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Asymmetric Transfer Hydrogenation of Unhindered and Non-Electron-Rich 1-Aryl Dihydroisoquinolines with High Enantioselectivity

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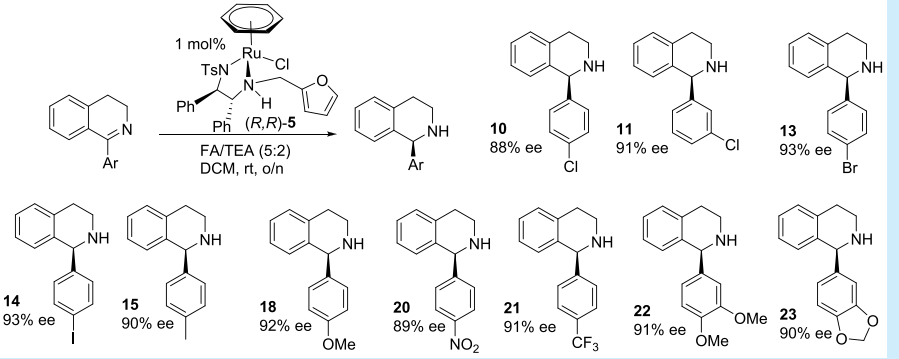

ABSTRACT: The use of arene/Ru/TsDPEN catalysts bearing a heterocyclic group on the TsDPEN in the asymmetric transfer hydrogenation (ATH) of dihydroisoquinolines (DHIQs) containing *meta*- or *para*-substituted aromatic groups at the 1-position results in the formation of products of high enantiomeric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

Since the first report by Noyori et al. in 1996[1] of the asymmetric transfer hydrogenation (ATH)[2] of one-substituted 3,4-dihydroisoquinolines (DHIQs) **1** to form asymmetric tetrahydroisoquinolines (THIQs) **2** (Figure 1)

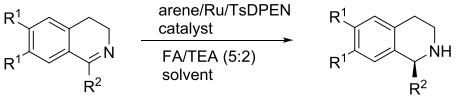

Figure 1. Dihydroisoquinoline (DHIQ) reduction by ATH with arene/Ru/TsDPEN complexes **1**–**4** (Figures 2 and 3).

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 the *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 that give products with high enantioselectivities (ee's) (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 be consistently reduced to products with high ee only if there is an ortho substituent on the

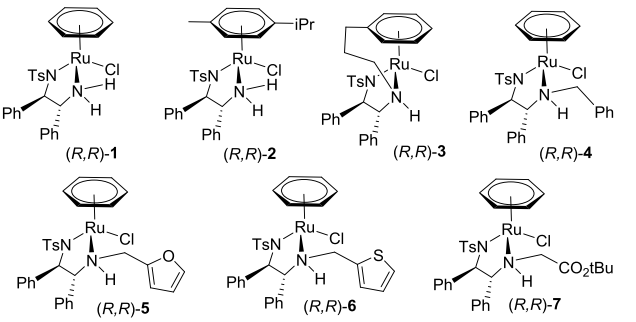

Figure 2. Catalysts employed in the ATH of DHIQs: **1**–**4**, known catalysts for this application; **5**–**7**, complexes reported in this paper.

aromatic ring at the one-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.

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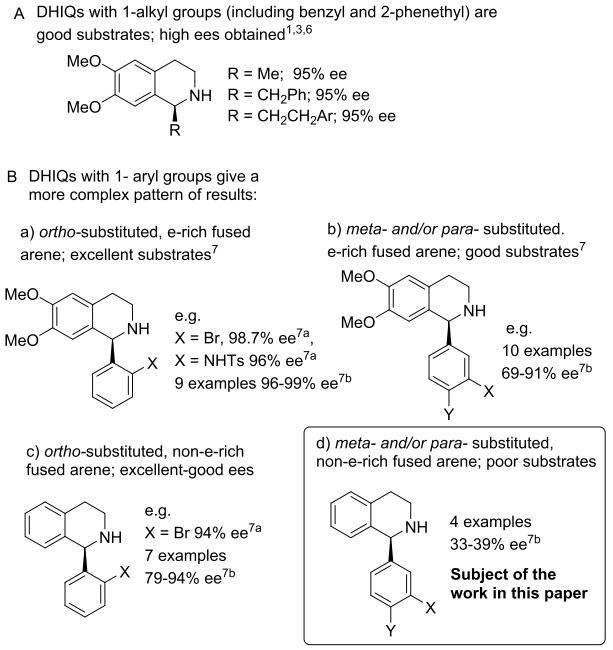

Figure 3. Summary of the state-of-the-art of DHIQ ATH using arene/Ru/TsDPEN catalysts (*R*,*R*)-**1** and (*R*,*R*)-**2** and closely related derivatives. Dihydroisoquinoline (DHIQ) reduction products are illustrated.

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 with 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 with 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

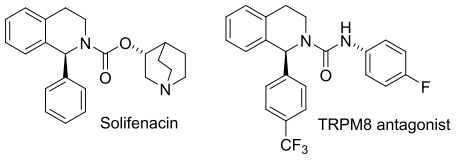

Figure 4. Structure of solifenacin, a muscarine acetylcholine receptor antagonist, and a recently reported TRPM8 antagonist that formed the basis for further optimizations.

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 Letter, 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.

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/electron-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 with a higher enantioselectivity than that with any other arene/Ru/TsDPEN ATH catalysts that we are aware of.

In our initial tests, we used catalyst (*R*,*R*)-**5** in the reduction of the parent 1-phenyl-DHIQ **8** in a formic acid 5:2 azeotrope (FA/TEA) alongside a range of catalysts (Figure 5, Table 1).

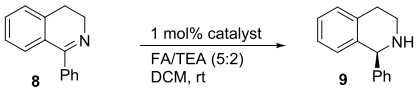

Figure 5. Asymmetric reduction of DHIQ **8** (Table 1).

Table 1. ATH of 2-Phenyl DHIQ 8[a]

entry	catalyst	*t* (h)	conv (%)	ee (%)
1	(*R*,*R*)-**1**	48	45	24
2	(*R*,*R*)-**2**	48	11	42
3	(*R*,*R*)-**3**	16	97	10
4	(*R*,*R*)-**5**	24	93	90[b]
5	(*R*,*R*)-**5**[c]	24	90	90
7	(*R*,*R*)-**6**	48	86	91
8	(*R*,*R*)-**7**	96	77	49
9	(*R*,*R*)-**4**	72	12	0

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

Because its ATH using catalyst (*R*,*R*)-**1** had been reported to give product **9** with only 29% ee (90% yield),[7b] this was felt to have obvious scope for improvement. To eliminate the significant effect of the solvent (we have preciously 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 with only 24% ee and 45% conversion. Using the cymene derivative (*R*,*R*)-**2**, product **9** was formed with only 11% conversion and 42% ee, and with tethered catalyst (*R*,*R*)-**3**, the result was worse, with a product formed with only 10% ee (although with a conversion of 97%). With furan-containing catalyst (*R*,*R*)-**5**, however, reduction to THIQ **9** was achieved with an impressive 90% ee (93% conversion and 70% isolated yield), and the enantioselectivity was unchanged in DCM and MeCN solvents. Catalyst (*R*,*R*)-**6**, bearing a thiophene ring, gave a reduction product with 91% ee but just 86% conversion after the same 48 h of reaction time, whereas ester-containing catalyst (*R*,*R*)-**7** gave a product with just 77% conversion (in 96 h) and 49% ee. Significantly, the reduction using the *N*′-benzyl-functionalized catalyst (*R*,*R*)-**4** gave a racemic product with just 12% conversion, highlighting the remarkable effect of the *heterocyclic* ring on the reduction selectivity.

Having made this unexpected observation, we tested the reductions of a further series of non-electron-rich DHIQs using catalyst (*R*,*R*)-**5** and obtained the products illustrated in Figure 6. It was found that para- and meta-substituted products were consistently formed with high ee, typically 90% or greater, and,

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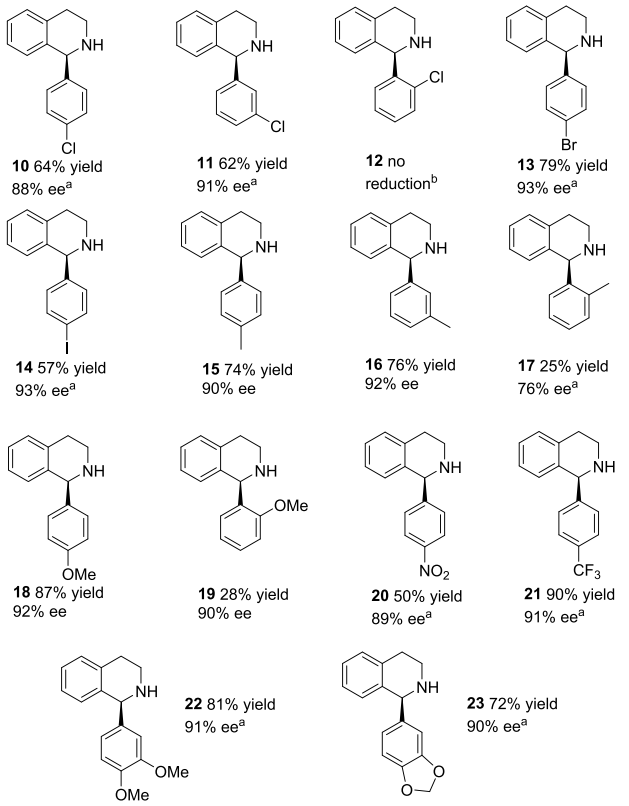

Figure 6. Products from non-electron-rich DHIQ reduction obtained in this project using catalyst (*R*,*R*)-**5** and the conditions shown in Figure 5 (overnight reaction time). Configurations were assigned by analogy to **9** (Table 1). [a]First report, to our knowledge, of the formation by ATH using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

where comparable, with higher ee than that 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 with 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, -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 also carried out on a 1.1 g (5 mmol) scale and gave a product with 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/methyloxyphenyl imines gave products **17** and **19**, respectively, in low yield, although with excellent ee. Hence there is a clear complementary (and mutually exclusive) pattern of selectivity between Noyori−Ikariya catalysts such as (*R*,*R*)-**1** and (*R*,*R*)-**2** and the heterocycle-functionalized (*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 the 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 ee's) shown in Figure 7.

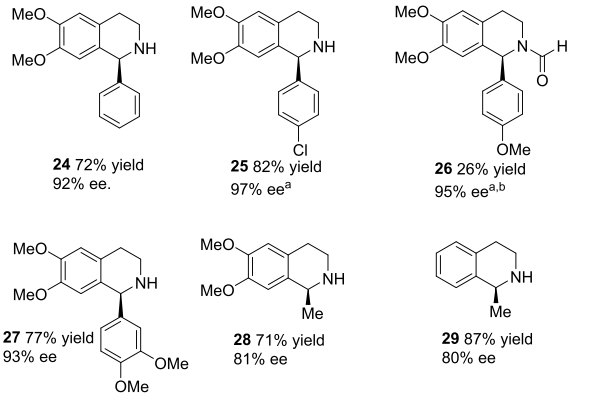

Figure 7. Products of the ATH of electron-rich 1-aryl and 1-methyl DHIQs in this project using catalyst (*R*,*R*)-**5** and the conditions shown in Figure 5 (overnight reaction time). [a]First report, to our knowledge, of the formation by ATH using arene/Ru/TsDPEN catalysts. [b]Formate formed.

As expected on the basis of previous literature reports,[1,6,7] dimethoxy-substituted 1-aryl imines were reduced with high ee with (*R*,*R*)-**5**, 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 that for the electron-poor products in Figure 6. It should be noted that the imine precursor of **26** was fully reduced; however, the product was formed as a mixture of formylated (major) and nonformylated (minor) amines. In addition, we compared catalyst (*R*,*R*)-**5** with the reported results for the formation of the methyl-substituted products **28** and **29**, and the products were formed with 81 and 80% ee, respectively; slightly lower ee values than have already been reported using (*R*,*R*)-**1** and (*R*,*R*)-**2** as ATH catalysts (Figure 1).[1−3,6]

It is not exactly clear 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 SO_2 of the tosyl group while a known η^6/CH interaction also operates to stabilize 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 the transitions state (ts) for the reduction to either enantiomer can be stabilized by similar interactions. The additional furan group (in (*R*,*R*)-**5**) may engage in an interaction that serves to stabilize 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, that is, those containing ortho-substituted aryl groups.

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

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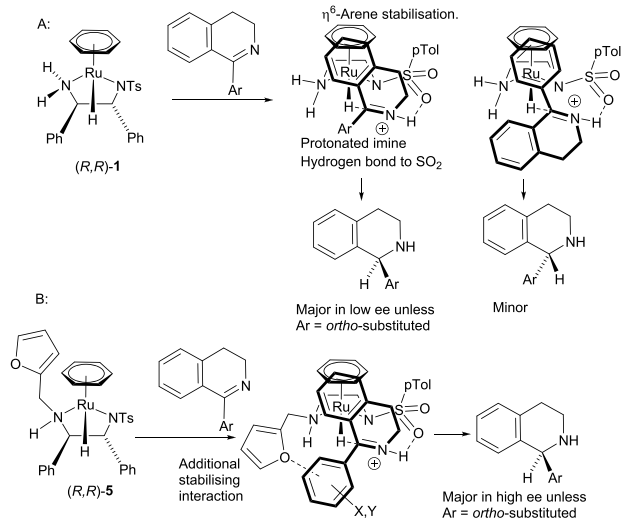

Figure 8. (A) Established mode of the reduction of the protonated imine cation using the known catalyst (*R*,*R*)-**1**. (B) Proposed mode of reduction with additional stabilizing interactions between the furan in catalyst (*R*,*R*)-**5** and the 1-aryl ring in the substrate.

important; replacement with a benzyl group does not have a beneficial effect.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02034.

NMR spectra and HPLC spectra relating to ee and dr determination (PDF)

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Notes

The authors declare the following competing financial interest(s): Y.X. is the founder and CEO of GoldenKeys High-tech Materials Co., Ltd.

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

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