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The sulfone group as a versatile and removable directing group for the asymmetric transfer hydrogenation of ketones

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Abstract: The sulfone functional group has a strong capacity to direct the asymmetric transfer hydrogenation (ATH) of ketones by [(arene)Ru(TsDPEN)H] complexes by adopting a position distal to the η^6-arene ring. This preference provides a means for the prediction of the sense of asymmetric reduction. The sulfone group also facilitates the formation of a range of reduction substrates and its ready removal provides a route to enantiomerically-enriched alcohols which would otherwise be extremely difficult to prepare by direct ATH of the corresponding ketones.

Asymmetric transfer hydrogenation (ATH) is a highly practical method for the synthesis of enantiomerically-enriched alcohols, being effective under mild conditions and avoiding the need for the use of high pressure hydrogen gas.[1] The [(arene)Ru(TsDPEN)Cl] class of catalysts first reported by Noyori *et al*. (e.g. **1**, Figure 1) are very efficient in this application, and reduce many classes of ketones, notably acetophenone derivatives and progargylic ketones, in high ee.[2] We, and others, have reported 'tethered' derivatives of the Noyori catalysts (e.g. **2**, Figure 1) which in some applications exhibit higher activity and stability.[3] Catalysts such as **1** and **2** have been employed in ATH for the synthesis of pharmaceutically relevant targets,[4] including multikilo applications[4a] and uses in high-volume flow chemistry.[4b] The triflate derivative, **3**, which readily ionizes in methanol, has been employed in closely related asymmetric hydrogenation (AH) of ketones.[5]

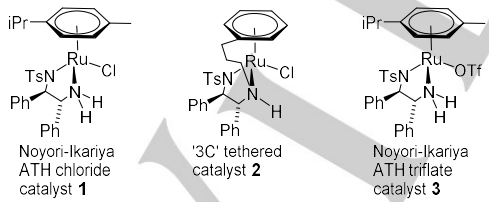

Figure 1. Noyori-Ikariya catalyst **1**, 3C-tethered derivative **2** and the Noyori-Ikariya triflate-derivative catalyst **3**. The active catalysts are generated through HCl elimination when the catalysts are activated.

However, despite its high value and practicality, this class of catalyst does not work well for all substrates. For example, in the asymmetric reduction of alkyl/alkyl ketones or substrates with minimal electronic or steric differences between the groups flanking the ketone,[6] the catalysts are less enantioselective. To address this shortcoming, we investigated the use of a temporary directing group to influence the selectivity of a reduction, followed by its removal, to 'unmask' what would previously have represented a very difficult target for ATH. In this regard, sulfones seemed promising, since they have been reported to be effective partners for ATH reactions (Figure 2). Zhang *et al*. reported, in 2009, the Dynamic Kinetic Resolution (DKR)/ATH of cyclic α–sulfone-substituted ketones **4** with catalyst (*S,S*)-**1** to products **5** in high dr and ee (Figure 2A).[7] Cyclic examples including the conversion of **6** to **7**, were exceptionally selective (Figure 2B).[7] In 2009, Wang *et al*. reported the use of catalyst (*R,R*)-**3** for asymmetric hydrogenation (AH) of α–sulfonyl and α–sulfonamidyl ketones **8** (Figure 2D) to alcohols **9** and the DKR/AH of related cyclic substrates.[8] The majority of examples contained an aryl substituent and gave >90% ees, although the reduction of $EtCOCH_2SO_2Ph$ in 84% ee[8]/80% ee[9] and $MeCOCH_2SO_2Ph$ in 82% ee[8]/91% ee[9] were also reported.[8] Later reports featured a one-pot formation, and then ATH, of sulfone-substituted ketones under aqueous conditions,[9,10] and the application of a silica-supported variant.[11] Bhanage and Vyas reported DKR/ATH of cyclic α-sulfone ketones using a proline-derived catalyst.[12]

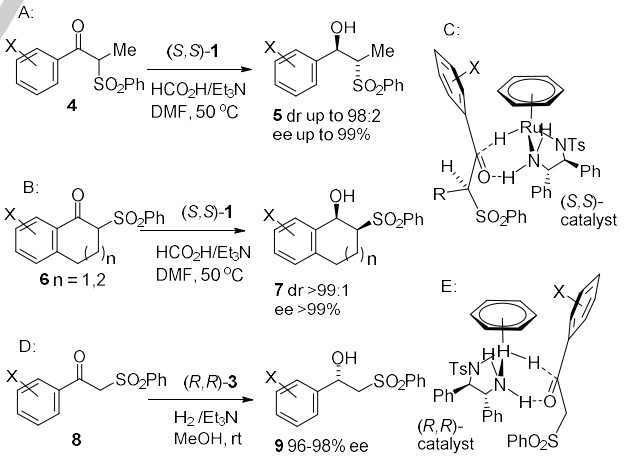

Figure 2. Reported classes of asymmetric reductions of sulfone-substituted ketones A: DKR/ATH of acyclic substrates, B: DKR/ATH of cyclic substrates, C: mode of hydride transfer for A and B, D: AH of sulfone-substituted acetophones, E: mode of hydride transfer for D.

Zhang *et al*. reported the reduction of α-sulfonamide ketones in very high ee and conversion using the '3C' tethered catalyst **2**.[13] Asymmetric hydrogenation of sulfone-containing acetophenone

derivatives has also been reported using other catalysts including Ru/diphosphine catalysts, and CBS reagents.[14(a)-(d)]

In reductions with [(arene)Ru(TsDPEN)Cl] complexes **1-3**, where acetophenone derivatives are most commonly studied, the sense of reduction indicates that the sulfone adopts a position in the transition state for ATH[15] in which it is positioned distal from the η^6-arene ring on the ruthenium hydride which is the active catalyst form in the reaction (Figure 2C and 2E). The η^6-arene is presumed to engage in a productive electrostatic interaction with the aromatic substituent on the substrate.

In contrast, very few reductions of alkyl-containing, α-sulfonyl ketones have been reported, possibly due to the perceived lack of fit to the traditional 'acetophenone-based' reduction model.[15] The potential for the use of a sulfone as a temporary directing group prompted us to examine what range of substituents could successfully partner a sulfone and whether it could hence be used as a removable group to facilitate the synthesis of otherwise challenging alcohol target molecules (Figure 3).

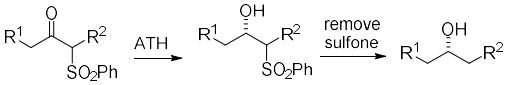

Figure 3. Investigations in this report, and strategy for synthesis of challenging alcohols in high ee.

Results and discussion.

We first prepared a diverse range of α–sulfonyl ketones **10a-10i** and studied their reductions using the 3C-tethered catalyst (*R,R*)-**2** (Figure 4).[3] The majority of these were prepared from the bromoketone using $PhSO_2Na$. Racemic **11h** was prepared by addition of $PhSO_2CH_2$ anion to PhCCCHO, and subsequently oxidised to the ketone **10h**. The ketone precursor to **11i** (i.e. **10i**) was prepared by addition of $PhSO_2CH_2$ anion to the Weinreb amide $PhCH_2CONMe(OMe)$**.**

The ATH (using formic acid/triethylamine – FA/TEA 5:2 azeotrope) of substrates **10a-10d** revealed an unexpected trend in which the product ee increased as the ring became smaller in the series from cyclohexyl (**11a,** 87% ee) to cyclopropyl (**11d**, 99% ee), although it remained high in each case (Figure 4). In representative cases, the results were compared with those for the ATH of the analogous thiol- or ether-containing substrates. It was found that these were consistently reduced in lower enantioselectivity in every case. The reduction of sulfone-containing cyclopropyl ketone **10d** gave product **11d** in a very high 99% ee, whereas the thiophenyl-substituted analogue gave a product in a reasonable ee of 87% whereas the phenoxy substrate gave a product of just 36% ee. Substrates containing sulfones and linear alkyl chains (**10e, 10f**) were also reduced; the product ees increased with the length of the chain, and were higher than for the reported reductions of substrates containing Me and Et substituents. Even a substrate containing a hindered t-butyl group, i.e. **10g**, was reduced in a valuable 86% ee. The substrate containing a triple bond, **10h**, was reduced in particularly high enantioselectivity to **11h** (99% ee) although the benzyl-substituted substrate **10i** gave a product **11i** of just 72% ee.

A derivative of the major enantiomer of the cyclohexyl-containing reduction product **11a** was prepared through reaction with (*S*)-1-phenylethylisocyate and the X-ray crystallographic structure of this (Figure 5A) allowed the product configuration to be assigned as *S*, in agreement with the comparison of the optical rotation to that reported (see Supporting Information) and also to the reported precedents.[7-13] The configurations of **11f**, the OPh derivative of **11f**, and of **11i** were also confirmed by optical rotation comparisons with those reported and the other products were assigned by analogy.

The results suggest that the sense of reduction of the examples follows the model for the earlier-reported (predominantly aromatic) substrates, i.e. in which the sulfone group favours the position in the t.s. in which it is distal from the η^6-arene of the complex (Figure 5B).[7-13]

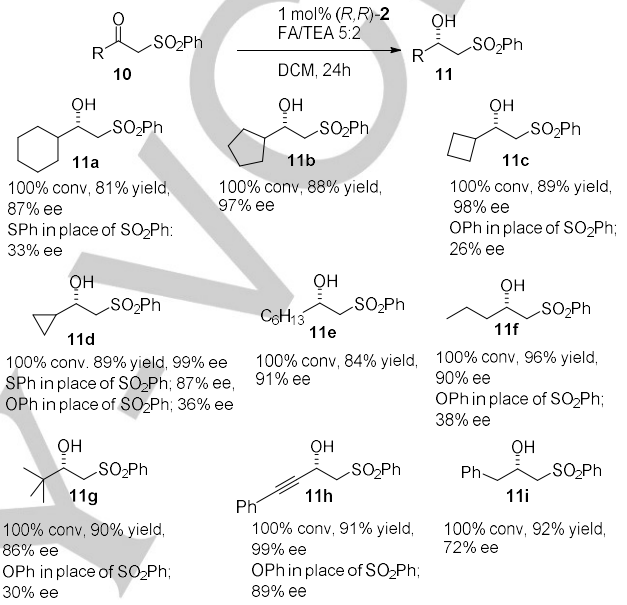

Figure 4. ATH of α-sulfonyl ketones with a tethered ATH catalyst and resulting products **11a-11i**, and comparisons to ees of corresponding ATH products containing sulfides and ethers in place of the sulfone.

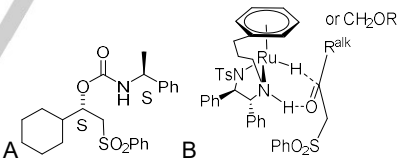

Figure 5. A. Structure of **11a** functionalised using (*S*)-1-phenylethylisocyate (X-ray structure is in Supporting Information). B. Proposed mode of reduction of sulfone-substituted alkyl ketones.

The cyclopropyl group is a particularly compatible substituent in substrates for ATH reactions, with reports having been published of applications to natural product synthesis in which ketones adjacent to cyclopropanes are reduced in high ee.[16] The sense of induction suggests that it is compatible with an interaction with the η^6-arene, which accords with our results (Figure 6A). We also found that product **12** was formed as a 53:47 mixture of two enantiomerically-enriched diastereosiomers (90 and >99% ee respectively) through reduction of the racemic *trans*-cyclopropane substrate (Figure 6B). Another example of a related ketone, bearing a phthalimide group (and hence a precursor to 2-hydroxy amines) was reduced in 96% ee by ATH to product **13** (Figure 6C) to further highlight the value of the cyclopropyl group.

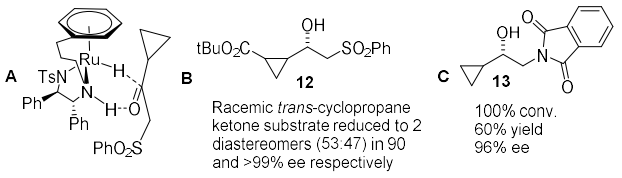

Figure 6. Cyclopropyl-functionalised ketones are also excellent substrates for ATH reactions. A. Likely mode of hydrogen transfer by ATH using (*R,R*)-**2**. B. ester-functionalized cyclopropane ATH product **12**. C. Phthalimide-containing ATH product **13** (ATH conditions as given in Figure 4).

Encouraged by these results, we investigated further derivatives with more challenging functionalisation. Previous studies in our group had revealed that aryloxy- and alkoxy- groups can adopt positions adjacent to the η^6-arene of the catalyst during reductions and it seemed that the pairing of these with a sulfone could create an ideal substrate for reduction. In the event, we found that oxygen-containing groups were tolerated well in ATH substrates; $PhOCH_2COCH_2SO_2Ph$ was reduced to **14** in 96 % ee and two related ketones were also converted in similarly high enantioselectivity to products **15** and **16** (Figure 7). Again, a corresponding sulfide-containing substrate was reduced in lower ee (81% ee), underlining the importance of the sulfone group to the control of the reduction (Figure 5C). A sulfone group one carbon further away from the ketone was less effective at directing the reaction, and a product **17** of 27% ee was formed. The reduction of a substrate containing a tBoc- protected amine opposed to a sulfone gave a product **18** of just 53% ee however.

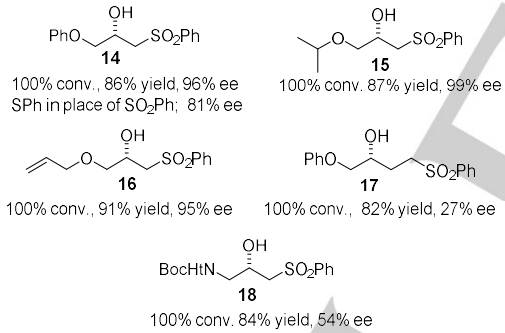

Figure 7. ATH products formed from alkoxy and amino-substituted ketone substrates containing sulfone groups (ATH conditions as given in Figure 4).

With the directing factors established, the dynamic kinetic resolution (DKR) of sulfone-containing substrates **19a-g** was examined next. This also proved successful, with products **20a-20g** of high dr and ee being obtained, i.e. where the substituent was adjacent to the ketone and able to racemize rapidly in order to facilitate the DKR process (Figure 8A and 8B). The absolute stereochemistry of **20c** was be confirmed by X-ray crystallography (Supporting Information) and others were assigned by analogy. In these examples, the starting materials **19a-19g** were prepared by addition of the corresponding sulfone anion to the precursor aldehyde followed by oxidation. In all cases, the sense of reduction to **20a-20g** followed that in the model previously described (Figure 5B) with the additional requirement for the avoidance of steric clashes between the substituent adjacent to the sulfone and the catalyst (Figure 8D), hence the preferred reduction of the *R*- enantiomer of the substrate when (*R,R*)-**2** catalyst was used.

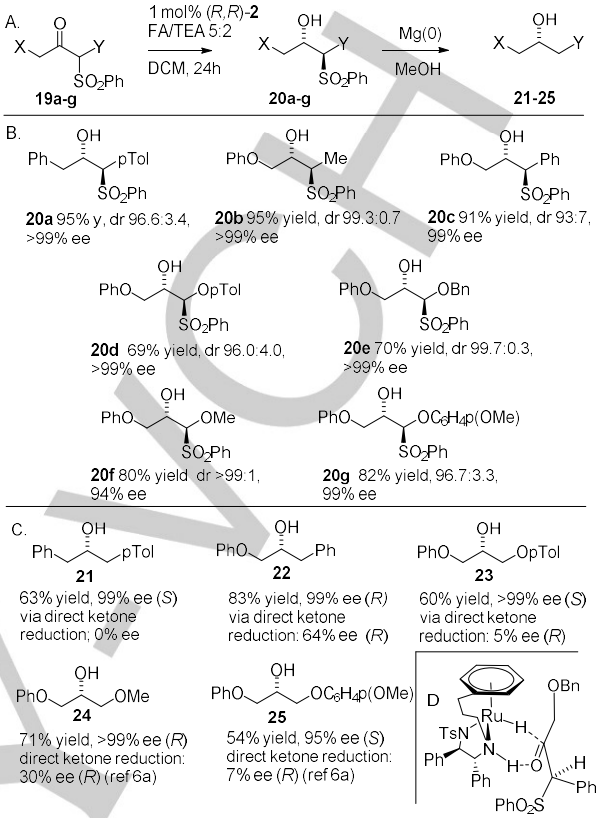

Figure 8. A. Diastereoselective ATH products with DKR where a racemizable center was present in the substrate. B. ATH/DKR products. The product ee is in each case of the major diastereoisomer. Products **20a-20g** were formed in 100% conversion. C. Products **21-25** of sulfone reduction. D. Proposed mode of reduction of **19a-19g** in the ATH/DKR reaction.

As previously outlined, this transformation provides access to a strategy for the synthesis of otherwise highly challenging asymmetric alcohol products in high ee. In order to demonstrate this, we reductively removed the sulfone group[17] from a representative number of products to generate the unsubstituted products **21** – **25** in high ee, which in each case was an alcohol with very little steric or electronic difference between the groups flanking it (Figure 9C). Traditionally such targets would be regarded as very difficult to prepare through direct ketone ATH. For each case, comparisons of enantioselectivities of reductions of the direct ketone precursors are included for comparison (see Supporting information). Product **21** was formed as a racemate by direct ketone reduction, and **23** was formed in just 5% ee. Direct reduction of the ketone precursor to **22** gave the best result of 64% ee, and in the same sense, resulting from the electronic difference between phenyl and phenoxy substituents. Compounds **24** and **25** have previously been reported by us,[6a] with ees of just 30% and 7% ee respectively obtained by direct ketone reduction. In the case of **25**, the opposite enantiomer of alcohol is formed by direct reduction (using the same configuration of catalyst), thus serving to confirm that the absolute sense of reduction of ketone **19g** matches that predicted by the model in Figure 8D. However by proceeding

through the sulfone intermediate, products of >99% ee (**24**) and 95% ee (**25**) respectively were obtained. The sharp contrast illustrates how a sulfone acts as a temporary group for achievement of the required syntheses. Attempted removal of the sulfone from **20e** did not yield the required alcohol product, possibly due to debenzylation and decomposition.
In cases where the existing chiral center was located distal from the sulfone), i.e. in **26** and **27**, a DKR was not achieved, and both product diastereoisomers were formed, with variable results (Figure 9) and some differences between the matched and mismatched substrate/catalyst enantiomer combinations.

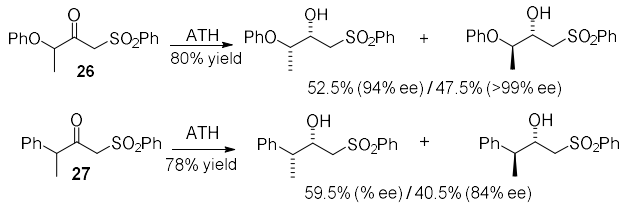

Figure 9. Attempted ATH/DKR where a racemizable centre was not present in the substrate. ATH conditions are as given in Figure 8. Relative stereochemistry was not confirmed.

In an extension of this strategy (Figure 10), an allylic alkene was prepared through reduction of the heterocyclic sulfone **28** (prepared from the anion of 2-(methylsulfonyl)benzo[d]thiazol-6-ylium and 2-phenoxyacetyl chloride) to alcohol **29** in 94% ee. Protection of the alcohol gave **30** and this step was followed by a Julia-Kocienski olefination reaction with benzaldehyde and deprotection to give *E*-**31** in 91% ee.[18]

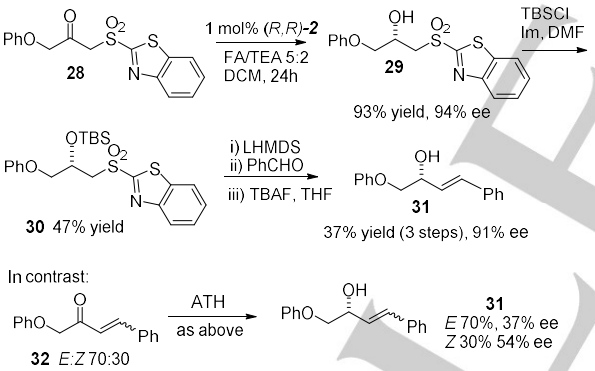

Figure 10. Formation of allylic alcohols in high ee via Julia-Kocienski coupling post ATH-DKR.

The comparator compound without the sulfone (**32**) was prepared as a mixture of E/Z isomers in a 70:30 ratio (see Supporting Information) and was reduced in much lower enantiomeric excess in contrast (two alkene isomers of **31** in just 37 and 54% ee respectively), again demonstrating the added value of the sulfone group in the generation of a practical and selective route to a product that would otherwise be extremely difficult to prepare in high enantiomeric excess.

Conclusions

In conclusion, we have demonstrated that the sulfone group is a powerful tool for directing efficient asymmetric reductions and provides an access to products which would otherwise be very difficult to generate in high enantiomeric excess through direct reduction.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, NMR spectra, X-ray crystallographic data and HPLC data (PDF).

Data sharing statement. The research data (and/or materials) supporting this publication can be accessed at http://wrap.warwick.ac.uk/TBA.

Notes

The authors declare no competing financial interests.

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Keywords: Asymmetric catalysis • ketone reduction • sulfones; alcohols • ruthenium.

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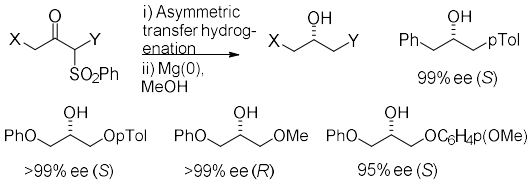

The sulfone group facilitates the formation of a range of reduction substrates through asymmetric transfer hydrogenation (ATH) of ketones and its ready removal provides a route to challenging enantiomerically-enriched alcohols.