Applications of N'-monofunctionalised TsDPEN derivatives in asymmetric catalysis.

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Abstract: This review contains an account of recent developments in the applications of N'-monoalkylated or N'-mono(thio)acylated(N-sulfonyl)-1,2-diphenylethylene-1,2-diamine (TsDPEN) derivatives to asymmetric catalysis. The coverage features examples of applications of derivatives as ligands in organometallic complexes for use in asymmetric reduction and oxidation reactions. The use of TsDPEN derivatives as catalysts in a diverse range of C-C and C-S bond formation reactions is also described in detail.

1. Introduction.

N-(p-Tosyl)-1,2-diphenylethylene-1,2-diamine (TsDPEN) **1** (Figure 1) is a widely used chiral diamine derivative with synthetic applications in asymmetric catalysis. The precursor to **1**, i.e. 1,2-diphenylethylene-1,2-diamine **2** (Figure 1), can be readily prepared in both enantiomerically pure forms. This can be achieved through the reaction of benzil with cyclohexanone and ammonium acetate to initially form a spiro-bicyclic diimine intermediate which is then reduced with metallic lithium and hydrolysed to give the racemate, subsequently resolved through the formation of its tartaric acid salt.[1a,1b] Enantiomerically-pure DPEN may also be prepared via the diol precursor, itself generated using a Sharpless asymmetric dihydroxylation reaction.[1c,1d] Enantiomerically-pure DPEN itself has found extensive applications as a component of asymmetric organometallic catalysts, and for ketone

hydrogenation in particular.[2] TsDPEN, and other sulfonylated derivatives, may then be prepared through an efficient monotosylation of the diamine.

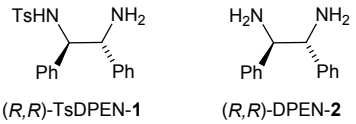

Figure 1. Structures of (*R,R*)-TsDPEN and DPEN.

Perhaps the most successful and established application to catalysis of TsDPEN is as a ligand in [η^6-arene)Ru(II)TsDPEN(Cl)] complexes such as **3a-3d** (Figure 2), which are now established as efficient and selective catalysts for asymmetric transfer hydrogenation (ATH) of ketones and imines.[3] In ATH applications, the simple preparation of the derived catalysts by the reaction of TsDPEN with an η^6-arene ruthenium(II) chloride dimer precursor makes the reagents highly practical. Derivatives containing alternative sulfonamide groups have also been reported. In contrast, very few examples of catalysis by N'-*monofunctionalised* TsDPEN derivatives (i.e. containing a single alkyl or acyl group on the non-sulfonylated amine) have been reported, which is surprising given the potential for modification of the properties of the catalyst whilst retaining a basic nitrogen functionality and NH-bonding potential in the likely catalytic cycles.

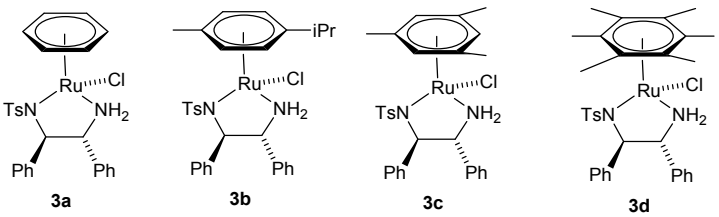

Figure 2. Asymmetric transfer hydrogenation (ATH) catalysts derived from (*R,R*)-TsDPEN.

Hence this review will specifically summarise developments in the use of N'-monoalkylated TsDPENs **4** and N'-(thio)monoacylated TsDPENs **5**, and related derivatives containing alternative sulfonamide substituents (Figure 3). However the coverage will not include 'tethered' complexes such as **6** as these have been reviewed previously.[4] Dialkylated TsDPEN derivatives will not be discussed, although some examples of their applications have been reported.[5]. Likewise, the applications of TsDPEN derivatives linked to an N'-imine or imidazoline will also not be described.[6]

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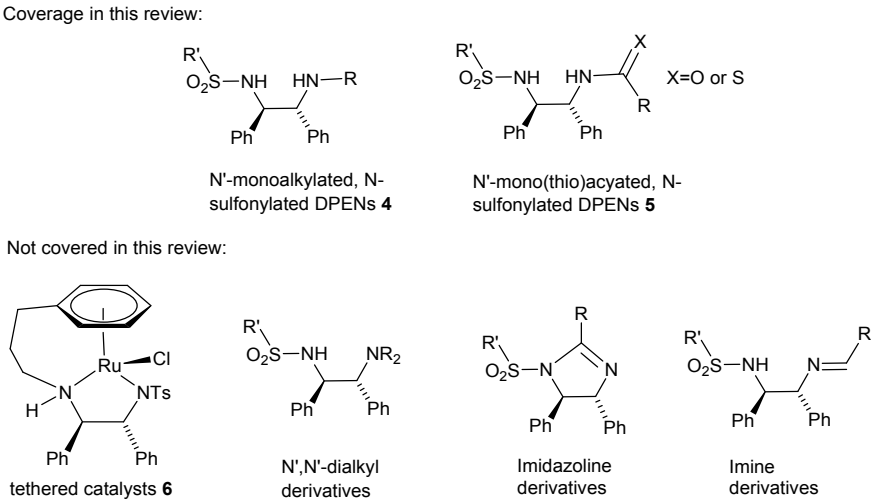

Figure 3. N'-monoalkylated and N'-mono(thio)acylated TsDPEN derivatives will be reviewed.

2. Use of N-alkylated TsDPEN in asymmetric transfer hydrogenation and hydrogenation:

In one of the earliest papers on ATH by Noyori et al. [3f] in which formic acid/triethylamine (FA/TEA) was used in the reduction, some specific observations were made on the importance of the electronic and steric nature of both the η^6-arene ring and the diamine. In terms of reactivity, complexes with an η^6-benzene (**3a**) were found to be the most reactive, followed by p-cymene and mesitylene (**3b, 3c**) and finally hexamethylbenzene complexes (**3d**) were the least reactive. However the mesitylene and p–cymene-containing complexes **3b** and **3c** gave the best reduction enantioselectivities. More significantly, it was stated that the presence of the primary amine in the TsDPEN part was highly important and that 'the $NHCH_3$ analogue showed a comparable enantioselectivity but with much lower reactivity; the $N(CH_3)_2$ derivative gave very poor reactivity and stereoselectivity.'. In light of the accepted mechanism by which the hydride derivatives of catalysts **3a-d** are believed to operate[2e,3], in which an N-H bond is essential, this is unsurprising. In 2011, Wills et al prepared and isolated the N'Me_2 derivative of **3a** and confirmed that it was a very poor catalyst for ketone ATH, but was effective at imine reduction (although products of low ee were formed), suggesting a different mechanism for imine reduction.[7].

In 2004, Ikariya and Koike reported a study on the rates of formation of formate derivatives of **3a-3d** (i.e. with a formate in place of Cl) from the corresponding ruthenium hydrides upon reaction with carbon dioxide [8]. Although most studies were focussed on the parent TsDPEN-

derived complexes, an N'-methylated derivative was also studied, and the rates were comparable. However the ruthenium hydride with two N' methyl groups, did not form the formate, indicating that the N-H bond was essential to the mechanism.

In 2009, Wills et al. reported a systematic study on N-alkylated TsDPEN derivatives **7** (Figure 4).[9] It was found that systematic variation of the alkyl group has some measurable effects, notably that addition of a methyl group actually generated a more active catalyst, and that the addition of linear alkyl chains has no detrimental effects on the catalysis of ATH of ketones or imines. The addition of more bulky chains reduced the activity of the complexes, although the ees were not significantly affected. An important observation was that the use of the η^6-benzene ring in the complexes was essential; complexes containing a substituted arene did not work effectively as catalysts, presumably due to the increased steric hindrance. The sense of reduction of the cyclic imine which was tested with these and other derivatives suggested that an open transition state is operating, rather than the more established ketone reduction transition state in which the operation of a hydrogen bond from the N-H to the ketone is essential.

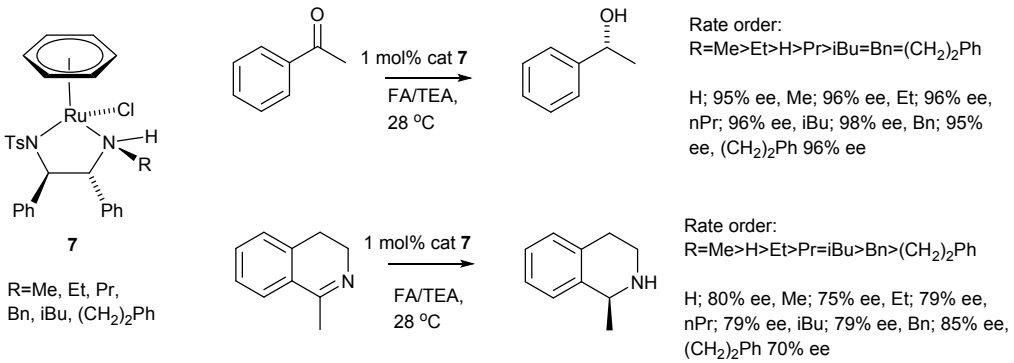

Figure 4. A series of N'-alkylated TsDPEN complexes which were effective at ATH of ketones and imines.

Having the ability to add a functional group to the basic nitrogen atom of TsDPEN without detrimentally affecting the catalytic properties of the complexes potentially allows for moderation of activity towards specific targets and a means to link the catalysts to a functional group which can moderate its properties e.g. with respect to solubility. Further examples of what could be tolerated at the 'basic' nitrogen atom were reported by Wills et al. and are illustrated in Figure 5.[10,11,12] It was found that several functionalised N'-benzyl groups

could be added without significantly altering the catalytic and enantioselective properties of the reagents in ketone and imine reduction. Although acetophenone reduction and the reduction of a dimethoxydihydroisoquinoline proceeded in good ee, reductions of cyclic imines lacking a fused aromatic ring were much less enantioselective (Figure 4)[10], and these remain an ongoing challenge. A chain to a hydroxyl group could be added without reducing the enantioselectivity of the catalyst.[11] Other groups which could be added include anthracene and a tri(BIPY)Ru complex (Figure 5), to give complexes which were all still competent in the reduction of ketones, underlining a high level of tolerance of functionality at the basic nitrogen atom of the complex.[12]

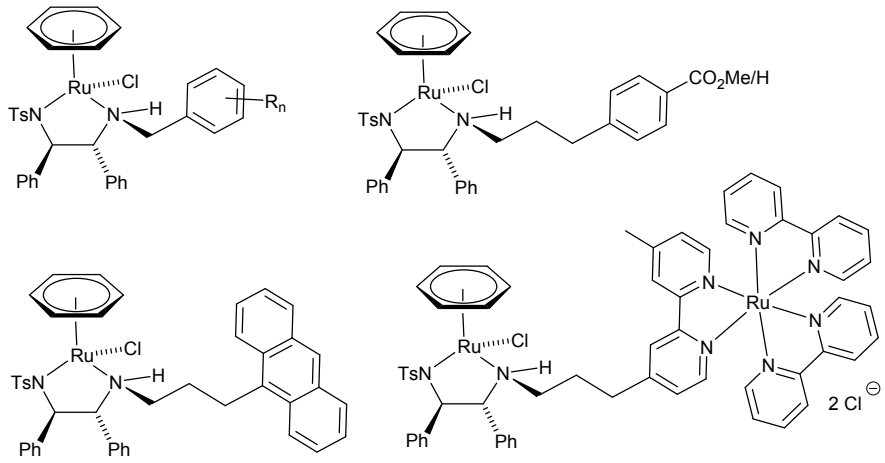

Figure 5. Examples N'-Alkylated TsDPEN derivatives which have been used in ATH of ketones and imines.

In an example published in 2015,[13] a tetraarylphosphonium (TAP)-functionalised ligand was prepared and converted to a Ru(II)-based catalyst **8** which was subsequently applied to the ATH of ketones in water (Figure 6). The salt was catalytically effective and a range of ketones were reduced in aq. FA/TEA (a 1.2:1.0 ratio was found to be optimal). Using this catalyst at 40 ^{o}C, a good number of ketones could be reduced in high ee and conversion. The catalyst could also be recycled and reused a number of times by precipitation from solution using ether, thus taking advantage of the modified solubility properties of the catalyst, which also proved to be very stable.

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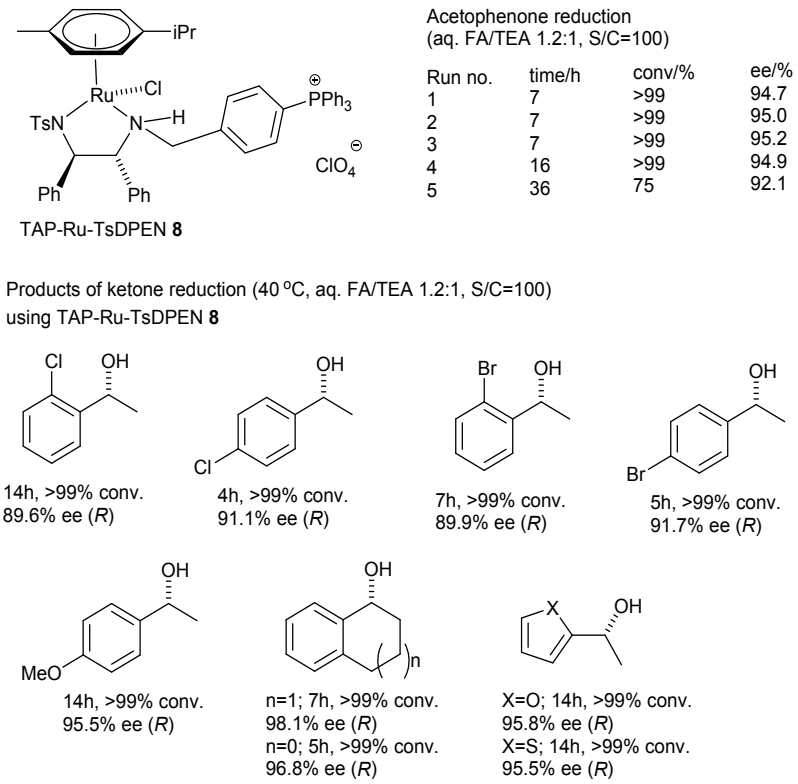

Figure 6. Use of a tetraarylphosphonium (TAP)-functionalised catalyst **8** in the asymmetric reductions of ketones.

Examples have been reported of ATH catalysts supported on heterogeneous supports.[14] The catalyst (**9**) in the report by Ma et al. is linked through both groups to a phosphate-functionalised polystyrene support (Figure 7).[15] The subsequent reaction of this to form an inorganic zirconium phosphate-phosphonate created a 'pillared' structure which could be separated after each catalytic use (using formic acid/trimethylamine in aqueous solution) by centrifugation and washing, and recycled. Throughout the recycling, the ee remained high, over five cycles, although there was evidence of some leaching of catalytic material from the system. Using the catalyst in aqueous solution permitted the reduction of a range of ketones in excellent conversions (yields >90% in most cases) and high ee.

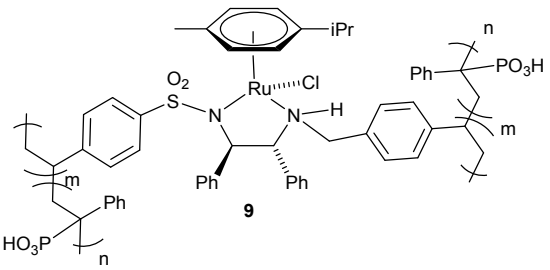

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Figure 7. A polystyrene-supported catalyst which was encapsulated into a zirconium phosphate-phosphonate inorganic support.

Touge reported the synthesis and applications of arene/Ru/TsDPEN complexes such as **10** containing boronic acid groups attached to the basic nitrogen atom [16], and these are reported to form effective catalysts for asymmetric reductions (Figure 8A). A catalyst derived from an N'-phosphoric acid-functionalised TsDPEN derivative was also reported.

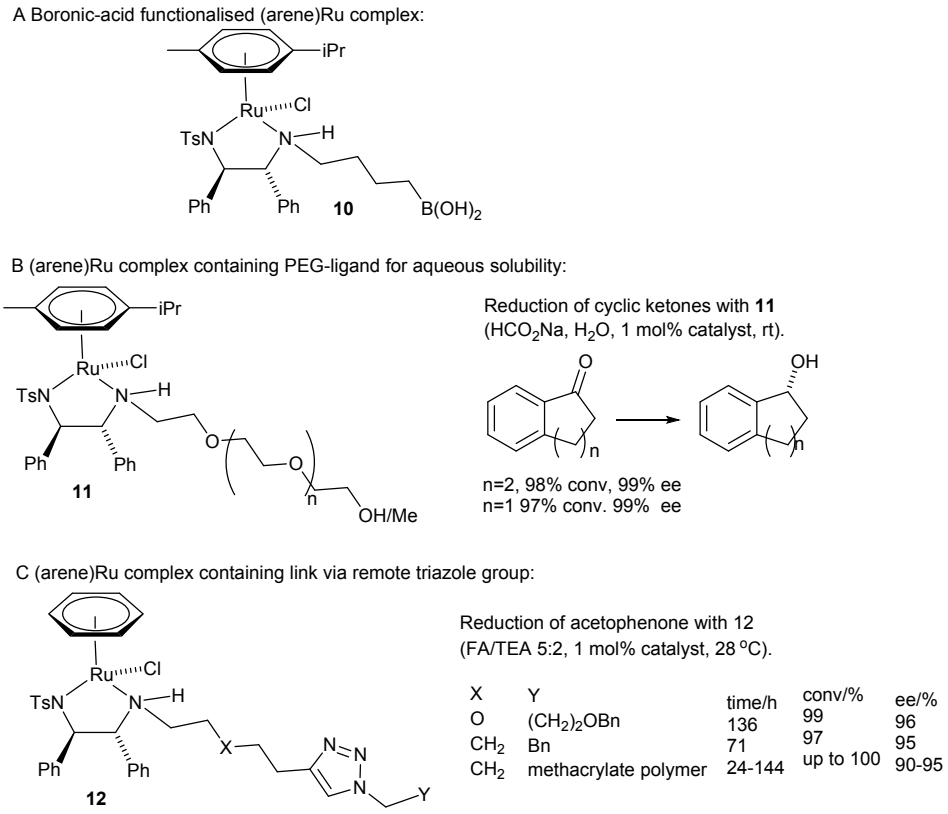


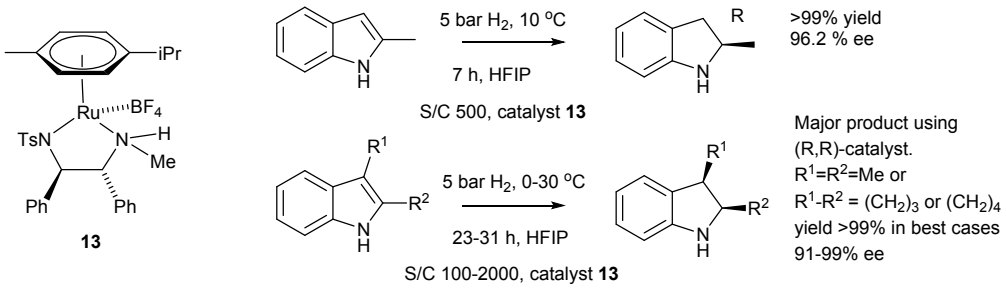
Figure 8. Modified arene/Ru/TsDPEN catalysts containing links to the N'-nitrogen atom of the TsDPEN ligand.

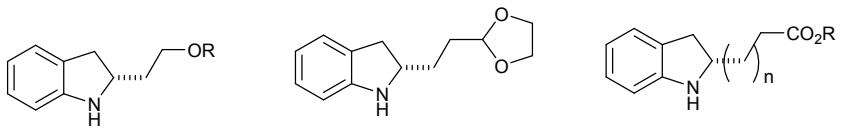
A series of modified TsDPEN-containing ligands bearing N'-PEG chains (200-2000 Daltons) were prepared by Li et al. through a reductive amination of the PEG aldehyde with TsDPEN (Figure 8B).[17] These modified ligands worked effectively in aqueous transfer hydrogenation of ketones using sodium formation as the reducing agent. A range of ketone reductions were reported and, more significantly, the PEG-based catalysts could be reused multiple times by extracting the reduction product from solution using hexane, then adding fresh formic acid and substrate. A similar reagent, attached through formation of a triazole, to a soluble polymer

made from methacrylate units, was also reported and demonstrated to be almost as effective as the unsubstituted reagents (Figure 8C).[18]

Touge and Arai investigated the asymmetric hydrogenation, i.e. using hydrogen gas rather than ATH, of a series of challenging indole substrates using arene/Ru/TsDPEN catalysts [19] and were encouraged by the observation made previously [8,9] that addition of the methyl group to the basic nitrogen atom of the ligand resulted in the formation of a more active catalyst. Indeed this modification led to the preparation of cationic catalyst **13** which exhibited a much higher level of activity and was able to catalyse the reduction of 2-methyl indole with full conversion and high ee within a few hours using 5 bar or less hydrogen and at 10 ^{o}C (Figure 9). The use of cationic catalyst, i.e. where the 'Cl' is replaced by BF_4 or TfO or some other bulky anion, has already been demonstrated to be important for the catalysis of hydrogenation, however the equivalent non N'-methylated catalyst was less reactive.

The catalyst was also successfully applied to the reduction of a range of mono and di-substituted (at the indole) substrates (Figure 9), giving the reduced products in high yields and enantioselectivities. 2,3-Disubstituted products were formed as the *cis*-diastereoisomers, whether cyclic or acyclic with respect to the newly-formed saturated ring. In each case the yields and ees were high and in one case the S/C was as high as 2000.





R=TBS: Using (*S,S*)-**13**:
94% yield, 92% ee
(30 ^{o}C, 7h)

R=Bn: Using (*S,S*)-**13**:
94% yield, 84% ee
(30 ^{o}C, 7h)

Using (*S,S*)-**13**:
90% yield, 90% ee
(30 ^{o}C, 7h)

n=2, R=Et: Using (*S,S*)-**13**:
95% yield, 91% ee
(10 ^{o}C, 30h)

n=0, R=Me: Using (*S,S*)-**13**:
91% yield, 72% ee
(30 ^{o}C, 27h)

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Figure 9. Asymmetric reduction of indoles using the N'-methylated cationic complex **13**, the non-N'-methylated complex was less active.

Halogenated indoles and substrates containing sensitive protecting groups such as benzyloxy and acetals were also selectively hydrogenated without damage to the functionality, allowing a series of post-reduction functionalisations to be carried out, such as Pd-catalysed coupling reactions. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was identified as the best solvent in these reductions and could be recovered and reused.

In the same year (2016), Fan et al independently reported their results on indole hydrogenation using the triflate analogue **14** of the N'-methylated catalyst, which proved to be the best out of a series of catalysts tested [20]. Again the reductions could be achieved in high conversion and ee at ambient temperature and 1 atmosphere of hydrogen using S/C of 100. The catalyst was however also effective at an S/C of 1000, with only a small loss of enantioselectivity. Using the (*R,R*) catalyst, the product of *R*- configuration was formed and disubstituted compounds were formed as the cis products (Figure 10). In addition, Fan et al. reported the reduction of imines containing a 3,3-disubstituted structure, which also proceeded in high ee and conversion, although in this case the Ru complex containing an unsubstituted basic amine, and either a triflate or a phosphate counter ion, proved to be the best catalyst. Likewise the same unfunctionalised catalyst was effective at the kinetic resolution of certain examples.

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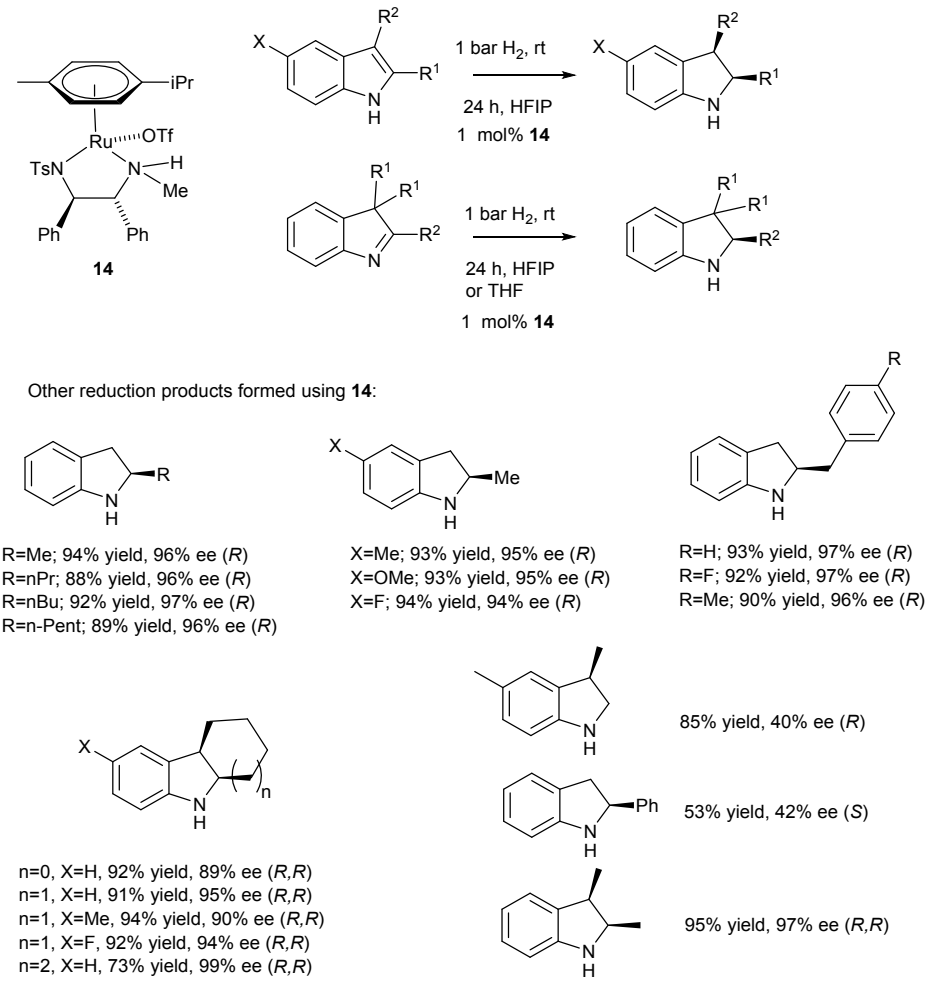

Figure 10. Asymmetric reduction of indoles using the N'-methylated cationic complex **14**; the non-N'-methylated complex was more effective in the latter application.

Fan et al. also reported the asymmetric hydrogenation of 2,2'-bisquinolines to form vicinal diamines using a series of [arene/Ru/TsDPEN] catalysts including **14-16** [21] (Figure 11). In several cases, the N'-methylated catalyst proved to be the best one in the application, although in others the unmethylated complex was better. An N'-benzyl complex **15** was tested but did not give improved results. Although the parent unsubstituted product is illustrated in Figure 11, a very wide range of substrates were tested, giving products in excellent yield and ee throughout; in the majority of cases the N'-Me catalyst was the most effective and gave the best result, although in some cases the unmethylated complex was slightly more efficient. In a series of mechanistic studies, including reduction of the enantiomerically pure semi-reduced product with each enantiomer of catalyst, it was established that the second reduction occurred with high diastereoselectivity, and was essentially fully controlled by the catalyst and not

significantly directed by the existing chiral centre. The products could be converted to derivatives such as the interesting asymmetric imidazolium salt **17**.

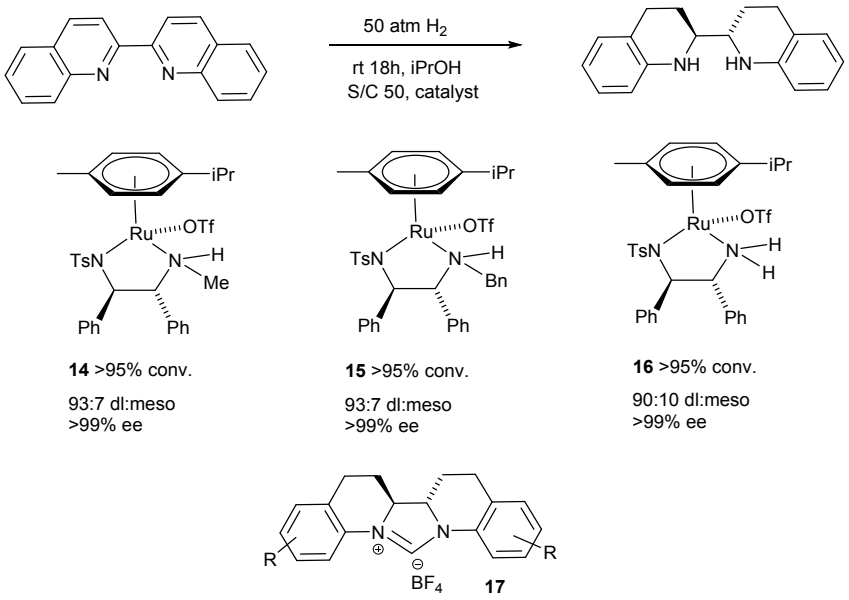

Figure 11. Asymmetric reduction of bis-quinolines using the cationic complexes **14-16**.

The asymmetric reduction of C=C bonds using arene/Ru(II)/TsDPEN catalysts has not been extensively reported however the example by Deng et al. contains some very good examples of selective reductions on highly activated alkenes. Usually two (non-ketone) electron-withdrawing groups are required for best results (Figure 12).[22] The N-methylated and N-ethylated ligands were used to form complexes in-situ. These worked effectively in the application but in this instance gave no improvement over the unsubstituted complex. The best results were obtained using TsDPEN catalysts containing modified sulfonamide groups; bulky groups being the most effective.

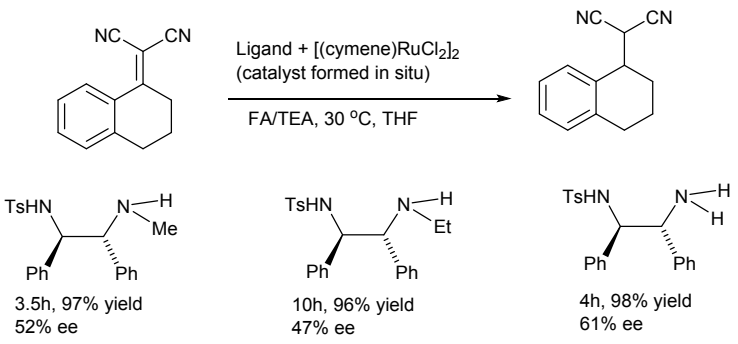

Figure 12. Asymmetric C=C reduction using arene/Ru(II) complexes formed from a series of TsDPEN ligands.

In some cases, TsDPEN-derived ligands can act in a tridentate fashion, with triazole and pyridine functionality (in **18** and **19** respectively) added to the TsDPEN, catalytically efficient complexes are formed with $Ru_3(CO)_{12}$. These reduce acetophenone derivatives at elevated temperatures in high ee using iPrOH as both the solvent and reducing agent, and in the absence of base (Figure 13).[23,24] The inclusion of both the tosyl and the triazole are essential for high activity with the ruthenium carbonyl reagent. A range of ketones were reduced in good ee (over 90% in the best cases) and notably ortho-substituted examples, which are often challenging substrates, gave products of high ee in the reductions. Both complexes are believed to form active ruthenium hydride complexes of a general structure similar to **20** (illustrated for the triazole derivative) which may be able to engage in hydrogen transfer to the ketone substrate through a transition state analogous to the Noyori-Ikariya [arene/Ru/TsDPEN] complexes described above.

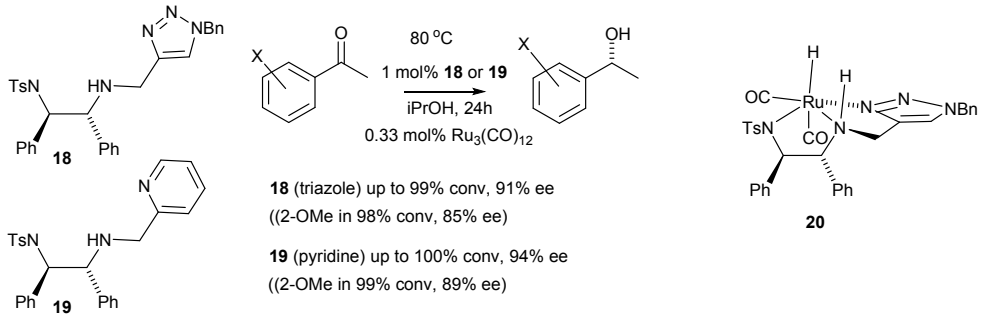

Figure 13. Application of tridentate derivatives of TsDPEN/$Ru_3(CO)_{12}$ to ATH of ketones.

Several N-alkylated ligands, with simple iridium trichloride salts, have been applied to the asymmetric hydrogenation of ketones in good ees, the alkyl group offering the opportunity to optimise the ee to some extent.[25,26] An 'N',N'-diTsDPEN bridged derivative has been prepared and used in a Ni complexes in the ATH of acetophenone.[27,28] A related bisTsDPEN, with a phosphine between diamines, has been used with an Ir(I) source in propiophenone reduction. In this application, in iPrOH/KOH, products were formed in ees of up to ca. 75% when $IrCl(COD)(PPh_3)_2$ was used as the Ir source.[29]

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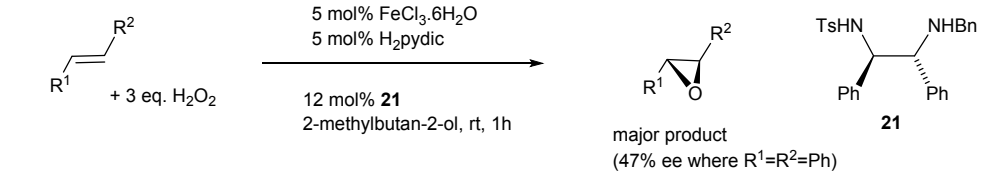
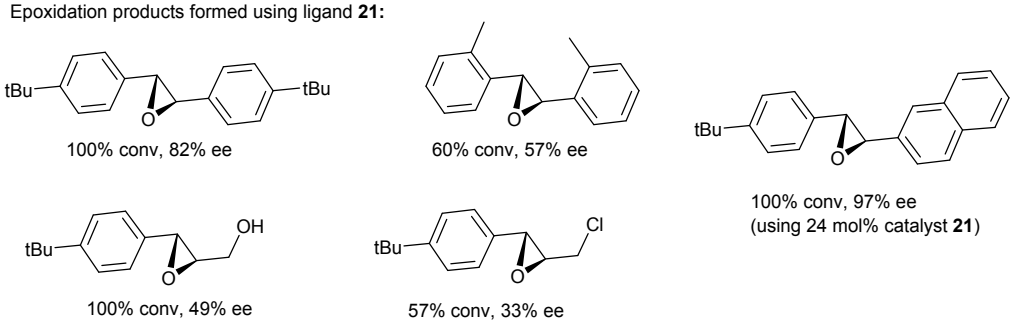
3. Use of N-alkylated TsDPEN in asymmetric oxidation reactions.

In 2007, Beller et al. reported the use of a N'-benzylated TsDPEN **21** for the asymmetric epoxidation of 1,2-disubstituted alkenes using $FeCl_3$ as the metal.[30] This proved to be the best ligand of a series tested, and an improvement over TsDPEN itself, which gave a product of just 28% ee compared to the 47 % obtained using **21** (Figure 14)**.** Application of the methodology to a range of substrates revealed that products of higher ees could be obtained; up to 97% ee for one substrate with the use of a slightly higher catalyst loading. This remains one of the few reported methods for asymmetric epoxidation reactions using a simple iron(III) salt and amine-based ligand. A detailed follow up paper by the same authors revealed that the system was also effective for the asymmetric epoxidation of monosubstituted alkenes, notably styrene derivatives, and further disubstituted substrates containing diverse substitutions.[31] A full mechanistic investigation using ESI-MS, UV-Vis and EPR spectroscopy indicated the presence of several iron complexes forming in situ and the formation of radical intermediates. An extension of the work using TsDPEN attached to multifunctional ligands e.g. **22** was reported in 2013 (Figure 14), which revealed an excellent level of reactivity and excellent selectivity in the best cases (up to 91% ee for stilbenes).[32] The larger size of the ligands provided a method for their recovery and reuse via precipitation and also through phase separation.



Epoxidation products formed using ligand **21:**



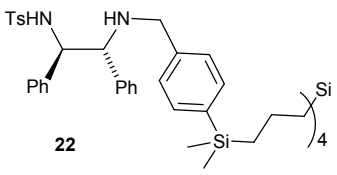
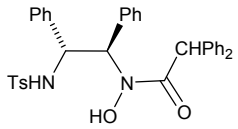
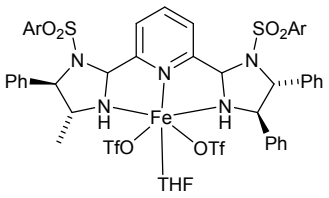


Figure 14. Epoxidation of alkenes using an iron catalyst with an N'-benzyl TsDPEN ligand and a dendrimeric derivative.

Malkov et al reported the use of a TsDPEN derived reagent **23** for the asymmetric epoxidation of allylic alcohols as a component of a vanadium-catalysed reaction, giving products of up to 94% ee (Figure 15) [33]. Also pertinent to the area is work by Xiao on the use of the Fe catalyst **24** for the catalysis of the oxidation of benzylic ethers to esters using oxygen gas as the oxidant (Figure 15).[34a] A closely related Fe(III) catalyst is also effective at the oxidative cleavage of C=C bonds (not illustrated).[34b]



23 TsDPEN-derived ligand used in vanadium-catalysed oxidation.



24 Fe catalyst for oxidation of benzylic ethers to esters using O_2

Figure 15. TsDPEN-derived ligand and iron complex used as catalysts.

4. Use of N-alkylated TsDPEN in asymmetric organocatalytic reactions.

Several N'-functionalised derivatives of TsDPEN have been used in organocatalytic applications. An early example described the use of an enzyme mimic catalyst containing an amide, urea and TsDPEN-linked unit for the control of amine additions to cyclic unsaturated 6-membered lactams. These were cleverly designed to bind at several positions to the substrates; several catalyst variations were tested including those containing a TsDPEN unit, and addition products of up to 62% ee were obtained.[35]

Ye et al. have reported a series of applications of TsDPEN-derived organocatalysts containing a primary amine, initially for control of asymmetric Michael additions of unsaturated lactones to enones (Figure 16).[36] In the examples shown, the enones contained alkyl or aryl substituents and gave products in very high ee. One example of a cyclic enone was featured and this was formed in 51% yield but still high ee (97% ee).

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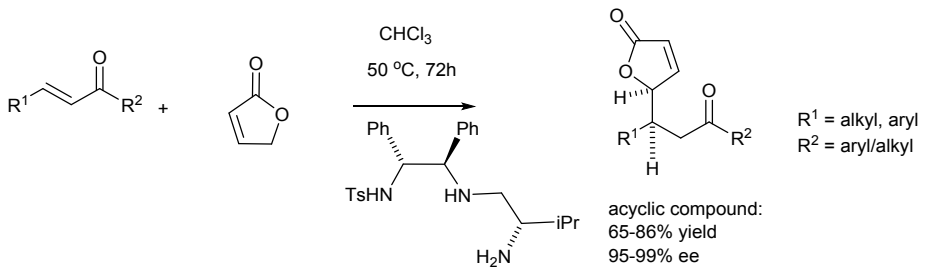

Figure 16. Asymmetric addition of unsaturated lactones to enones.

The use of an amine-containing TsDPEN to control the addition of a cyclic unsaturated lactam to an enone has been reported; the addition of N-Boc-L-Tryp was found to be essential for high enantioselectivity in the reaction (Figure 17).[37] The mechanism is reported to proceed via the formation of an enamine between the primary amine of the ligand and the enone, with addition of the enol form of the unsaturated lactam being directed by hydrogen bonding interactions with the tosylated diamine.

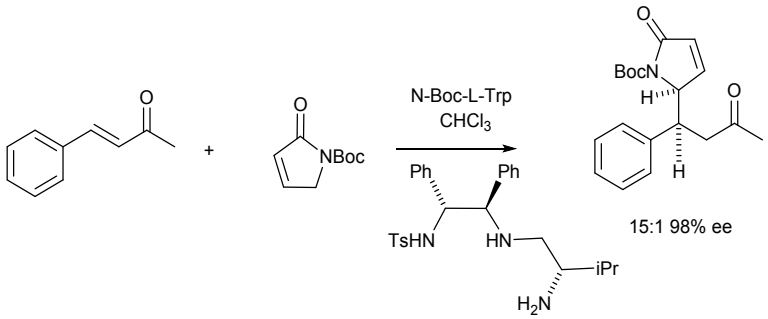

Figure 17. Asymmetric additions of cyclic lactam to an enone.

The use of the ligands used in the above reaction on a more complex substrate has been reported; note that the reactions had to be carried out at 50 °C; at a lower temperature the fully cyclised products were not formed (Figure 18).[38] Use of different catalyst enantiomers resulted in formation of diastereoisomeric products as would be expected from catalyst-control of the reactions.

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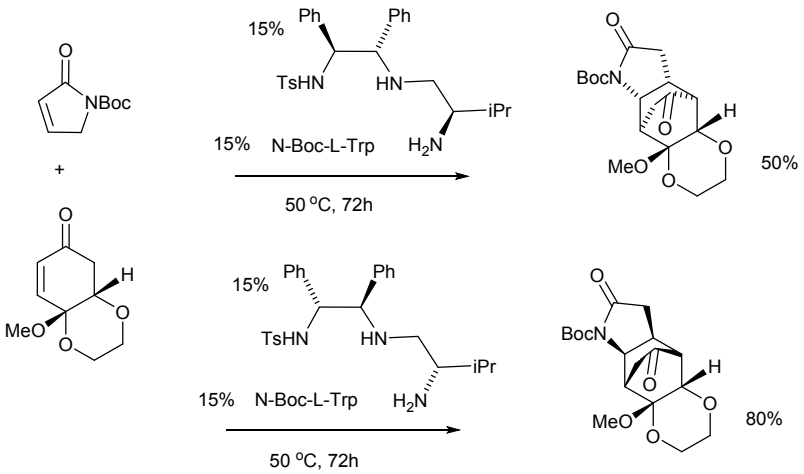

Figure 18. N'-Alkylated TsDPEN derivatives used to functionalise a complex enone substrate.

A squaramide-sulfonamide was applied to control a series of vinylogous aldol reactions.[39] A number of catalysts were tested and of these the TsDPEN-derived **25** gave a product of 92% ee in initial screening (Figure 19). The presence of the sulfonamide was shown to be critical for the high selectivity. However an alternative catalyst, bearing a single substituent on the diamine side chain, gave better results and was selected for further optimisation and successful application to a wide range of substrates.

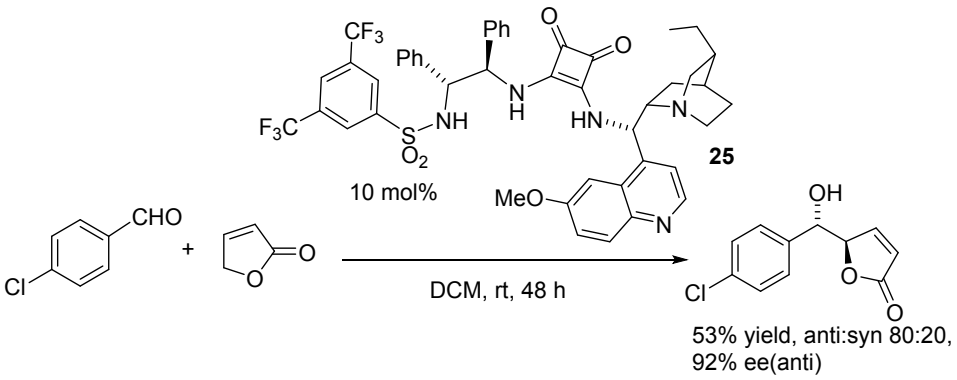

Figure 19. Squaramide-based catalyst used in the asymmetric addition of cyclic lactone to an aldehyde.

The use of arene/Ru/TsDPEN to catalyse addition of acetylacetate to cyclic enones has been described. Alongside unfunctionalised TsDPEN, which gave the best results, were tested N'-MeTsDPEN and other asymmetric catalysts.[40] A very wide range of TsDPEN derivatives were also tested in the addition of a β-ketoester to nitrostyrene however the best one was TsDPEN itself and this was applied to a range of additions.[41]

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5. Use of N-alkylated TsDPEN in Lewis acid-catalysed additions.

In a very recent paper[42], a complex of cobalt with ligand **26** was effective at the control of asymmetric additions of cyclic beta-ketoesters to nitrostyrene (Figure 20) in 91-98% ee. A variety of metals were tested, with cobalt (II) giving the best results and subsequent optimisation with respect to solvent and ratios of reagents delivering a system which was very efficient and enantioselective, even at 1 mol%. On the basis of a detailed mechanistic study and molecular modelling, the intermediacy of a bimetallic complex such as **27** in the catalytic cycle is speculated.

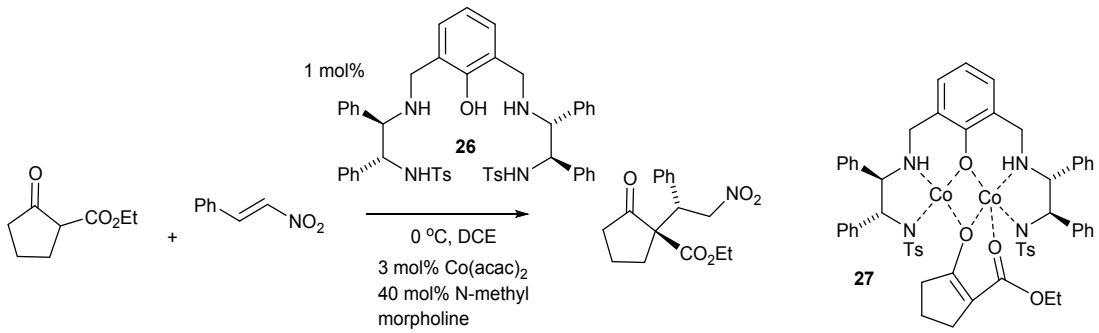

Figure 20. Co(II)-catalysed addition of cyclic ketone to nitrostyrene.

A similar catalyst, based this time on Ni(II) and for Mannich addition to imines (Figure 21) has proved to be highly effective.[43] In this case, the best of the ligands, **28**, contained a p-nitrophenylsulfonamide substituent on each of the two DPEN units and a bridging phenol group was essential to the operation of the catalyst. In this case a Ni(II) metal is used and again a bimetallic complex is anticipated to be the active catalyst.

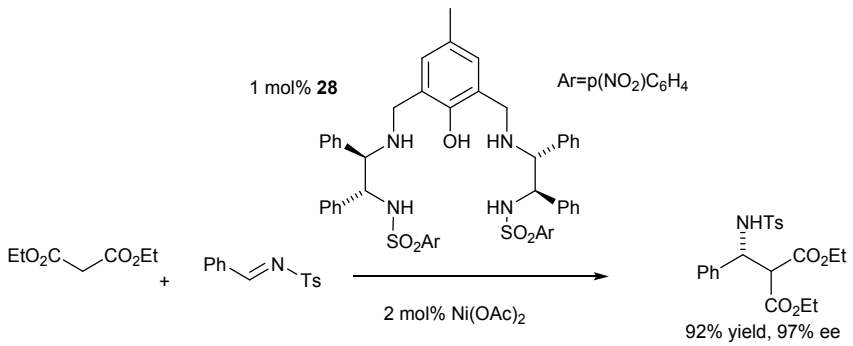

Figure 21. Asymmetric catalysis of addition of diethylmalonate to an imine.

6. Use of N-acylated TsDPENs in asymmetric organocatalytic reactions.

Of a series of organocatalysts tested, **29a** proved to be the most effective one for the formation of highly enantiomerically-pure 3-aminodihydrocoumarin products containing tertiary amine derivative groups which would otherwise be very difficult to prepare (Figure 22).[44] Using 5 mol% catalyst, the cascade reaction could be scaled up to a gram scale for one example.

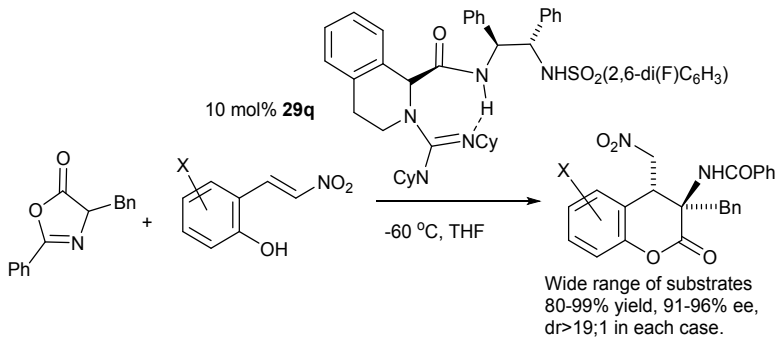

Figure 22. Guanidine catalyst used in asymmetric additions to nitrostyrene derivatives.

Another use of an analogous catalyst was reported for the synthesis of spirooxindoles using almost same catalyst. Following optimisation, a range of substrates were asymmetrically cyclised using catalyst **29b** under mild conditions (Figure 23).[45] This included substrates which contain an NHTs in place of the OH of the side chain of the amide substrate.

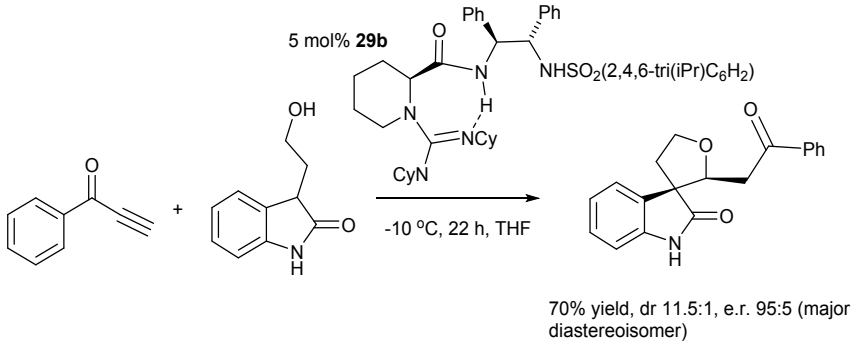

Figure 23. Spirooxindole synthesis using catalyst **29**.

A cyclisation was also reported with an analogous ligand type to that described above, resulting in the formation of cyclohexanes through a Michael-Henry reaction sequence which created six stereogeneic centres in one step.[46]

A further example of the same class of catalyst, in this case **30**, was used to control the asymmetry of additions of alkynes to isatins to create a new chiral centre has been reported.

Products with ees of up to 96% were formed in this addition reaction (Figure 24).[47] A TsDPEN derived catalyst also promoted the reaction in 87% yield and 82% ee.

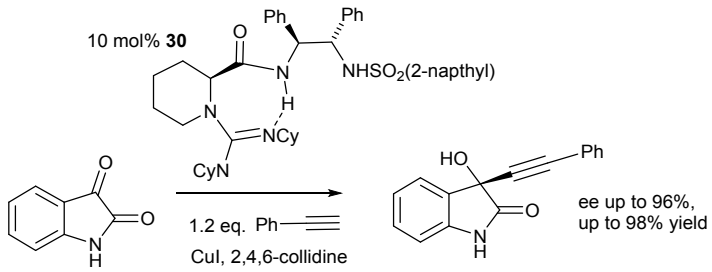

Figure 24. Asymmetric addition of alkynes to isatins.

7. Use of N-thiourea TsDPEN derivatives in asymmetric catalysis.

TsDPEN-based, thiourea-containing reagents have proved to be very successful as organocatalysts in a number of reactions. Wang has published several papers on diverse applications using **31** (which has come to be described by other researchers as 'Wang's ligand'). Ligand **31** has emerged as one of the best of a series generated and tested in the reaction of acetylacetone with nitrostyrene derivatives (Figure 25).[48] The catalyst was optimised with respect to the sulfonamide group, with the bis-(trifluoromethyl) being the optimal choice. The catalysts are understood to operate through an interaction of the thiourea/TsDPEN component with the nitro function and a hydrogen bonding interaction of the tertiary amine with the nucleophilic enol intermediate. These interactions co-operate to direct the reagents together in a controlled and selective manner.

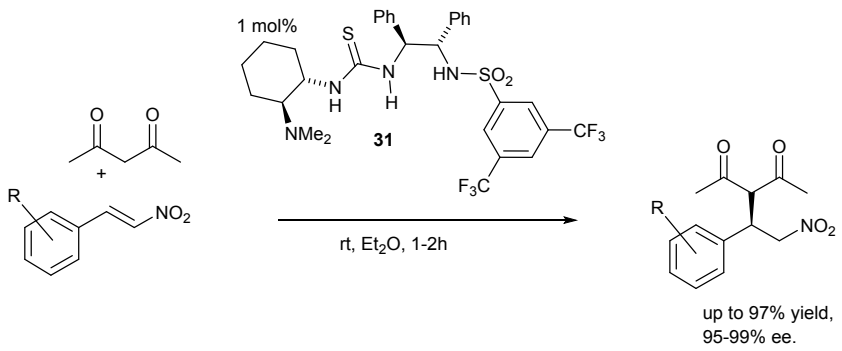

Figure 25. Wang's ligand (**31**) applied to asymmetric additions to nitrostyrene.

Wang also reported the use of ligand **31** to direct the addition of α-substituted-β-ketoesters to nitroolefins, giving products in up to 84% ee.[49] However in this case it was found that a more

effective catalyst could be produced by replacing the sulfonamide group with a hydroxyl group, resulting in improved diastereoisomeric ratios and ees in these cases.

Ligand **31** was successfully applied to the control of the addition of nitroalkanes to nitroalkenes (Figure 26).[50] Using 10 mol% of the catalyst, at low temperature, an excellent level of versatility was demonstrated and products were formed in drs as high as 98:2 and in 99% ee in the best cases. Once again the tests indicated that the sulfonamide containing the two trifluoromethyl groups on the phenyl ring was the most selective one in this application, presumably reflecting the importance of the hydrogen-bonding interactions in the transition state for the addition (a catalyst containing an N-methylated sulfonamide led to no product). In one case the addition of 2-methyl-nitroethane was evaluated, giving an addition product in 88% yield and 64% ee. A range of aromatic groups could be tolerated (o-, m- and p- substituents as well as furyl and cinnamyl groups), and there was some scope for variation from nitroethane, with nitropropane and 2-phenylnitroethane also working well.

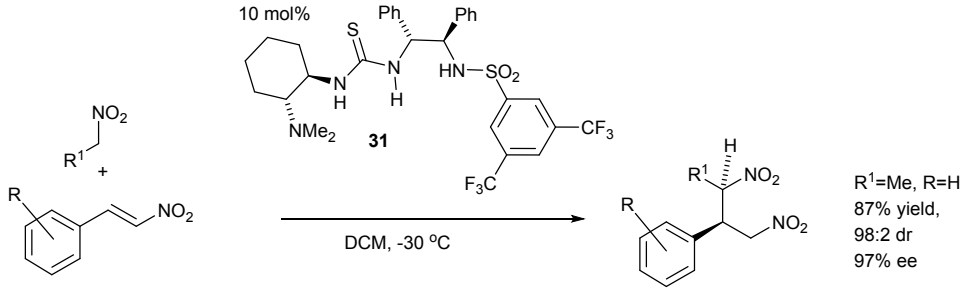

Figure 26. Diastereo- and enantioselective addition to nitrostyrenes.

In a further paper in 2010, catalyst **31** was once again found to be the best one of a series for the control of the addition of α-aryl substituted cyclopentanones to nitroolefins.[51] This reaction generates two diastereoisomers as is the case with other additions, and however the addition is highly diastereoselective, and products with ees as high as 95% were generated for a wide range of substrates.

Xiao et al. tested a range of thiourea catalysts for activity in the addition reactions of thiols to a multi-unsaturated substrate, the thiourea being established as an excellent reagent for the activation of unsaturated nitro reagents. Once more, it was catalyst **31** that emerged as the best of the series tested (Figure 27).[52] In this reaction, a remarkable series of reactions takes place in a cleverly-designed sequence. Control of the initial addition of thiophenol to the nitroalkene

is critical and this is controlled by the catalyst thiourea group and associated hydrogen bonds. The diastereoselectivity of the subsequent cyclisation step results in formation of a complex ring system in a one pot process, which forms the basis of an efficient chroman ring synthesis. In further studies, triazoles and also anilines were found to be suitable replacements for the thiophenol in the addition step, giving products in ees of 92% and 86% respectively. A reaction at rt with 3 mol% **31** for 12h gave a product of 91% yield and 90% ee.

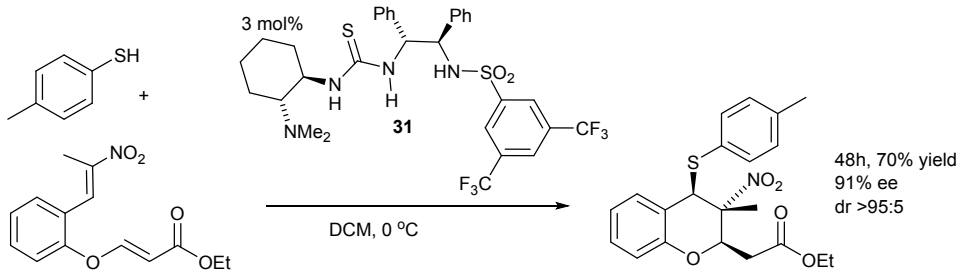

Figure 27. Addition/cyclisation reactions catalysed by **31**.

The theme of thiophenol addition to unsaturated esters was extended by Wang et al in 2011, with a description of the use of catalyst **31** to control the addition of thiols to 4,4,4-trifluorocrotonates in high ees; up to 95%.[53] The addition products could be cyclised to thiochromanones in high yield. One of the products is a key intermediate of the inhibitor of MMP-3, (*R*)-γ-trifluoromethyl γ-sulfone hydroxamate. Wang also described the use of **31** successfully in the related additions of thiols to unsaturated esters containing a heavily fluorinated group in the ester.[54] The method can be adopted to synthesise an antidepressant agent, thiazemin.

A series of efficient asymmetric addition reactions of this to trifluorocrotonyl pyrazoles were also reported, similar to and related to the one above (53). Again it was catalyst **31** which proved to the most effective of those tested (Figure 28).[55]

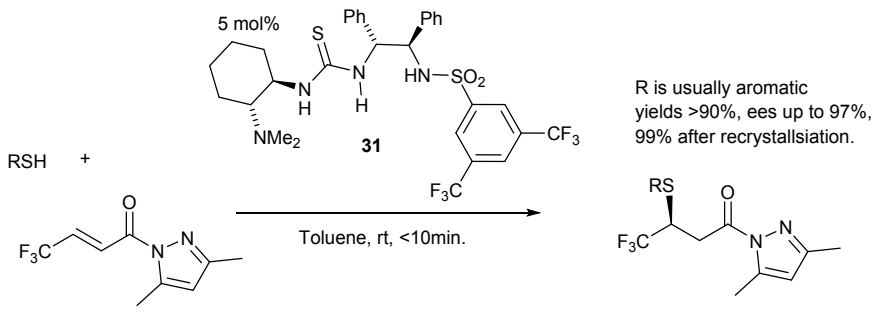

Figure 28. Asymmetric catalysis of thiol additions.

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Thioadditions continue to be strong theme and a line of productive research using catalyst **31**. In a 2013 paper, Wang described a desymmetrisation process through additions to spirocyclic oxindoles.[56] A further application of catalyst **31** was to the control of the addition of cyclic ketoesters to diethyl azodicarboxylate, representing an efficient method for the amination of the ketoester.[57] In this process, using up to 10 mol% of catalyst, the addition product was formed in up to 95% yield and 95% ee, at -78 ^{o}C. Again the multiple hydrogen bonding organocatalyst is able to strongly control the direction of the addition reaction. In the addition of a curcumin derivative to nitrostyrene, ligand **31** was reported to give an ee of 81% however an improved result was obtained in this instance by a closely-related organocatalysts containing a quinine group complimenting the TsDPEN /thiourea unit, in which case the conversion and ee could be pushed to 97 and 96% respectively.[58] An excellent result was obtained for a challenging addition/spirocyclisation which formed four contiguous stereocentres in one operation using catalyst **31** however (Figure 29).[59]

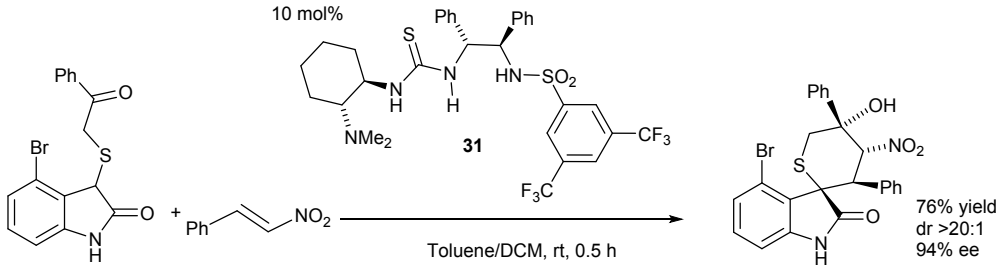

Figure 29. Four contiguous stereocenters formed by a one-pot Michael-Henry-cascade-rearrangement reaction.

Xiao et al. reported an intramolecular crossed Rauhut-Currier reaction using thiourea **32**, which emerged as the optimal catalyst of those tested.[60] In this case the initial addition of the CBzNHOBoc reagent was followed by its elimination to leave an unsaturated product with a single chiral centre in an ee as high as 92% (Figure 30). The reaction had to be run at low temperature in order to achieve the highest ee, at the cost of an extended reaction time. The reaction was applied to a range of substrates.

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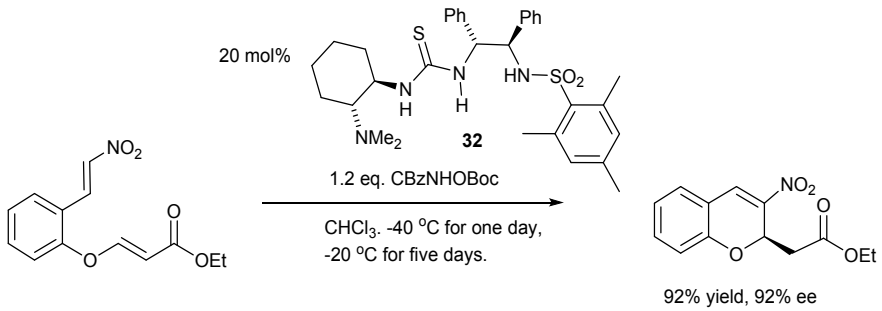

Figure 30. Intramolecular crossed Rauhut-Currier reaction catalysed by **32**.

Shao et al., in 2016, found that catalyst **33** was ideal for the control of the addition reaction of an alkynone to nitrostyrene (Figure 31).[61] The activating group in the substrate was removed by careful treatment with acid at the end of the reaction; using a larger amount (2 eq) of TsOH resulted in formation of a β-diketone. Extending the range of substrates was successful, with the most selective reactions giving products in up to 97% ee. In the mechanism, once more the thiourea forms a critical bond to the nitro group, with the direction of nucleophilic addition speculated to be directed by the other functional group via a series of hydrogen bonds.

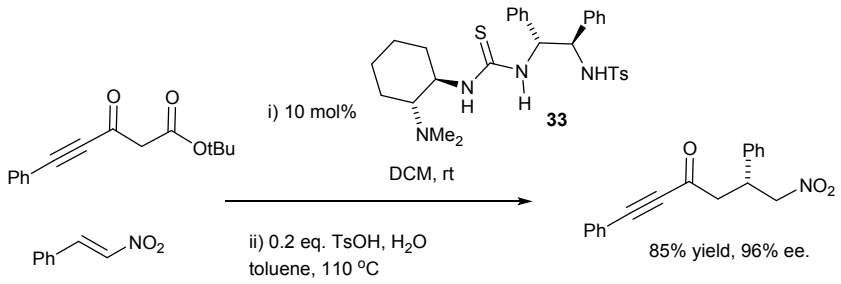

Figure 31. Asymmetric addition and decarboxylation.

Shi et al. reported a highly enantioselective cyclisation of 3-isothiocyanato oxindoles with trifluoromethylated 2-butenedioic acid diesters promoted by organocatalyst **34**, which was the best ligand of a series used in the cycloaddition (Figure 32).[62] A wide range of functional groups are tolerated in the reaction, making it very versatile.

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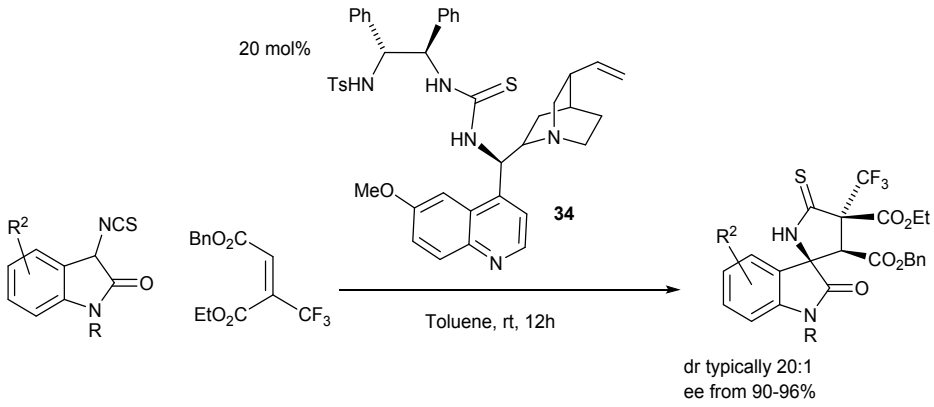

Figure 32. Enantioselective [3+2] cycloaddition.

The N-mesylated ligand containing a quinine group, **35** (similar to that used in Figure 32), was found to be effective at the control of the addition of 3-aryloxindoles to phenylvinylsulfone (Figure 33).[63] This represents a very elegant example of the ability of the modified thiourea to control additions to sulfones, presumably also through multiple hydrogen bonding interactions.

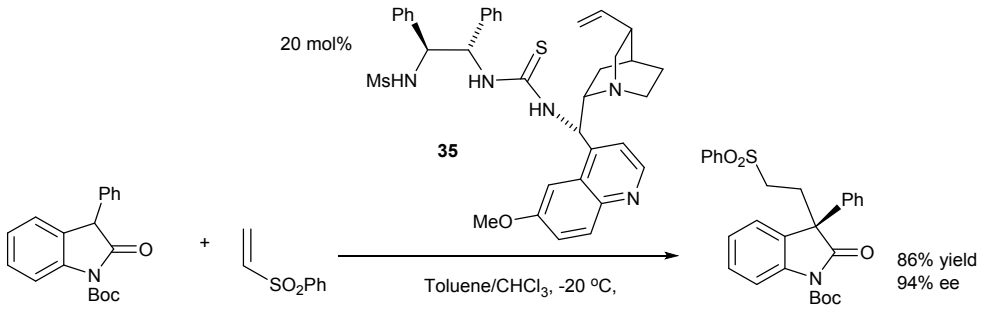

Figure 33. Asymmetric Michael addition of 3-aryloxindoles to phenyl vinyl sulfone.

TsDPEN derivatives were one of a series in an addition reaction of aryloxazoles to a 1-1-diphosphate ethene but was not the best of those tested.[64] The best catalyst was similar to the one used in Figure 33 but with a ArNH in place of the TsDPEN unit.

The reactions of isatins with isocyanoacetates have been studied using TsDPEN-containing thioureas as catalysts. Catalyst **35** was the best of a series tested in this application (Figure 34).[65] In this case the isocyanate formed the basis of a second ring fused in a spiro fashion and under optimised conditions a good level of stereocontrol. Multiple hydrogen bonding interactions are again likely to be responsible for control of absolute stereochemistry here, and better results were obtained with some of the substituted substrates.

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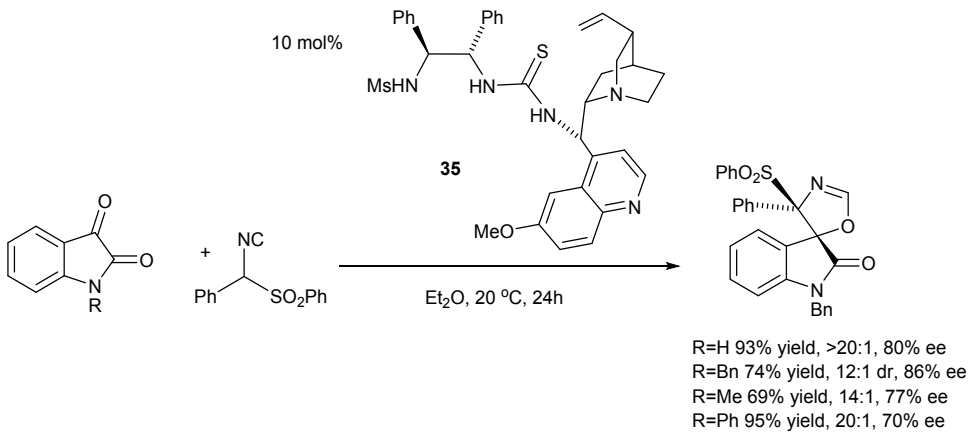

Figure 34. Asymmetric cycloaddition reaction of isocyanoacetates to isatins.

Catalyst **35** once again proved effective in an asymmetric application – in this case the reaction of alpha-cyano ketones with isatylidiene malononitriles (Figure 35).[66] In this case the cascade cyclisation took place to form the heterocyclic product in remarkably high ees. The initial screening with the N-benzylated malononitrile gave a product of 72% but then switching to the N-methylated derivative with the addition of 1 mol% of morpholine at lower temperature raised the ee to 90%. The application was applied to a wide range of substrates, all of which gave products in very high yields of typically 98-99% and with ees as high as 97% in the best cases.

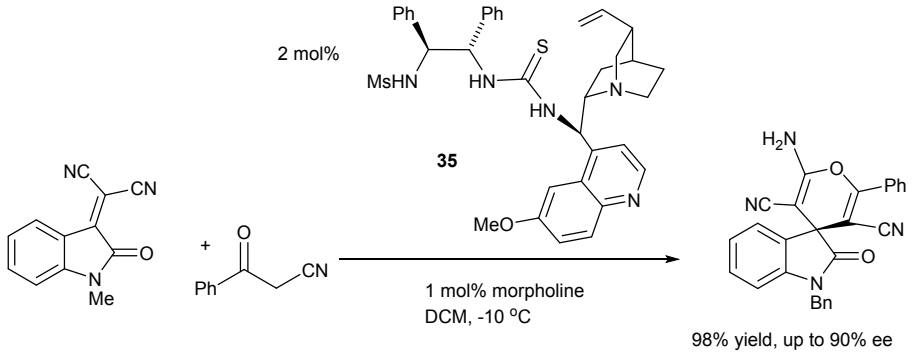

Figure 35. Asymmetric synthesis of spiro[4H]-pyran-oxindoles.

Ligand **36** was optimised for use in addition to isatins (Figure 36).[67] There was a very interesting and unexpectedly positive effect from the addition of methanol. This was applied to a good range of targets and extended to acyclic alpha-keto esters with related ligands, although further screening and optimisation revealed an alternative ligand to be the optimal

one – containing a squaramide linkage and a dialkylated DPEN unit rather than a TsDPEN.[67b]

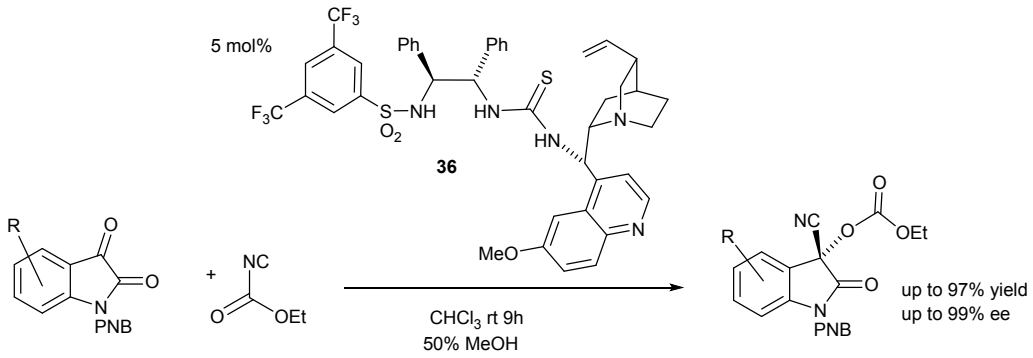

Figure 36. Asymmetric Cyanoethoxycarbonylation of Isatins.

For the conversion of oxime tosylates to cyclic azirines by an intramolecular process, TsDPEN/thioureas were but were not the best ones of the series tested.[68] The use of Wang's catalyst gave a product in 72% yield and 56% ee however. Ligand **37** was used in enantioselective reactions of ketimine with a pyrazoleamide (Figure 37).[69] The first reactions allowed for Nosyl cat. to give 60% yield, 98:2 dr and 97% ee before the conditions were optimised. Under same conditions a tosyl derivative gave a product of 53% yield, 97:3 dr and 96% ee.

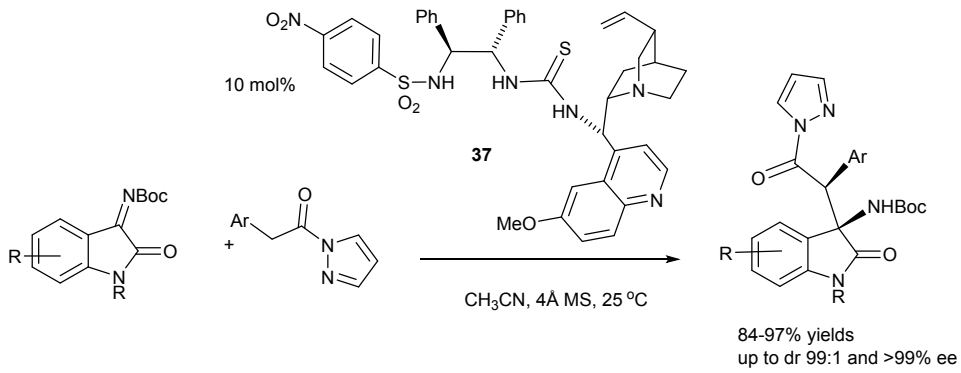

Figure 37. Enantioselective Mannich reaction of pyrazoleamides with isatins.

Thiourea **38**, containing a 4-nitrophenylsulfonamide and an attached basic nitrogen functionality, did prove to be the optimal one tested in the enantioselective Michael addition of 5H-oxazol-4-ones to unsaturated ketones (Figure 38).[70] Compared to other related catalysts these were found to be more effective and they are derived from L-*tert*-leucine. Products were obtaining in >90% ee in the best cases.

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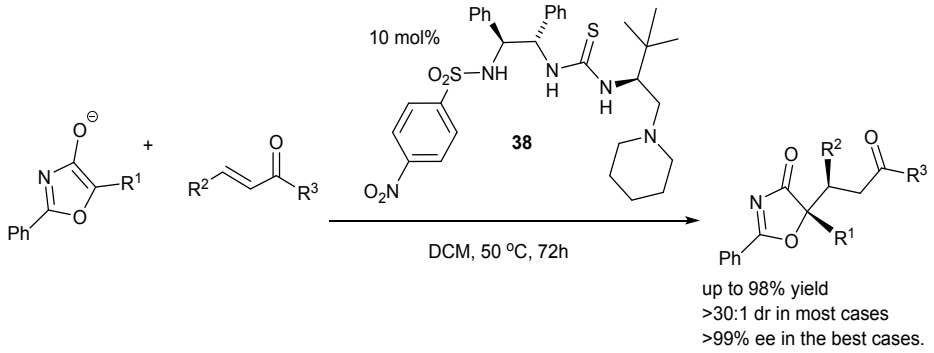

Figure 38. Asymmetric Michael addition of 5H-oxazol-4-ones to α,β-unsaturated ketones.

Peng et al. reported an intramolecular addition to a nitrostyrene to form a 1,2-diamine in high ee. The TsDPEN-containing catalysts gave good results but in these cases the best results were obtained with a 1,2-cyclohexyldiamine-containing catalyst.[71]

The enantioselective addition of simple ketones, including acetone and acetophenone, to nitroolefins can also catalysed by thiourea/TsDPEN catalysts. In this case a series of catalysts containing adjacent primary amine functionality were evaluated and tested in the application. Of these the compound containing a TsDPEN and a cyclohexyldiamine proved to be highly effective (Figure 39).[72] In this case the primary amine is believed to form an enamine with the ketone reagent whilst the thiourea and TsDPEN bind the nitro group, serving to hold both reagents in close proximity and within a well-defined transition state for the addition reaction. Evidence for this was provided by the non-reactivity of N'.N'-dimethylated catalyst i.e. which was unable to form the required enamine.

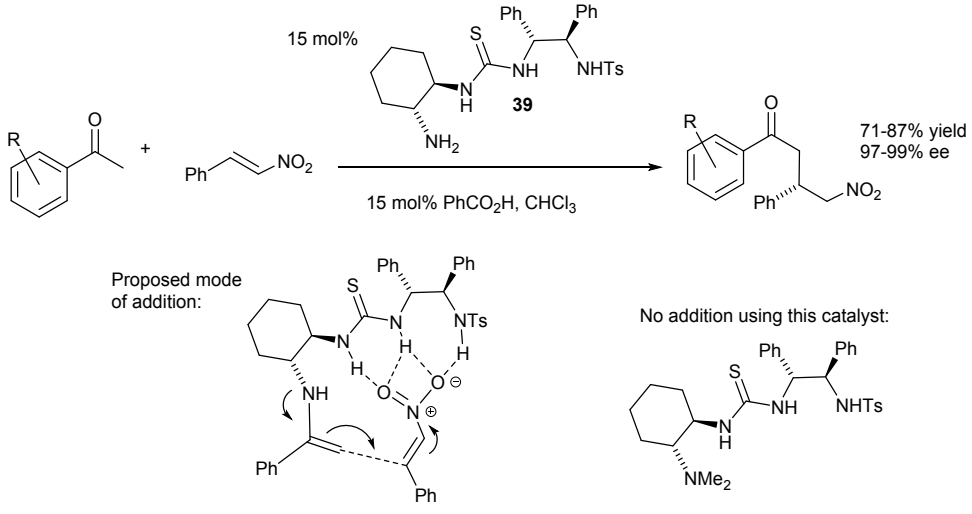

Figure 39. Asymmetric addition of ketones to nitrostyrene.

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In a related later report by Shao et al. in 2017, the enantiomeric catalyst was found to be efficient at directing the addition of acetophenone to a complex nitroalkene in a high ee of 97% (Figure 40).[73] In this reaction the diastereoisomer of the catalyst (i.e. **40**, derived from (*S,S*)-TsDPEN rather than the (*R,R*)-TsDPEN) was less efficient, as was the mesyl derivative of the catalyst and a phosphorylated derivative.

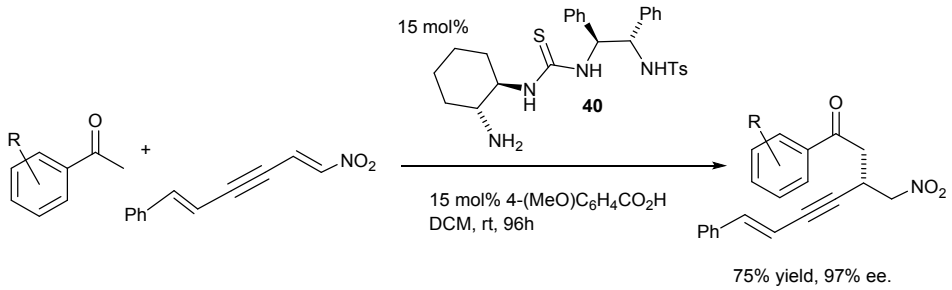
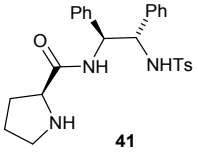


Figure 40. Asymmetric additions to nitrodienynes.

Compounds containing a combination of proline and TsDPEN have been applied to asymmetric aldol reactions.[74] Amide **41** (Figure 41) was one of a series of catalysts for an asymmetric aldol reaction reported by Zhao and Samanta in 2006, and gave a product of 33% ee.[74a] The proline is believed to form an enamine intermediate in a key step in the mechanism. Singh et al published a detailed study on the synthesis of all four diastereosiomers of the catalysts and their applications to the asymmetric aldol reactions of ketones with aromatic aldehydes.[75] All of the isomers were effective catalysts, giving the aldol product of cyclohexanone with 4-fluorobenzene in 92:8-91:9 diastereoisomeric ratios and 87-90% ee, indicating that the proline residue was having the major effect and the TsDPEN unit a moderating one on the overall selectivity. Wills et al use a series of similar compounds for asymmetric transfer hydrogenation reactions of ketones; products of up to 90% ee were formed, with the proline component again dominating the selectivity but with a contribution from the TsDPEN unit.[76]



41

Figure 41. Compound used in aldol reactions and transfer hydrogenations.

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8. Miscellaneous asymmetric catalytic reactions using N'-alkylated or acylated TsDPEN derivatives.

Several papers have contained reports of the selective acylation of diarylmethyl compounds by acylation of a remote phenol, which is obviously a very challenging reaction. This has been achieved using a peptide or protein with a terminal amine group which acts as an acylation catalyst and in some of these applications some of the catalysts contain a TsDPEN functionality.[77,78,79,80] In the example in Figure 42, an optimised small peptide **42** was found to be highly effective at directing the reaction, as evidenced by the high ee obtained.[80]

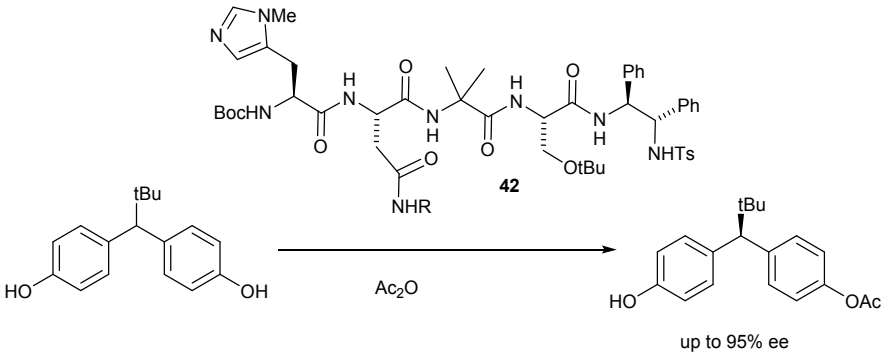

Figure 42. Enantioselective remote acylation using a peptide catalyst.

In a very interesting application, an N-aryl TsDPEN derivative **43** was used to create a catalyst with a helical chirality which then acts to efficiently direct the asymmetric condensation of aldehydes with the phenol shown in Figure 43.[81]

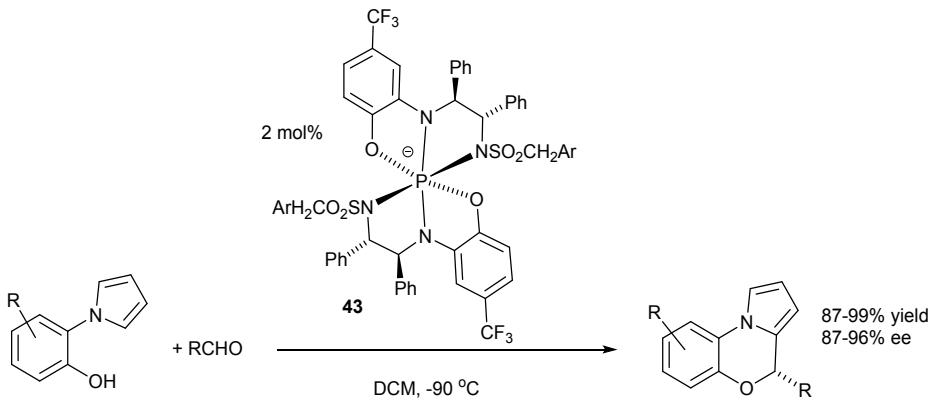

Figure 43. Asymmetric catalysis using a hexacoordinated chiral phosphate ion.

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Building upon excellent results using silyl chloride reagents to promote asymmetric reactions, Leighton et al. reported the use of a silicon-based catalyst **44** for the asymmetric Diels-Alder reaction between methacrolein and cyclopentadiene in up to 37% ee (Figure 44).[82] However the analogous cyclohexyl diamine-derived ligand was better in this case, giving a product of 94% ee (20 mol% catalyst, DCM, -78 ^{o}C, 8h).

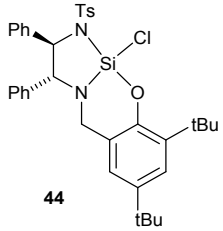

Figure 44. Catalyst used in Diels-Alder reaction catalysis.

Some applications have been reported in which a N'-functionalised TsDPEN-derived catalyst was tested but was not the best in the application. In an indole functionalisation [83] a TsDPEN gave a product of only 23% ee and lower than for an analogous catalysts containing the cyclohexyldiamine backbone structure. A DPEN –based catalyst **45** was used in a 1,3 dipolar cycloaddition (Figure 45). The best ligand however contained a iBu group in place of the Ts group, and gave a product of 98% ee.[84]

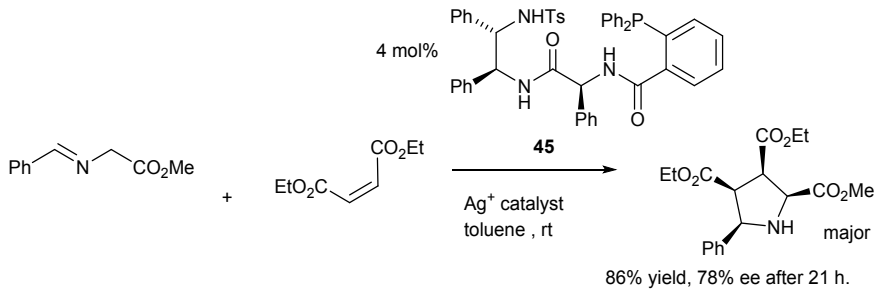

Figure 45. Asymmetric 1,3 dipolar cycloaddition using a TsDPEN-based ligand.

In the addition of acrylonitrile to nitrostyrene, a cross Rauhut-Currier-type, Wang's catalyst was evaluated and gave a product in 68% yield and 45% ee after 12 h.[85] A TsDPEN ligand is one in a series used in an asymmetric hydrosilylation of an imine in up to 90% ee with best

catalyst the TsDPEN example gave 92 yield/82% ee but the best were around 93-94% ee.[86] Addition of an indole to 2-amino-4H-chromenes where a TsDPEN-containing ligand was one of several studied but not the best. The best contained a simple di-meta-(CF_3)benzylsulfonamide group in place of the TsDPEN.[87]. The addition of alpha-amino aldehydes to 3-indoylmethanols using an enamine catalysts. TsDPEN-containing tested but not the best one – an OH-containing (in place of the NHTs) was the best one in this application.[88] TsDPEN catalysts were used in reactions of nitromethane derivatives in additions to enones. A simpler thiourea catalyst, containing a valinol-derived, tosylated diamine in place of the TsDPEN unit, was the best of the series tested.[89] Derivatives of TsDPEN have also featured in several catalysts based on the dppf scaffold.[90,91,92]

9. Conclusions.

In this review, we have highlighted the rich diversity of reagents which have been prepared from a single readily-available enantiomerically-pure building block and their numerous applications in asymmetric catalysis. In many cases, the TsDPEN-derived ligands and catalysts have proved to be the most effective of a series that were tested. Even after the development of a large number of reagents and applications, there is clearly still significant potential for further applications of TsDPEN derivatives to asymmetric catalysis, and no doubt further exciting developments will soon be reported.

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