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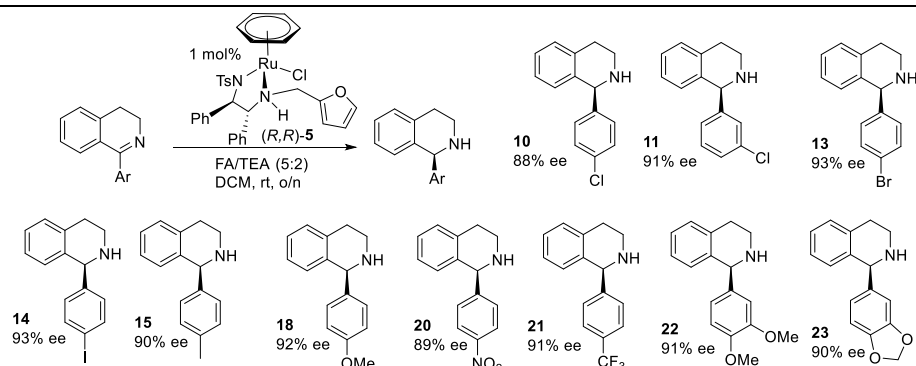
Asymmetric transfer hydrogenation of unhindered and non electron-rich 1-aryl dihydroisoquinolines in high enantioselectivity

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Supporting Information Placeholder



ABSTRACT: The use of arene/Ru/TsDPEN catalysts bearing a heterocyclic group on the TsDPEN in the asymmetric transfer hydrogenation (ATH) of dihydroisoquinolines (DHIQs) containing *meta*- or *para*-substituted aromatic groups at the 1-position results in the formation of products of high enantiomeric excess. Previously, only 1-(*ortho*-substituted)aryl DHIQs with an electron-rich fused ring, gave products of high ee, therefore this approach solves a long-standing challenge for imine ATH.

Since the first report by Noyori *et al.* in 1996¹ of the asymmetric transfer hydrogenation (ATH)² of 1-substituted-3,4-dihydroisoquinolines (DHIQs) **1** in order to form asymmetric tetrahydroisoquinolines (THIQs) **2** (Figure 1) using Noyori-Ikariya catalysts (arene/Ru/TsDPEN type) such as **1** and **2**, there has been a great deal of interest in this class of reaction.³ Other catalysts, including the related tethered catalysts such as **3**⁴ and N'-alkylated TsDPEN-based catalysts such as **4**⁵ (Figure 2) have been applied to the ATH of DHIQs. 1-Alkyl (including 1-benzyl and 2-phenethyl) DHIQs are generally excellent substrates which give products in high enantioselectivity (Figure 3) when catalysts **1** and **2** are used in the reactions.^{1,3,6} In contrast, 1-aryl substituted DHIQs exhibit a more complex pattern of reactivity with this class of catalyst and previous work has indicated that they can only be consistently reduced to products of high ee if there is an *ortho*-substituent on the aromatic ring at the 1-position of the substrate (Figure 3).^{1,7} This is presumably due to the requirement for the presence of a hindered substituent at this position.

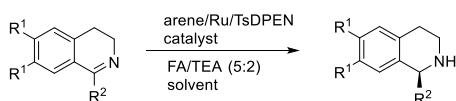


Figure 1. Dihydroisoquinoline (DHIQ) reduction by ATH with arene/Ru/TsDPEN complexes **1-4** (Figure 2, Figure 3).

In addition, an electron-rich aromatic ring in the *fused arene* component of the DHIQ (typically one or two methoxy groups)^{6,7} is also beneficial for the formation of products of high ee to be generated in the reductions of 1-aryl DHIQs. In contrast, very few reports have appeared on the ATH of non-*electron-rich* 2-aryl/non *ortho*-substituted DHIQs.^{7b} DHIQ ATH has also been reported using the Rh(III) and Ir(III)/Cp* derivatives of the Noyori-Ikariya Ru(II) catalysts, with a similar pattern of results observed but also some complex observations reported from a study of the kinetics of the reductions.⁸ Therefore this class remains an unsolved challenge for ATH with arene/Ru/TsDPEN catalysts such as **1-4** even some 24 years since Noyori *et al.*'s first report, despite their potential for the synthesis of valuable pharmaceutical target molecules such as solifenacin^{9a} and TRPM8 antagonists^{9b} (Figure 4). Other approaches to the enantiomeric synthesis of 1-aryl THIQs include the use of Ir/chiral diphosphines in asymmetric hydrogenation,¹⁰ the incorporation of ATH catalysts into a protein structure,¹¹ and enzymatic methods.¹² In this report we describe a practical solution to the challenge presented by unhindered/electron-poor 1-aryl DHIQs based on the accessible (arene)/Ru/TsDPEN class of ATH catalysts.

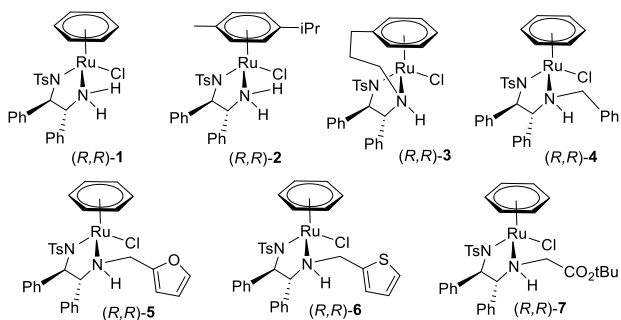


Figure 2. Catalysts employed in the ATH of DHIQs - 1-4; known catalysts for this application, 5-7 complexes reported in this paper.

During the course of an ongoing project on N-alkylated TsDPEN ligands in the complexes we evaluated heterocycle- and ester-containing catalysts 5-7 (Figure 2)¹³ in the ATH of *unhindered/e-poor 1-aryl DHIQs* and found that these worked very well with these challenging substrates, with 5 being the best in our studies. In common with other reports on DHIQ ATH,⁶ we used a 5:2 azeotropic combination of formic acid and triethylamine (FA/TEA) as the hydrogen source. Products were formed in higher enantioselectivity than with any other arene/Ru/TsDPEN ATH catalysts that we are aware of.

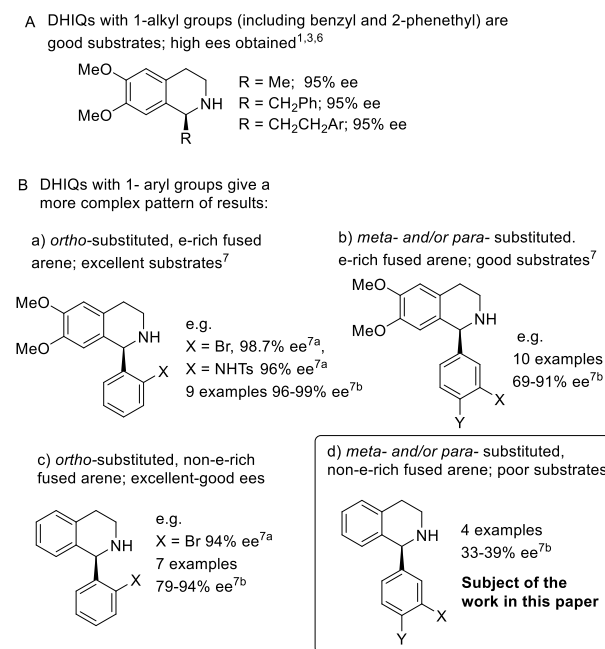


Figure 3. Summary of state of the art of DHIQ ATH using arene/Ru/TsDPEN catalysts (*R,R*)-1 and (*R,R*)-2 and closely related derivatives; dihydroisoquinoline (DHIQ) reduction products illustrated.

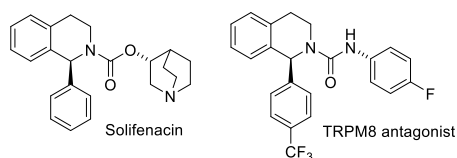


Figure 4. Structure of solifenacin, a muscarinic acetylcholine receptor antagonist, and a recently reported TRPM8 antagonist which formed the basis for further optimisations.

In our initial tests, we used catalyst (*R,R*)-5 in the reduction of the parent 1-phenyl-DHIQ 8 in formic acid 5:2 azeotrope (FA:TEA) using a range of catalysts. Since its ATH using catalyst (*R,R*)-1 had been reported to give a product 9 in just 29% ee (90% yield)^{7b}, this was felt to have obvious scope for improvement. In order to eliminate a significant

effect of solvent (we have previously found that catalysts (*R,R*)-5-7 perform most effectively in DCM), our repeat of the reduction of substrate 9 with catalyst (*R,R*)-1 in DCM gave a product of just 24% ee and 45% conversion. Using the cymene derivative (*R,R*)-2, the product 9 was formed in just 11% conversion and 42% ee., and with tethered catalyst (*R,R*)-3 the result was worse with a product formed in just 10% ee (although a conversion of 97%). With furan-containing catalyst (*R,R*)-5, however, reduction to the THIQ 9 was achieved in an impressive 90% ee (93% conversion and 70% isolated yield), and the enantioselectivity was unchanged in DCM and MeCN solvent. Catalyst (*R,R*)-6, bearing a thiophene ring, gave a reduction product in 91% ee although just 86% conversion after the same 48h reaction time, whereas ester-containing catalyst (*R,R*)-7 gave a product in just 77% conversion (in 96h) and 49% ee. Significantly, reduction using the N¹-benzyl-functionalised catalyst (*R,R*)-4 gave a racemic product in just 12% conversion, highlighting a remarkable effect of the *heterocyclic* ring on the reduction selectivity.

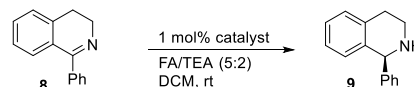


Figure 5. Asymmetric reduction of DHIQ 8 (Table 1).

Table 1. ATH of 2-phenyl DHIQ 8^a

Entry	Catalyst	t/h	Conv/%	ee/%
1	(<i>R,R</i>)-1	48	45	24
2	(<i>R,R</i>)-2	48	11	42
3	(<i>R,R</i>)-3	16	97	10
4	(<i>R,R</i>)-5	24	93	90 ^c
5	(<i>R,R</i>)-5 ^b	24	90	90
7	(<i>R,R</i>)-6	48	86	91
8	(<i>R,R</i>)-7	96	77	49
9	(<i>R,R</i>)-4	72	12	0

a. conditions as given in Figure 5, solvent is DCM unless otherwise indicated. b. solvent is MeCN. c. Product isolated in 70% yield at 96 h (98% conversion). In all cases the configuration of 9 was the same (and as illustrated) and determined by correlation with the reported result using (*R,R*)-1.^{7b}

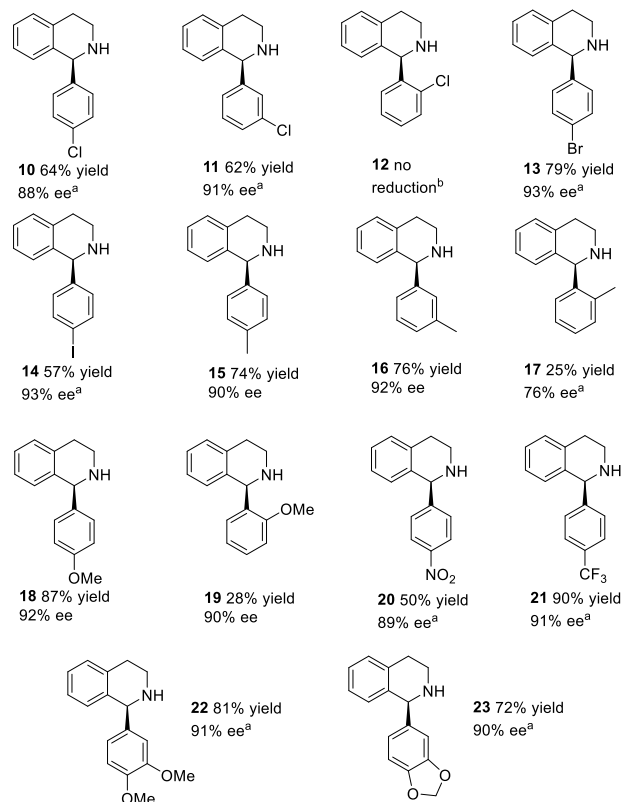


Figure 6. Products from non e-rich DHIQ reduction obtained in this project, using catalyst (*R,R*)-5 and the conditions shown in Figure 5, o/n reaction time. Configurations were assigned by analogy with **9** (Table 1). a. First report of formation by ATH using arene/Ru/TsDPEN catalysts to our knowledge. b. 85% yield, 92% ee reported using (*R,R*)-1.^{7b}

Having made this unexpected observation, we tested the reductions of a further series of non e-rich DHIQs using catalyst (*R,R*)-5, and obtained the products illustrated in Figure 6. It was found that *para*- and/or *meta*- substituted products were consistently formed in high ee, typically 90% or greater, and where comparable, in higher ee than reported for catalyst (*R,R*)-1 (**15**; 36% ee, **16**; 36% ee, **18**; 39% ee, **19**; 79% ee).^{7b} Several of the products were reported, to the best of our knowledge, for the first time in high ee using an arene/Ru/TsDPEN catalyst in ATH (indicated in Figure 6). Tolerated substituents included *meta*- and *para*- chloro, and methyl and *para*-bromo, iodo and methoxy, nitro and trifluoromethyl groups (not all *meta*- substituted substrates were tested), as well as *meta*-/*para*- combinations of electron-rich groups. The synthesis of amine **15** was carried out on a 1.1g (5 mmol) scale and gave a product of 91% ee in 71% isolated yield. In contrast, the furan-catalyst (*R,R*)-5 is less effective at the ATH of *ortho*-substituted aryl substituted substrates; the reduction of the *ortho*-chlorophenyl substrate gave no product **12**, and the *ortho*-methyl/methoxyphenyl imines gave products **17** and **19** respectively in low yield although in good-excellent ee. Hence there is a clear complimentary (and mutually exclusive) pattern of selectivity between Noyori-Ikariya catalysts such as (*R,R*)-1, (*R,R*)-2 and the heterocycle-functionalised (*R,R*)-5. This may reflect the extra steric hindrance around catalyst (*R,R*)-5 which is less accommodating to a bulky 2-aryl substituent, however the formation of a racemic product using catalyst (*R,R*)-4 in the prototype substrate test indicates the importance of an additional involvement of the furan in the reaction transition state.

The study was also extended to a series of electron rich substrates and the simpler 1-methyl substrates, with the resulting THIQs (yields and ees) shown in Figure 7.

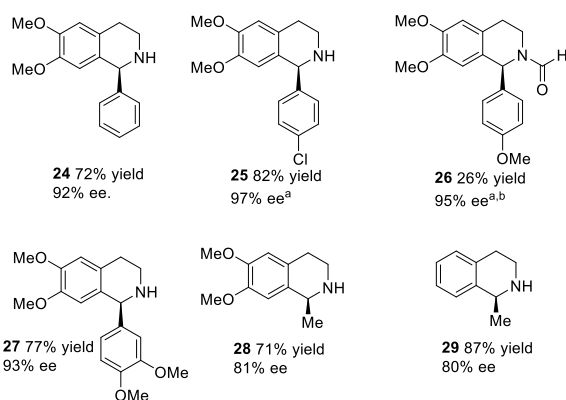


Figure 7. Products of ATH of electron-rich 1-aryl and 1-methyl DHIQs in this project, using catalyst (*R,R*)-5 and the conditions shown in Figure 5, o/n reaction time. a. First report of formation by ATH using arene/Ru/TsDPEN catalysts to our knowledge. b. formate formed.

As expected on the basis of previous literature reports,^{1,6,7} di-methoxy-substituted 1-aryl imines were reduced in high ee with (*R,R*)-5 and slightly higher than similar reported examples using catalyst (*R,R*)-1 (**24**; 84% ee, **27**; 75% ee),^{7b} however the difference was not as significant as for the electron-poor products in Figure 6. It should be noted that the imine precursor of **26** was fully reduced by TLC however the product was formed as a mixture of formylated (major) and non-formylated (minor) amines. In addition, we compared catalyst (*R,R*)-5 with the reported results for formation of the methyl-substituted prod-

ucts **28** and **29** and the products were formed in 81 and 80% ee respectively; slightly lower ee than have already been reported using (*R,R*)-1 and (*R,R*)-2 as ATH catalysts (Figure 1).^{1,2,3,6}

It is not clear exactly how the modified catalyst (*R,R*)-5 controls the asymmetric reduction in these cases. However the control of the enantioselectivity of the reduction is believed to involve a transition state in which the protonated iminium ion forms a H-bond to the SO₂ of the tosylate group whilst a known η^6 /CH interaction also operates to stabilise the transition state (Figure 8A),³ which is analogous to the control of ketone reductions with this class of catalyst.¹⁴ However the selectivity is likely to be low because transition state (ts) for reduction to either enantiomer can be stabilised by similar interactions. The additional furan group (in (*R,R*)-5) may engage in an interaction which serves to stabilise the ts leading to the observed major enantiomer (Figure 8B). The lack of selectivity observed with catalyst (*R,R*)-4 suggests that this is an electronic effect involving the heteroatom rather than a simpler steric or π -stacking effect. Conversely, the additional steric hindrance in (*R,R*)-5 results in slower reduction (and hence incomplete conversions) for more hindered substrates i.e. containing *ortho*-substituted aryl groups.

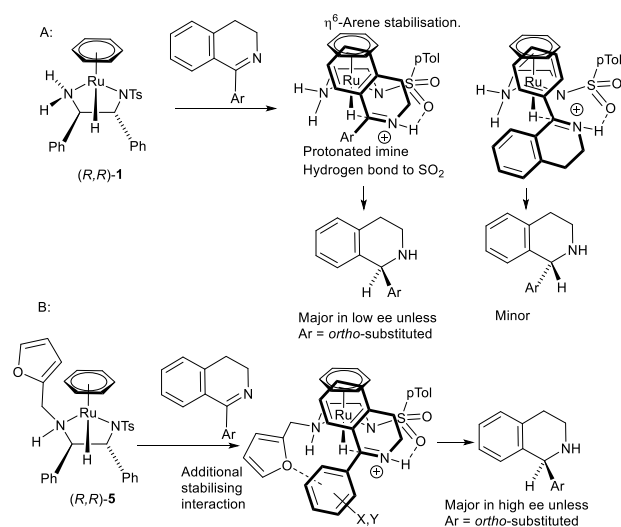


Figure 8. A. established mode of reduction of protonated imine cation using known catalyst (*R,R*)-1. **B.** proposed mode of reduction with additional stabilising interaction between the furan in catalyst (*R,R*)-5 and the 1-aryl ring in the substrate.

Conclusions

In conclusion, we have demonstrated that the addition of a heterocyclic group to the basic nitrogen atom of the TsDPEN ligand in an arene/Ru/TsDPEN ATH complex renders it an excellent catalyst for the reduction of a previously very challenging class of DHIQ substrate for this application. The value of the methodology is highlighted by the formation of products **9** and **21**, which are precursors of pharmaceutical target molecules (Figure 5). The mode of action remains to be fully understood but the presence of a heterocycle is important; replacement with a benzyl group does not have a beneficial effect.

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Conflict of interest

Author Y. Xu is founder and CEO of GoldenKeys High-tech Materials Co., Ltd.

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 free of charge on the ACS Publications website: NMR spectra and HPLC spectra relating to ee and dr determination are available as Supporting Information.

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