Asymmetric transfer hydrogenation (ATH) of *ortho*-hydroxyphenyl ketones; utilizing directing effects which optimize the asymmetric synthesis of challenging alcohols

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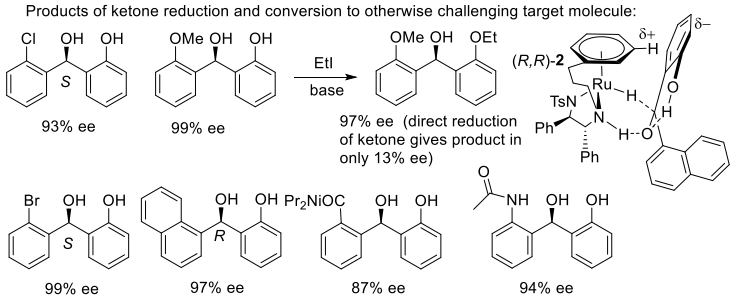
Supporting Information Placeholder



ABSTRACT: A systematic range of *ortho*-hydroxyphenyl ketones were reduced under asymmetric transfer hydrogenation (ATH) conditions using a C3-tethered catalyst **2**. The combination of two directing effects i.e. an *ortho*-hydroxyphenyl coupled to a bulky aromatic on the opposite side of the ketone substrate, combine in a matched manner to deliver reduction products of very high enantiomeric excess.

1. INTRODUCTION

Asymmetric transfer hydrogenation (ATH) of ketones using [(arene)Ru(TsDPEN)Cl] type catalysts such as **1** or tethered derivatives such as **2** or **3** (Figure 1A) is now a well-established method for the enantioselective synthesis of alcohols.[1] In most cases, a combination of formic acid and trimethylamine (FA:TEA, typically a 5:2 azeotrope) is used as the reducing agent and solvent. Although acetophenone derivatives, containing a combination of an aromatic ring and an alkyl group flanking the ketone, are the most commonly-studied targets (Figure 1B),[1,2] there remains a need to expand the methodology to more challenging substrates.[3] For some time,[1b] it has been known that electronic differences alone can exert some control over the reduction of benzophenones by complex **1** and its derivatives (Figure 1B). In recent research, Ikariya and coworkers reported the ATH of benzophenones using catalyst **3** and found that the addition of an *ortho*-substituent to one of the aromatic rings flanking the ketone resulted in the formation of products with very high ee (Figure 1B).[4] The increased enantioselectivity is believed to arise through an out of plane orientation of the hindered group resulting in its positioning distal to the η^6-arene ring of the catalyst (Figure 1C).[5] The same principles of electronic and steric-drive differentiation have also been applied to the reductions of aromatic/2-pyridyl (and closely related) ketones to good effect by Zhou *et al.*[6]

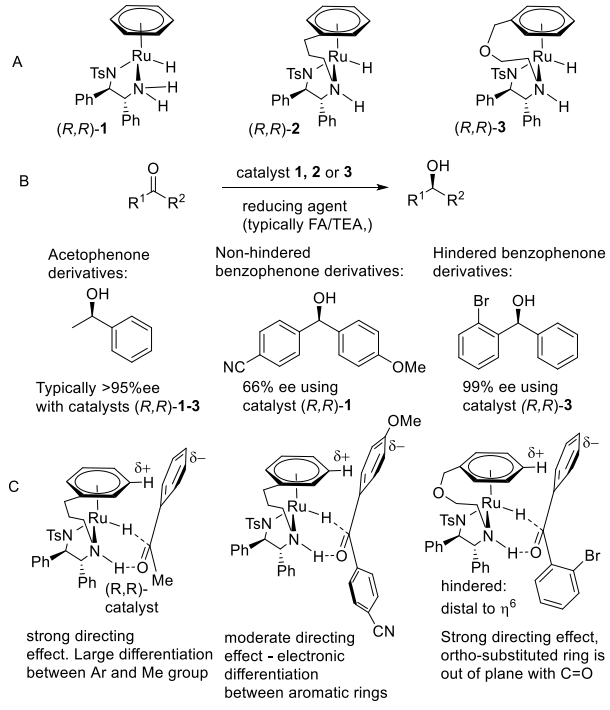


Figure 1. A. [(arene)Ru(TsDPEN)Cl] complexes for ATH. B. Reductions of acetophenone and benzophenone derivatives using

[(arene)Ru(TsDPEN)Cl] complexes ((*R,R*)-configuration ligand) catalysts such as **1** - **3**. C. Mode of hydrogen transfer for each class of substrate.

The related reductions of propargylic ketones containing a hindered *ortho*- substituted aromatic ring, in high enantiomeric excesses, operate through an analogous directing effect.[7] Herein we report a systematic study of substrates containing the *ortho*-hydroxyphenyl group. We demonstrate how the correct choice of substituents can be used to deliver products of very high enantiomeric excess, including examples that would otherwise be very difficult to access by other methods.

2. RESULTS AND DISCUSSION

Although we used the '3C-tethered' complex **2** throughout the study,[1] we also employed 'benzyl-linked' **4**,[8a] 'OMe-substituted' **5**[8b] and the untethered 'Ru/TsDPEN' catalyst **6**,[1] all of which have previously been either used and/or developed in our research group (Figure 2). The (*R,R*)- form of the catalysts **2**, **4** and **5** were used however the (*S,S*)- enantiomer of **6** was employed.

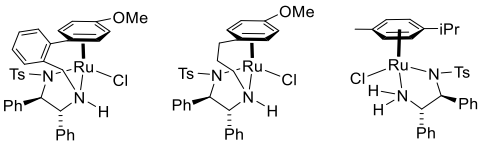


Figure 2. Other ATH catalysts which were employed in this study.

In the ATH of *ortho*-hydroxyacetophenone and *ortho*-methoxyacetophenone, the former are reduced using (*R,R*)-**2** in typically >98% ee[2b] and the latter in ca. 70-80% ee,[9] although there are some exceptions.[8b] Whilst an *ortho*-methoxy group may result in the movement of an aryl group out of the plane with the ketone, an *ortho*-hydroxyphenyl group will remain in-plane due to its lower steric demand, and potential hydrogen bond between the OH and the ketone.

Asymmetric reductions of a systematic range of *ortho*-hydroxyphenyl ketones **7a-7k** were carried out in DCM (to aid solubility) with a catalyst loading of 1 mol% at rt to give products **8a-k** (Figure 3). Alcohol **8a** was formed in 73.4% ee and *S*- configuration, which was confirmed by comparison by chiral HPLC and optical rotation, with the reported details for this compound.[9a] In contrast, 2-(hydroxy(phenyl)methyl)phenol **8b** generated by ATH using the same catalyst (*R,R*)-**2** was formed as the *R*- enantiomer in 80% ee and the configuration was confirmed by comparison of the HPLC data to that reported.[9b] The configuration was also confirmed by methylation of our sample of (*R*)-**8b** to the (*R*)-(2-methoxyphenyl)(phenyl)methanol **8a** (Supporting Information). With knowledge of the individual, and opposite, directing effects of *ortho*-OH and *ortho*-OMe on benzophenone reduction, it was gratifying to find that **7c**, containing both groups, was reduced to **8c** in an exceptionally high 99% ee. The X-ray crystallographic structure (Supporting Information) revealed the expected *S*- configuration of the product, presumably formed through reinforcement of the individual directing effects of each substituent. The other catalysts were tested for the reduction of **7c** and gave less satisfactory results (Figure 3B); even at extended reaction times of 168h (7 days), reductions were incomplete and the ees were lower. Finally within this series, the reduction of **7d** to a product **8d** of much lower 64% ee serves to confirm that it is the steric effect of the *ortho*-OMe in **7c** which improves the ee, not its high electron density. In fact, as illustrated by **7d**, increasing the electron density of the ring opposing the *ortho*-hydroxy phenyl serves to *reduce* the enantioselectivity of the ATH reaction.

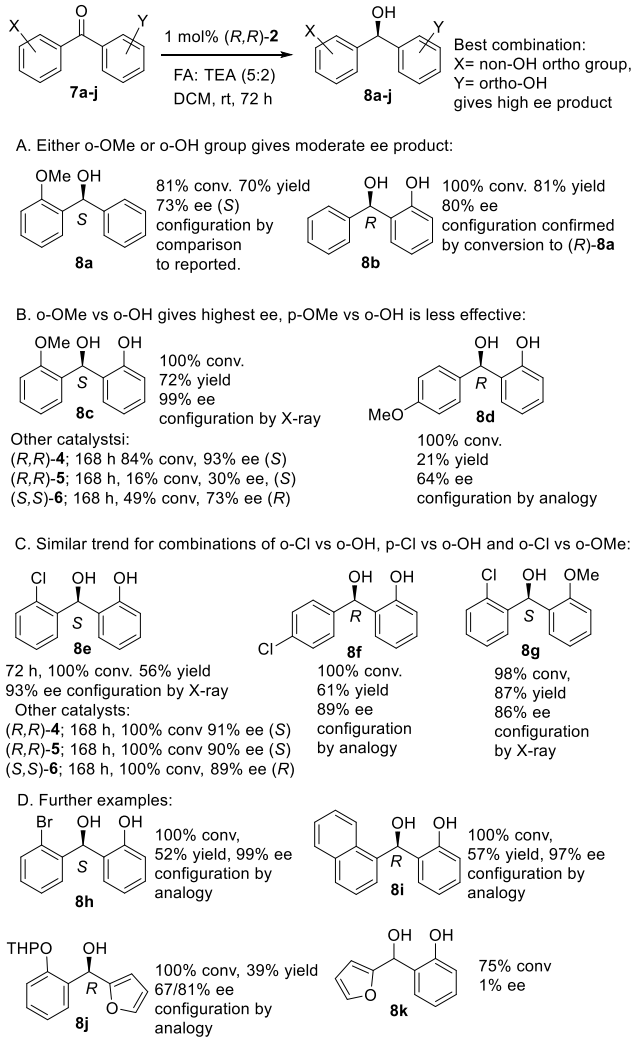


Figure 3. General procedure for ATH of *ortho*-hydroxyphenyl ketones using (*R,R*)-**2** and products obtained. The alcohol products are illustrated with the right hand ring being the one closest to the η^6-arene ring of the catalyst during the reduction (Figure 4).

In further tests with chlorine-substituted substrates, the configurations and ees of products **8e-8g** reveal the same pattern, in which the combination of one *ortho*-hydroxyphenyl ring and another sterically-demanding *ortho*-substituted ring in the substrate deliver the highest ee products. For product **8e**, formed in 93% ee, the X-ray structure confirmed the *S*- configuration (Supporting Information). Tests of other catalysts were completed on **7e** and products were formed in full conversions but slightly lower ees. In this case the less electron-rich opposing ring does not create a significant countereffect to the ee if the chlorine is in the *para*- position (**8f**) and even the *ortho*-OMe substrate can deliver a product of good ee (**8g**; an X-ray structure confirmed the *S*- configuration (Supporting Information)). The high ees of 99% for *ortho*-bromo product **8h** and 97.2% for 1-naphthyl-substituted **8i** also highlight the potential for excellent ee when a hindered arene is present in the substrate. Furan-containing substrates can also give alcohols in good ee with an opposing bulky substituent in the substrate (67-81% ee for **8j**) but essentially no selectivity if the furan opposes an *ortho*-hydroxy phenyl (racemic formation of **8k**).

The results indicate that the electron-donating *ortho*-hydroxylphenyl group makes its aryl ring more electron-rich but without distorting the geometry of the ketone, possibly maintaining it via a hydrogen bond to the ketone. This favours electrostatic interaction

with the η^6-arene ring of catalyst in the ATH in the proposed reduction transition state. A bulky *ortho*-substituent on the opposing aromatic ring, however, will force that ring out of plane and provide an additional directing effect in the reduction step (Figure 4).

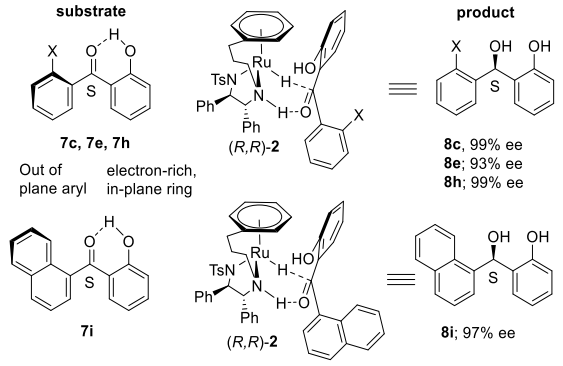


Figure 4. Proposed approach of substrate to catalyst (*R*,*R*)-**2** for formation of **8c**, **8e**, **8h** and **8i**. The combination of one *ortho*-hydroxyphenyl group opposing a hindered aryl ring delivers products of highest ee.

The high ees of products **8c**, **8e**, **8h** and **8i** also follow what would be predicted from the general model (Figure 4). Using catalyst (*R*,*R*)-**2** in the ATH of (2-chlorophenyl)(2-methoxyphenyl)methanone gave **8g** in 86% ee. In this case the high ee likely derives from the electronic differences between the arene rings, even though both contain *ortho*-substituents (the MeO- substituted ring adopting the position adjacent to the η^6-arene ring).

In an illustration of the application of the methodology to an otherwise challenging ATH product, alcohol product (*R*)-**8l** was prepared by ethylation of (*S*)-**8c**, from ATH, of 99% ee (Figure 5A). The ee of **8l** was measured as 97%; a slight decrease due to a small amount of racemisation. Notably, the configuration of the same alcohol (*R*)-**8l** of just 13% ee produced by direct ATH of ketone **7l** (Figure 5B). This result underlines the value of the *ortho*-hydroxy directing effect and its application to the highly enantioselective synthesis of a product (**8l**) which would otherwise be extremely difficult to generate in high ee by direct reduction or other synthetic approaches.

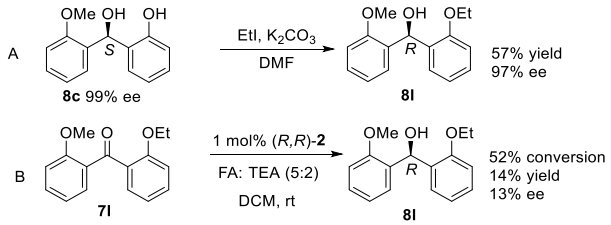


Figure 5. Synthesis of **8l** in high ee can be achieved via the *ortho*-hydroxyphenyl intermediate but not by direct reduction of the direct precursor ketone.

Given the results above, and having established the requirements for high enantioselectivity in reductions, we investigated the compatibility of the *ortho*-hydroxyphenyl-directed approach to a broader range of substrates (Figure 6). ATH of a corresponding amide-containing substrate **7m** to **8m** gave a product of moderate ee (61% ee), However the reduction to **8n** was achieved in full conversion and a much higher ee of 94%, which illustrates that the *ortho*-hydroxyphenyl group can be successfully combined within a highly hindered substrate to good effect. The importance of the hydroxyl group itself to the high enantioselectivity was underlined by the lower ees (and incomplete conversions) obtained for products **8o** and **8p**, which contain equally electron-rich substituents in varying positions on the aromatic ring. Additionally, the amide-containing ketone **7q** (Figure 6C) was reduced to **8q** in 87% ee, which is high for a complex and sterically-hindered substrate of this type. In contrast, the *ortho*-methoxy ketone **7r** gave product **8r** of just 11% ee and very low conversion (20%), reflecting its hindered nature. However **8r** was formed in 86% ee by O-methylation of **8q**, again reflecting the value of the *ortho*-hydroxy directing group route for the synthesis of a product that would otherwise be essentially inaccessible in high ee by direct ATH of a precursor.

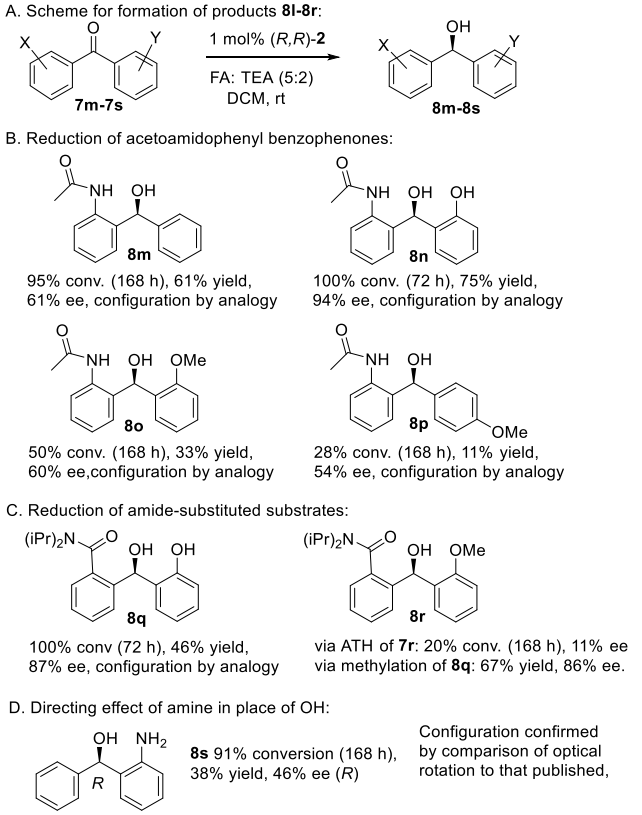


Figure 6. Extension of *ortho*-hydroxyphenyl directing group to a broader range of substrates **7m**-**7s**, and comparisons.

ATH of an *ortho*-aminophenyl containing ketone **7s** with catalyst (*R*,*R*)-**2** gave the alcohol product **8s** of *R* configuration (Figure 6D, confirmed by comparison of optical rotation to published value), but in only 46% ee, indicating that a free *ortho*-amino group is less effective at the direction of benzophenone ATH than the *ortho*-hydroxyphenyl.

Catalysts *(R,R)*-**2** and **4**-**6** were also employed in the asymmetric reduction of imines **9**-**11** derived from *ortho*-hydroxyphenylketones. An excellent precedent for this class of substrate was reported by Mangion *et al*,[10] and we took the opportunity to investigate its scope. (Figure 7).

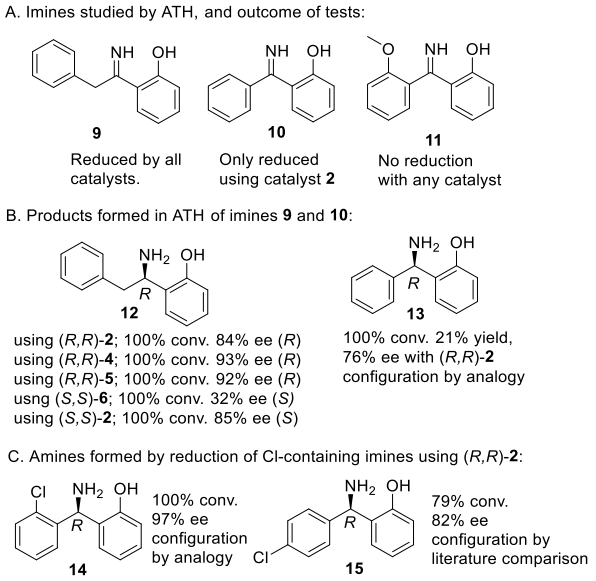


Figure 7. Imines **9-11** and reduction products of all imines investigated. Reduction was carried out using ammonium formate in DCM, at 70 ºC in a sealed tube, overnight.

The ATH of imines **9-11** was carried out using ammonium formate/DCM, (70 °C, sealed tube)[10] in order to avoid hydrolysis, following the literature procedent. Full reduction of imine **9** was obtained using all four catalysts in ATH reactions and the ees of asymmetric amine **12** were good in all cases apart from catalyst **6**, which gave a product of lower ee. Catalyst (*S,S*)-**2** gave a product of essentially identical ee to the (*R,R*)- catalyst. The product configuration follows that reported by Mangion *et al.* for the reduction of the molecule which provided a precedent for our study.[10] However, only catalyst (*R,R*)-**2** gave 100% conversion of imine **10** to amine **13,** which was of 75% ee; the other three catalysts did not give any conversion. For imine **11** bearing the larger groups on both sides of the ketone, no catalysts were effective. Two more chiral amines, **14** and **15**, both containing chloro-substituted aromatic rings, were formed by reduction of the precursor imines in full conversions and excellent ees. Following the earlier precedents, the *ortho*-chlorophenyl product was formed in higher ee than the *para*-chlorophenyl product, reflecting the additional steric directing component in addition to the difference in electron density between the two aromatic rings flanking the ketone. The reduction of the imine derived from ortho-hydroxy acetophenone was not successful (Supporting Information).

The reductions have the potential to create enantiomerically enriched precursors to otherwise challenging synthetic targets. For example compound **16**, which is a sphingosine 1-phosphate receptor inhibitor.[11] which could potentially be prepared from a precursor such as **17**. The potential for this is demonstrated by the conversion of enantiomerically-enriched **8h** to compound **18** using a Suzuki reaction (Figure 8) with only a small loss of ee.

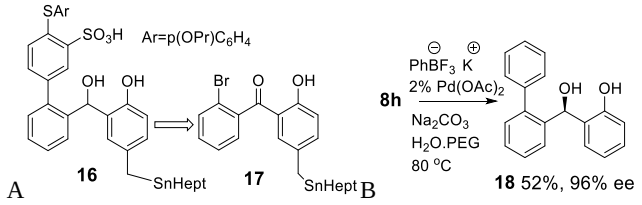


Figure 8. A. potential route to **22** from a ketone **23** related to those in this report. B. conversion of **8h** to the phenyl-substituted derivative **24**.

3. CONCLUSIONS.

In conclusion, hindered ketones and imines can be reduced effectively in ATH using a range of catalysts, provided that an *ortho*-hydroxyphenyl ring opposes a sterically hindered aromatic ring on the substrate. The low conversions and ees of asymmetric reduction of certain direct ketone substrates can in several cases be improved by generating the product via the corresponding *ortho*-hydroxyphenyl ketones. Where tested, (*R,R*)-**2** proved to be the best catalyst of the series tested.

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Conflict of interest

The authors declare no conflicts of interest.

Data sharing statement

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

ASSOCIATED CONTENT

Supporting Information.

† Electronic Supporting Information (ESI) available: NMR spectra and HPLC spectra relating to ee and dr determination and X-ray data (CCDC 1978883-1978886) are available as Supporting Information.

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