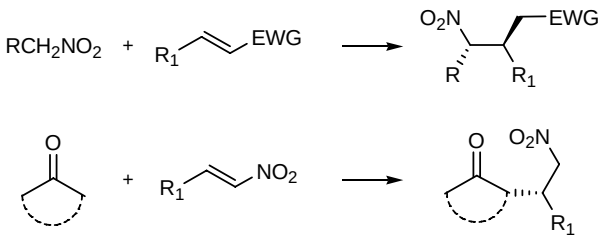


Figure 17. Immobilized bis-sulfonamide ligands in the ATH of aromatic ketones.



Scheme 4. Michael addition of nucleophiles to α,β-unsaturated systems with an electron-withdrawing group.

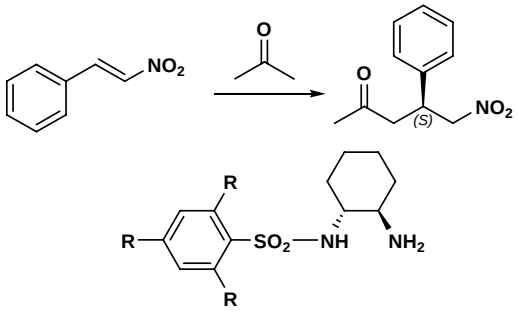


Figure 18. Michael addition of acetone to nitrostyrene catalysed by chiral mono-sulfonamides.

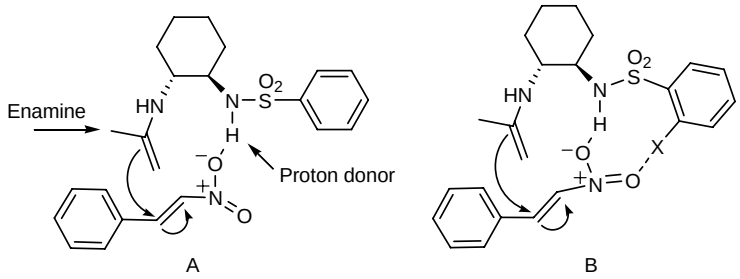


Figure 19. Proposed transition states in the Michael addition of acetone to nitrostyrene.

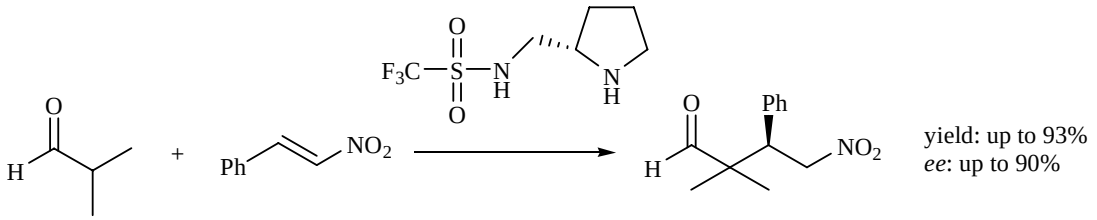


Figure 20. Pyrrolidine sulfonamide catalysts in the conjugate Michael addition of isobutyraldehyde to nitrostyrene.

Wang and coworkers [31] reported the conjugate addition of isobutyraldehyde to nitrostyrene, catalyzed by pyrrolidine sulfonamide with good yields and enantioselectivity (Figure 20). Another organocatalytic use of sulfonamides is in the addition of ketones to nitrostyrene as shown in Figure 21, with good yields, enantioselectivity and diastereoselectivity (dr) [32-33].

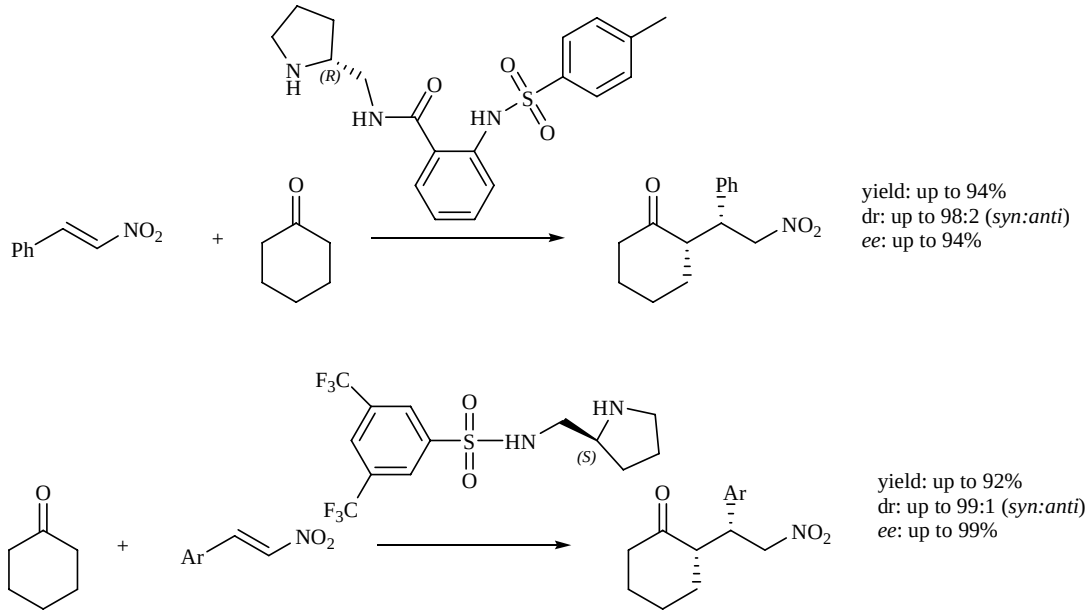


Figure 21. Sulfonamide type catalysts in the conjugate Michael addition of ketones to nitrostyrene.

Xiao and coworkers [34] reported a new class of pyrrolidinyl-sulfamides as organocatalysts in the Michael addition, giving good yields and enantioselectivity. Other authors reported certain other sulfonamide type catalysts for the asymmetric Michael addition (Figure 22) [35-36].

4. Aldol reaction catalyzed by chiral sulfonamides

The asymmetric aldol reaction plays an important role in catalytic organic synthesis. Recently, the organocatalyzed aldol reaction has proven to be a useful method for the synthesis of optically pure β-hydroxy carbonyl compounds, which are useful building blocks in the synthesis of complex biologically active molecules [37]. Revial and coworkers [38] reported several proline derived sulfonamides and tested them as chiral organocatalysts in the enantioselective aldol reaction (Figure 23). They obtained enantioselectivity upto 98% and yields upto 88%. The authors suggested a transition state involving an initial enamine formation between the ketone and praline and hydrogen bonding between the aldehyde and the sulfonamide NH of the organocatalyst as shown in Figure 24.

Yang and coworkers [39] designed organocatalysts using *O*-phenylenediamine as the backbone tethered to proline ligands, which gave moderate yields (63-68%) and enantioselectivity in the aldol reaction of cyclohexanone and aromatic aldehydes (Figure 25).

Chiral organocatalysts immobilized on polymers, dendrimers, silica gel and ionic ligands have been widely used in the asymmetric aldol reaction [40]. Pedrosa and coworkers [41] reported a novel sulfonylpolystyrene-supported prolinamide as catalyst for the enantioselective aldol reaction in water (Figure 26). The reaction gave yields of 81%, dr 78:22 (*anti*:*syn*) and ee 90%.

It was reported that, malonic acid half thioester when added enantioselectively to benzaldehyde in the presence of sulfonamide derived cinchona alkaloid as organocatalyst (Figure 27), gave aldol product in 99% yield and 94% ee in methyl *tert*-butyl ether (MTBE) as solvent [42].

N-(Heteroarenesulfonyl)prolinamides catalyzed the aldol reaction between acetone and trihalomethyl lactones. The investigators used different heterocyclic sulfonamides tethered to proline as catalyst, resulting in yields up to 97% and ee up to 89% [43]. The authors suggested a transition state where the ligand behaves as a bifunctional catalyst (Figure 28).

The introduction of a phenoxy group at the hydroxyl function of *N*-arylsulfonyl derivatives of *trans*-4-hydroxy-L-prolines (Figure 29) gave better

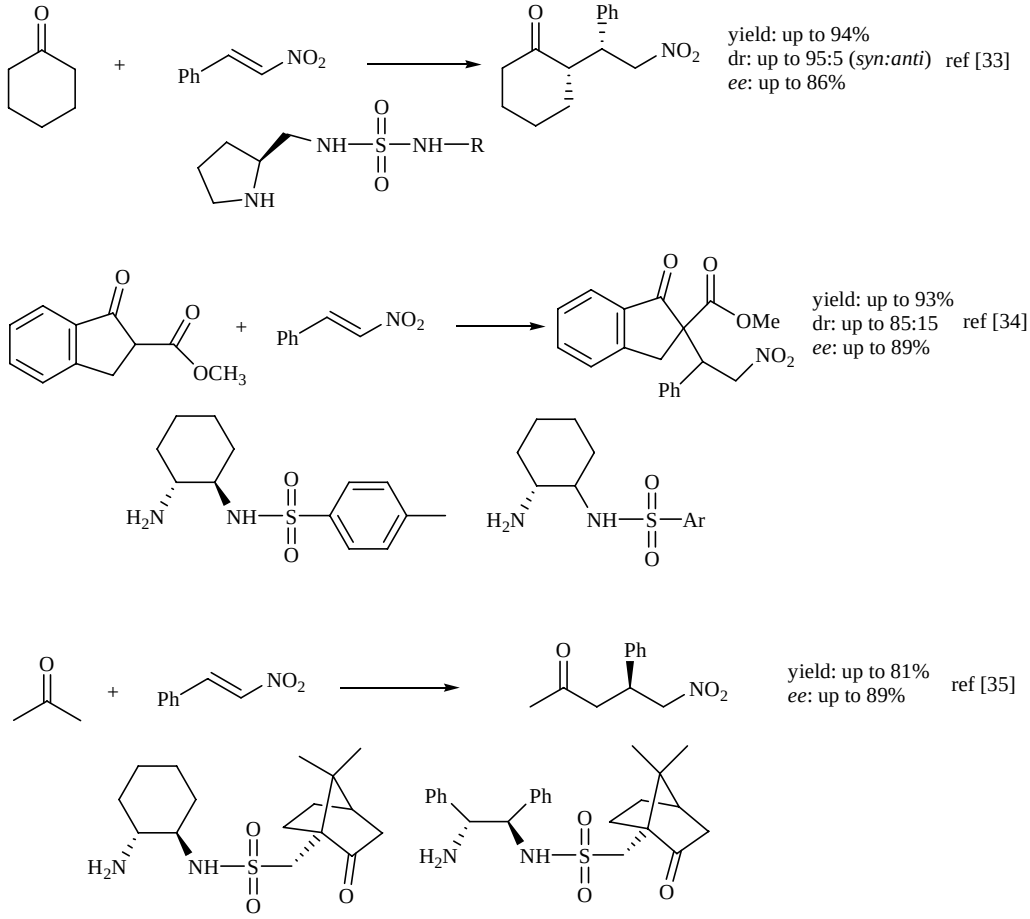


Figure 22. Sulfonamide type catalysts in the conjugate Michael addition.

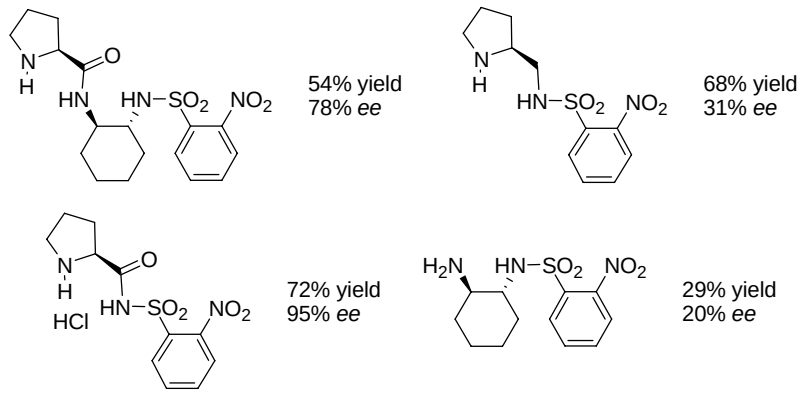


Figure 23. Proline derived sulfonamides as chiral organocatalysts in the aldol reaction.

results compared to the proline catalyst in Figure 28. Addition of cyclohexanone to benzaldehyde gave the final aldol product in yields up to 98%, de 98:2 (*anti*:*syn*) and ee > 94% [44-45].

Sulfonamide derived from the non-natural aminoacid homo-proline (Figure 30) catalyzed the acetone and cyclohexanone addition to *p*-nitrobenzaldehyde in moderate yields and low ee [46].

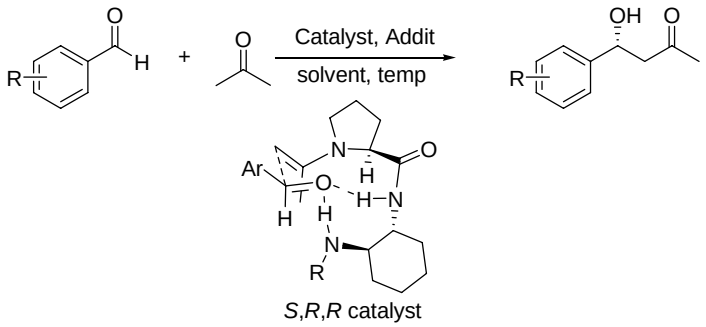


Figure 24. Transition state of sulfonamides in the aldol reaction.

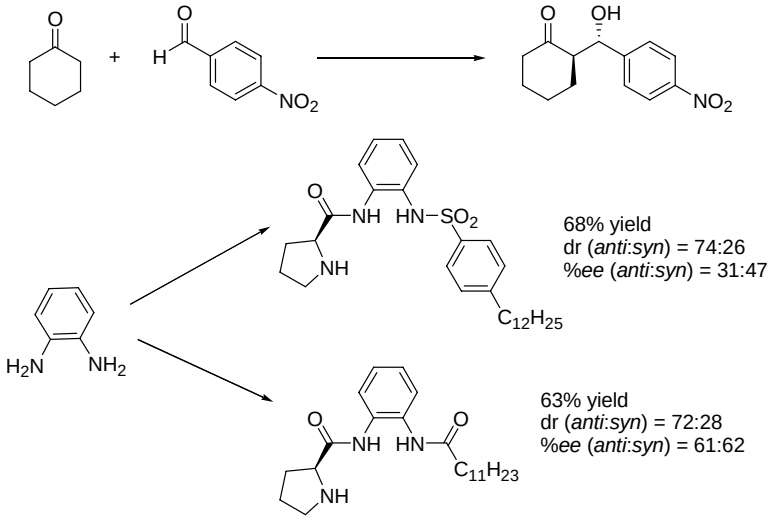


Figure 25. Proline organocatalysts in the aldol reaction of cyclohexanone and aromatic aldehydes.

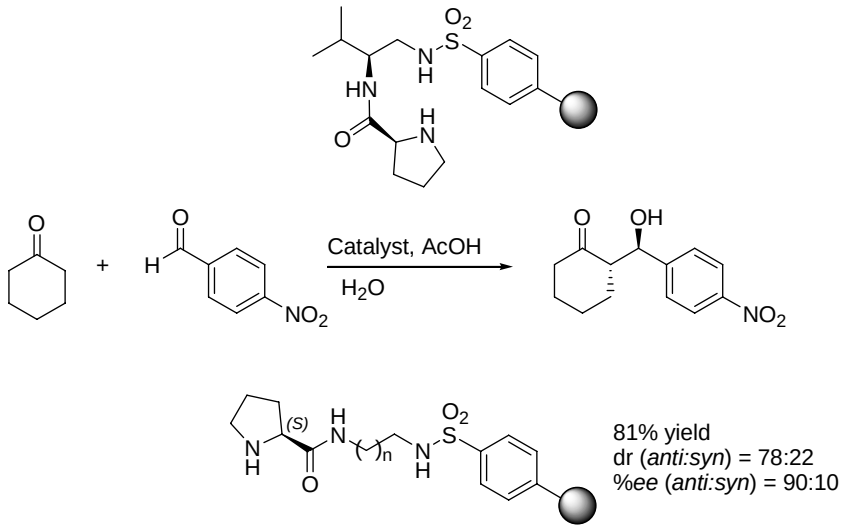


Figure 26. Sulfonylpolystyrene-supported prolinamide as catalyst the enantioselective aldol reaction in water.

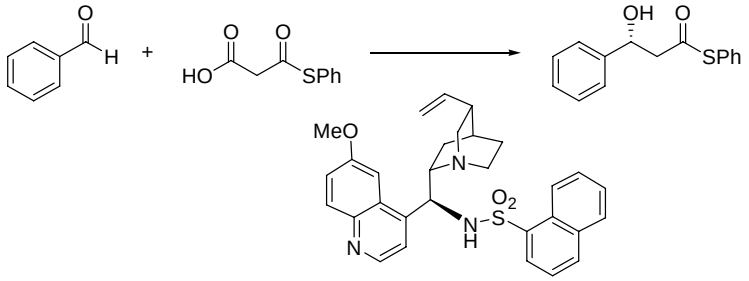


Figure 27. Sulfonamide derived cinchona alkaloid as organocatalyst in the aldol reaction.

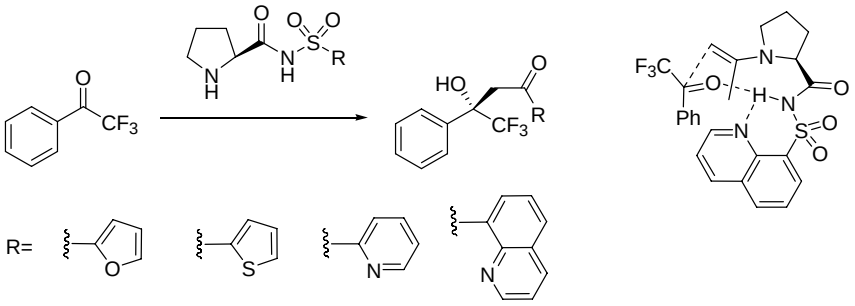


Figure 28. *N*-(Heteroarenesulfonyl)prolinamides as organocatalysts in the aldol reaction.

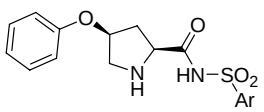


Figure 29. Hydrophobic organocatalyst in the aldol reaction.

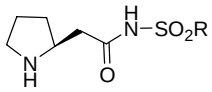


Figure 30. Homo-proline-sulfonamide organocatalysts in the aldol reaction.

It has been reported that the use of $-C_4F_9$ fluorus (*S)*-pyrrolidine sulfonamide as an organocatalyst gave the Aldol product in excellent yield and enantioselectivity in water. The products were obtained in yields upto 92% and dr 20:1 with ee upto 97% [47]. The authors proposed a transition state involving a bifunctional interaction (Figure 31).

Miura *et al*. [48, 49] reported the use of simple mono-sulfonamides as organocatalysts in the aldol reaction of cyclohexanone to *p*-nitrobenzaldehyde in brine (Figure 32). The final product was obtained in good yields (up to 94%) and de (up to 86:14, *anti*:*syn*) and ee up to 90%.

A chemo- and stereo-selective asymmetric direct cross-aldol reaction between aliphatic aldehydes and α-chloroaldehydes was reported using proline and a novel axially chiral amino sulfonamide as organocatalysts. The products were obtained in moderate yields (61-91%) and ee > 98% [50]. A transition state was proposed, where the ligand behaves as a bifunctional catalyst (Figure 33).

A highly enantio- and diastero-selective anti-aldol process (up to > 99% ee, > 99:1 dr catalyzed by *N*-(*p*-dodecylphenylsulfonyl, *anti*:*syn*) (Figure 34) was reported by Carter and coworkers [51, 52].

A series of pyrrolidinyl-camphor containing organocatalysts were synthesized and tested in the aldol reaction of cyclohexanone to *p*-nitro-benzaldehyde [53], the sulfonamide ligand gave a yield of 95%, dr 66:34 (*anti*:*syn*) and ee of 65% (Figure 35). Most organocatalysts used in the aldol reaction behave as a bifunctional catalyst having a primary or secondary amine function to interact with the carbonyl group and a proton donor group to hydrogen-bond with acceptor aldehyde.

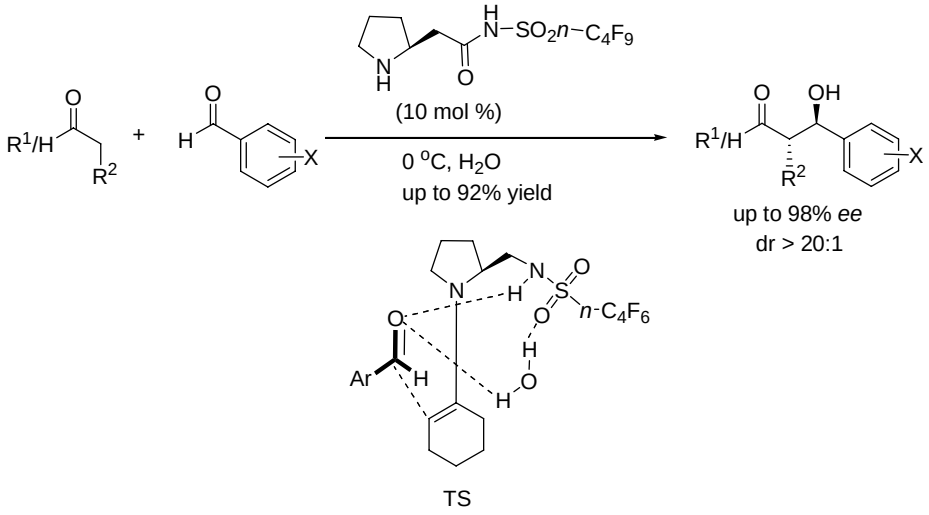


Figure 31. Fluorus (*S*) pyrrolidine sulfonamide as organocatalyst in the aldol reaction and the proposed bifunctional transition state.

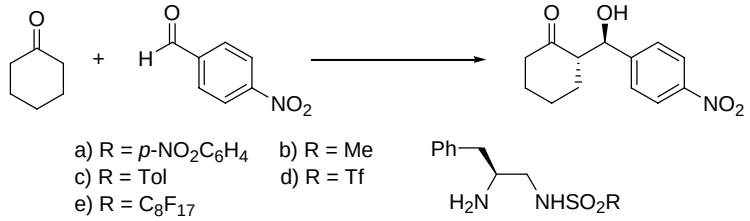


Figure 32. Mono-sulfonamides as organocatalysts in the aldol reaction of cyclohexanone to *p*-nitrobenzaldehyde.

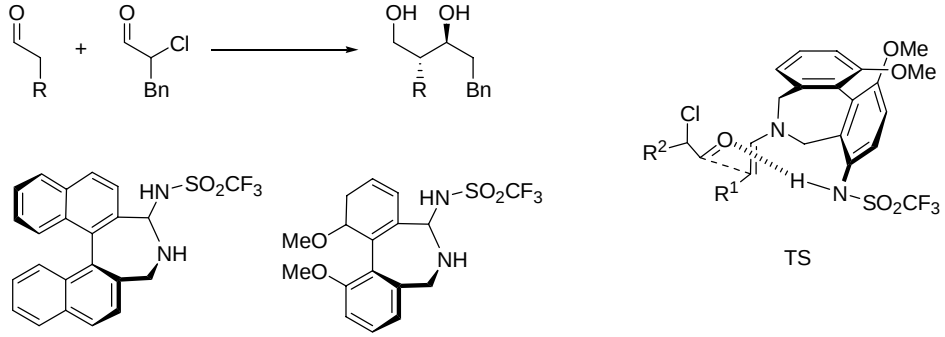


Figure 33. Sulfonamides as organocatalysts in the asymmetric direct cross-aldol reaction and proposed bifunctional transition state.

5. Application of bis-sulfonamides in Diels-Alder reaction

The highly enantioselective catalytic Diels-Alder reaction of achiral components has been of great interest to synthetic chemists. In an earlier work, Corey and coworkers [54] reported the enantioselective Diels-Alder reaction of an achiral C_{2v}-symmetric *Z*-dienophile with a diene in the

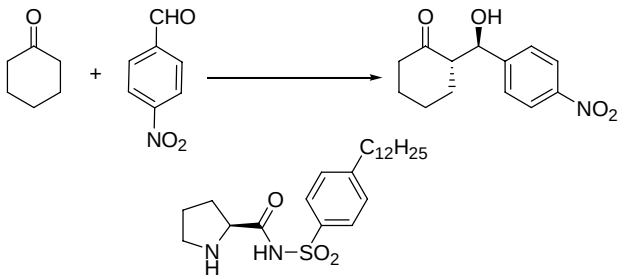


Figure 34. Sulfonamide organocatalysts in the *anti*-aldol reaction.

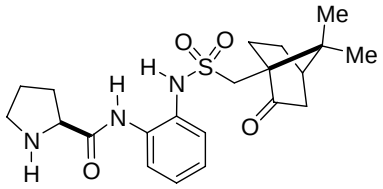


Figure 35. Pyrrolidinyl derived camphor sulfonamide as organocatalysts in the aldol reaction.

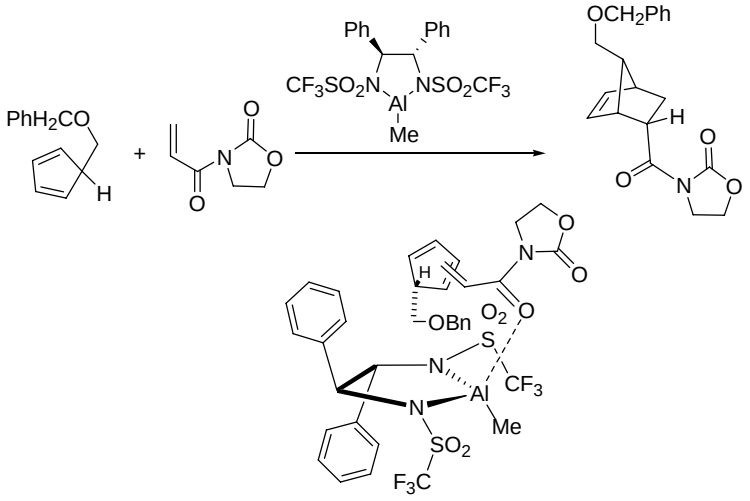


Figure 36. Transition state involving a chiral diazaluminolidine in the Diels-Alder reaction.

presence of chiral diazaluminolidine. The cycloadduct was obtained in 93% yield and 94% enantioselectivity. The authors proposed a transition state, where the dienophile is bonded to the aluminum (Figure 36).

Kocienski and coworkers [55] used the same diazaluminolidine catalyst to carry out enantioselective [2+2] cycloaddition of differently substituted (trimethylsilyl)ketenes to aldehydes (Figure 37). The products were obtained in yields up to 85% and enantioselecivity up to 83%. They also provided a plausible transition state for this reaction (Figure 38).

Chiral acids derived from sulfonamides and (S)-valine with borane were used as catalysts in the cycloaddition of α,β-unsaturated aldehydes (Figure 39). Products were obtained in moderate yields (45-95%) and ee (25-72%) [56].

Magnesium complexes derived from (*R*)-2-[2-(alkyl- or (*R*)-2-[2-[(alrylsulfonyl)amino]phenyl]-

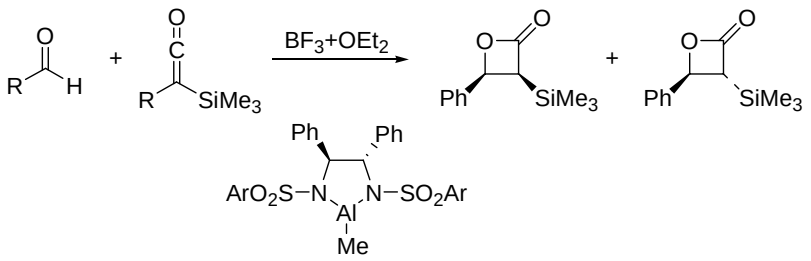


Figure 37. Sulfonamide as catalyst in the [2+2] cycloaddition.

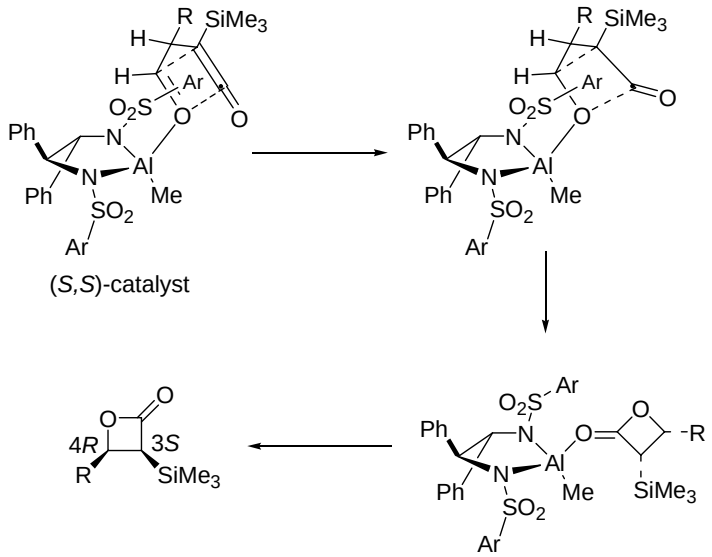


Figure 38. Plausible transition state for sulfonamides in the [2+2] cycloaddition.

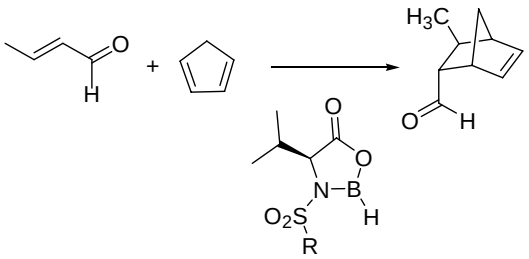


Figure 39. Sulfonamides as catalyst in the cycloaddition of α,β-unsaturated aldehydes.

4-phenyl-1,3-oxazolines were found to be efficient Lewis acid catalysts for the Diels-Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one with cyclopentadiene as shown in Figure 40 [57].

A report by Tonoi and Mikami [58] deals with chiral bis-trifluoromethanesulfonylamide as chiral Brønsted acid catalyst for the asymmetric hetero Diels-Alder reaction with Danishefsky's diene and glyoxylate or phenylglyoxal (Figure 41).

Rajaram and Sigman [59] used a camphor-sulfonamide-derived organocatalyst as proton donor in the cycloaddition of dienes to aldehydes (Figure 42) with good yields (42-80%) and ee (71-92%).

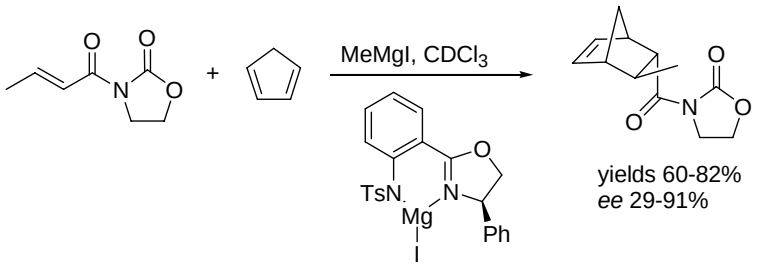


Figure 40. Magnesium complexes as Lewis acid catalyst for the Diels-Alder reaction.

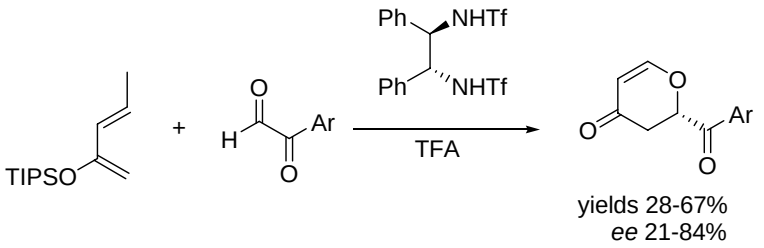


Figure 41. Sulfonylamide as chiral Brønsted acid catalyst for the asymmetric hetero Diels-Alder reaction.

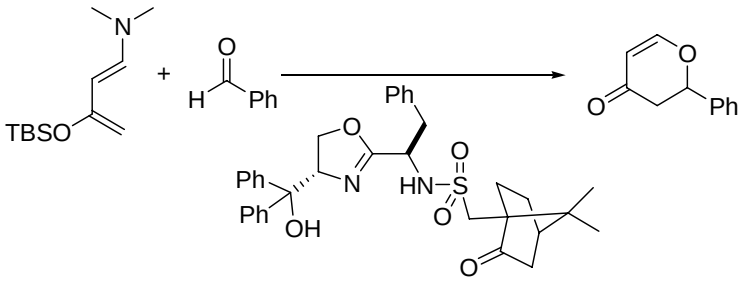


Figure 42. Camphor-sulfonamide as proton donor catalyst for the asymmetric hetero Diels-Alder reaction.

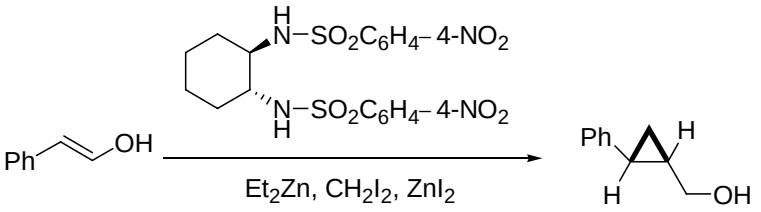


Figure 43. Bis-sulfonamide catalysts in cyclopropanation.

6. Application of bis-sulfonamides in cyclopropanation and epoxidation

The Simmons-Smith reaction was first reported in 1958 by the DuPont researchers. The procedure employs a geminal diiodide and zinc-copper complex with an olefin to give a cyclopropanated compound. Kobayashi [60] and Denmark's group [61] independently developed a synthetic methodology for the cyclopropanation of an allylic alcohol in the presence of a chiral sulfonamide ligand (Figure 43). The addition of a mixture of cinnamyl alcohol, chiral cyclohexan disulfonamide, diethylzinc and

zinc iodine to a mixture of dichloromethane and diethylzinc resulted in cyclopropyl alcohol in yields up to 98% and ee up to 82%.

Denmark and O'Connor [62] proposed a mechanism where the cinnamyl alcohol reacts with diethylzinc to form a zincalkoxide, the bis-sulfonamide forms a zinc complex and the dichloromethane + zinc iodine, leads to an iodomethylzinciodide (Figure 44). The intermediaries of these complexes were supported by NMR spectroscopy. The reaction proceeds through a transition state to the cyclopropanation product.

Imai and coworkers [63] reported a fluorous disulfonamide (Figure 45) which afforded the corresponding cyclopropylmethanols in 69-96% yield with 49-83% ee.

The same group of researchers used the above ligand along with diethylzinc and diiodomethane to synthesize (+)-2,2-diphenylcyclopropylmethanol, which was subsequently converted to the optically active cibenzoline (Figure 46), an antiarrhythmic agent [64].

Balsells and Walsh [65] reported the asymmetric cyclopropanation of allylic alcohols using sulfonamide/Schiff base ligands as catalyst, with diethylzinc and diiodomethane (Figure 47). The cyclopropyl alcohols were obtained in good yields (92-98%) and ee (40-78%).

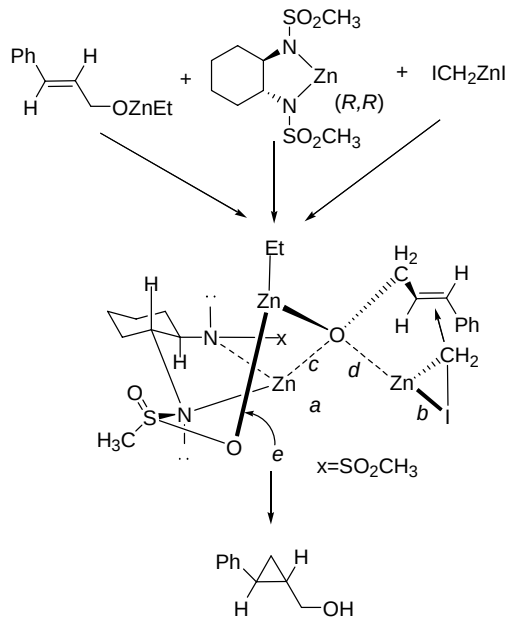


Figure 44. Proposed transition state for the cyclopropanation.

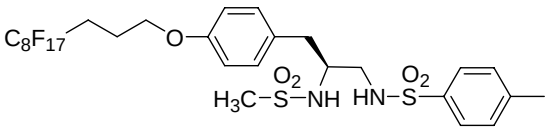


Figure 45. Fluorous bis-sulfonamide catalysts in cyclopropanation.

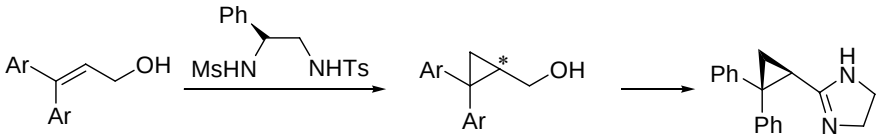


Figure 46. Bis-sulfonamide catalysts used for synthesis of cibenzoline.

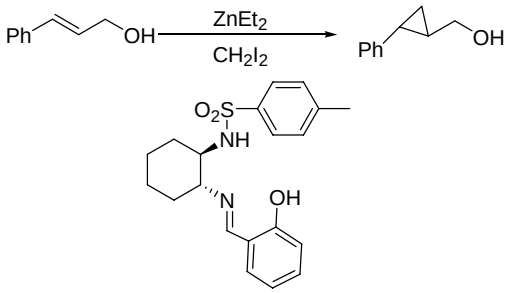


Figure 47. Sulfonamide/Schiff base catalyst in cyclopropanation.

Arvidsson and coworkers [66] showed that aryl sulfonamides derived from (2*S*)-indoline-2-caboxylic acid catalyzed the addition of sulfur ylides to α-β-unsaturated aldehydes (Figure 48) in moderate yields (30-61%) and excellent ee (> 88%). The mechanism involved is very similar to that proposed by Kunz and MacMillan [67] for the indoline-2-carboxylic acid, where an iminium ion is formed between the indoline-2-carboxylic acid and α,β-unsaturated aldehyde, to give a charged species that interacts with the sulfur ylide (direct electrostatic activation) leading to an organized transition state as shown in Figure 49.

Walsh and coworkers [68, 69] reported an efficient protocol for the enantioselective addition of allyl groups to conjugated enones. This transformation was coupled with diasteroselective epoxidation. Rearrangement of the resulting epoxy alcohols provide highly functionalized alcohol-type products with excellent ee (Figure 50).

7. Application of sulfonamides in α-oxidation and α-aminoxylation of carbonyl compounds

In addition to the reactions detailed above, optically pure sulfonamide ligands are used as catalysts in the α-functionalization of carbonyl compounds. Adolfsson, Córdova and coworkers [70] used a library of proline derived sulfonamides to add nitrosobenzene to cyclohexanone leading to α-oxidation of the carbonyl compound (Figure 51). The authors proposed a transition state involving the *si*-face (Figure 52).

Evans and Nelson [71] used a bis-sulfonamide-Mg complex as catalyst to carry out the enantioselective α-amination of carbonyl compounds.

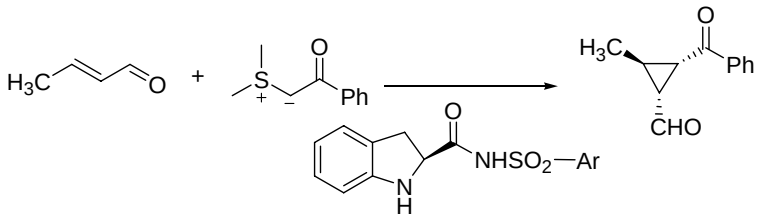


Figure 48. Sulfonamides as catalysts in the addition of sulfur ylides to α-β-unsaturated aldehydes.

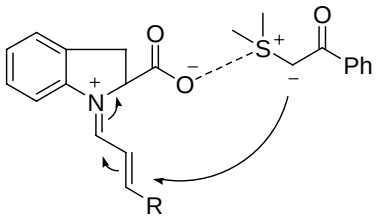


Figure 49. Proposed transition state in the addition of sulfur ylides to α-β-unsaturated aldehydes.

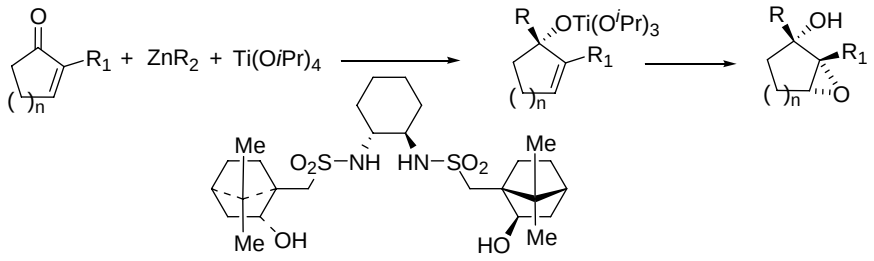


Figure 50. Bis-sulfonamides as catalysts in a diasteroselective epoxidation.

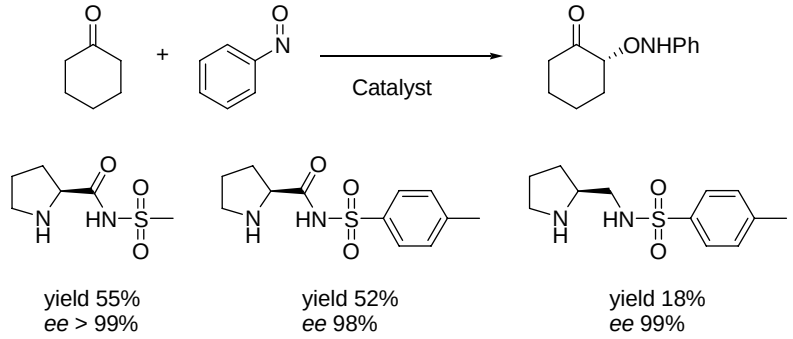


Figure 51. Proline sulfonamides used in α-oxidation of cyclohexanone.

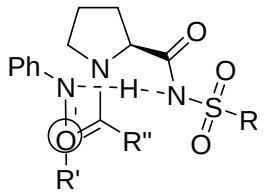


Figure 52. Proposed a transition state for α-oxidation of cyclohexanone.

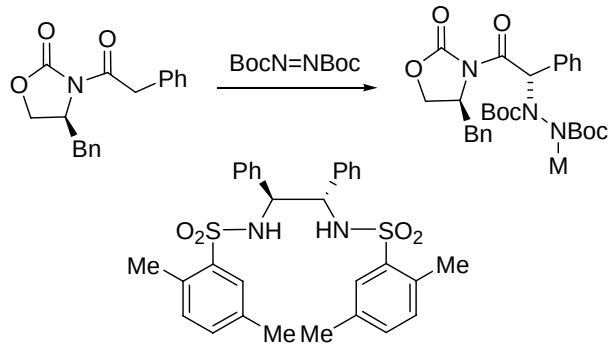


Figure 53. Bis-sulfonamide-Mg complex used in α- amination of *N*-acyloxazolidinones.

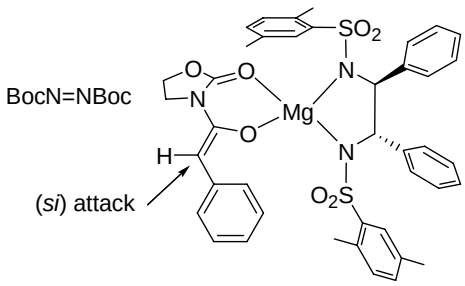


Figure 54. Chiral magnesium bis-sulfonamide-complex.

The Mg-complex catalyzed the α-amination of *N*-acyloxazolidinones with high yields (up to 95%) and excellent enantioselectivity (up to > 99%) (Figure 53). They proposed that the asymmetric induction proceeds via the intermediacy of the chelated tetrahedral magnesium enolate complex depicted in Figure 54.

CONCLUSION AND PERSPECTIVES

In this review we have summarized the use of enantiomerically pure mono- and bis-sulfonamides as catalysts in a variety of chemical transformations, such as Aldol reactions, Diels-Alder reaction, Simmon-Smith cyclopropanation, α-oxidation, α-amination of carbonyl compounds and in Michael addition reactions. Unfortunately, the scope of these ligands is restricted to the limited availability of structurally different and enantiomerically pure 1,2-diamines.

With the increasing demand for optically pure compounds, these sulfonamides could have a large role to play as catalysts in the synthesis of biologically active molecules.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST STATEMENT

The authors confirm that this article has no conflicts of interest.

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