Asymmetric transfer hydrogenation of aryl heteroaryl ketones using Noyori-Ikariya catalysts

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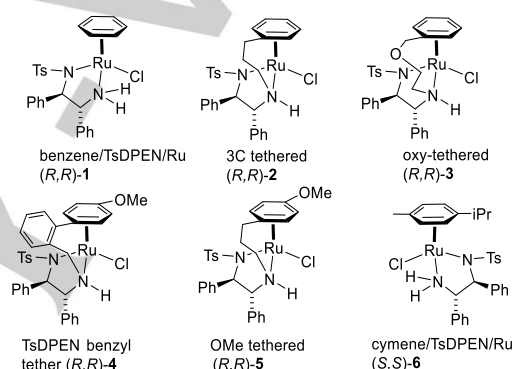
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Abstract: A range of ketones flanked by a combination of an aromatic and a heterocyclic ring (furan, thiophene, *N*-methylimidazole) were reduced under asymmetric transfer hydrogenation (ATH) conditions. Using a range of [(arene)Ru(TsDPEN)Cl] precatalysts, including tethered derivatives, the reduction enantioselectivity was high (up to 99% ee) in cases where the aromatic ring contained an *ortho*-substituent. The enantioselectivity is influenced by a combination of steric and electronic factors which for the furan and thiophene series, follow literature precedents. In the case of the *N*-methylimidazole-containing ketones, an unexpected switch in enantioselectivity took place upon variation of the opposing aromatic group. Pyrrole-containing ketones were resistant to reduction. This study demonstrates the asymmetric transfer hydrogenation (ATH) of a range of hindered heterocyclic ketones, in high conversion and ee, using Noyori-Ikariya catalysts.
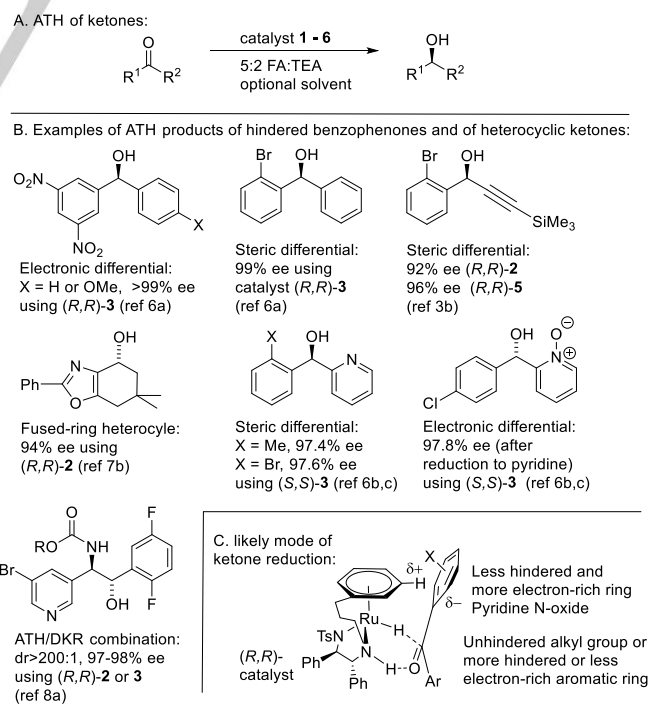
Introduction

Asymmetric transfer hydrogenation (ATH) of ketones, using formic acid / triethylamine azeotrope (FA:TEA, 5:2) provides an efficient route for the enantioselective synthesis of alcohols.[1-6] Numerous ketone reduction applications using ATH with ruthenium-based Noyori-Ikariya type catalysts such as **1** – **6** (Figure 1) have been published in recent years. Acetophenone derivatives,[2] propargylic ketones[3] and perfluorinated ketones[4] are well suited to ATH using Noyori-Ikariya catalysts and have provided the basis for numerous successful ATH studies, as has dynamic kinetic resolution (DKR) coupled with ATH.[4c,5] However it would be desirable to continue to expand the methodology to a wider range of substrates, including what might traditionally be considered to be challenging ketones for ATH. In the case of benzophenones, which have similar groups flanking the ketone, significant electronic differences between substituents can improve the reduction enantioselectivity, as can differences in steric hindrance (Figure 2).[6] The use of substrates containing an *ortho*-substituted aromatic ring adjacent to the ketone to facilitate enantioselective reduction has also been applied to propargylic ketones.[3b] There have been relatively few reports on the asymmetric reductions of analogous heteroaromatic ketones, despite the known compatibility of heteroaromatics with ATH conditions,[6b,6c,7] including DKR-ATH applications (Figure 2).[8] The application of ATH to the reduction of pyridine and pyridine *N*-oxide analogues of benzophenones by Zhou *et al* represents an

excellent example of where highly enantioselective reduction can be achieved (Figure 2) by applying the desirable design features to the substrates.[6]

Figure 1. [(arene)Ru(TsDPEN)Cl] complexes for ATH of ketones.


Figure 2. A. reduction of ketones by ATH using formic acid/triethylamine. B. Reduction products of benzophenones and heterocyclic ketones using ((*R,R*)-configuration catalysts) catalysts **1** - **6**. Electronic or steric differences between

the substituents facilitate high asymmetric induction. C. Likely mode of hydrogen transfer illustrated for (*R,R*)-configuration catalyst. (*S,S*)-Configuration catalyst will give the opposite absolute configuration product but *via* the same directing effects.

Whilst the factors which control the sense of ATH reductions are known to be complex,[9] for the examples illustrated the model in Figure 2C serves to summarise the likely approach of substrate to catalyst in the key hydride-transfer step.[6,7] Other catalyst systems have also been applied to the successful asymmetric reduction of benzophenones and their heterocyclic derivatives.[10] Apart from the examples which have been reported, the ATH of substrates containing a combination of heterocyclic and aromatic groups is relatively under-explored to date.

Results and Discussion

Given the lack of information on the ATH of ketones containing a combination of aromatic and heterocyclic groups flanking the ketone, we undertook a study on a systematic group of substrates (Figure 3).
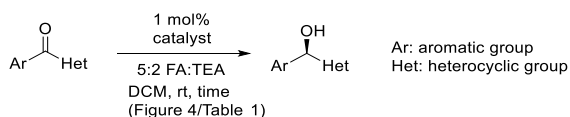

Figure 3. ATH reactions which were investigated in this study.

As well as investigating the effect of substrate structure, we also took the opportunity to compare the activity and selectivity of a number of ATH catalysts. Therefore we focussed on the use of the '3C-tethered' **2**,[1] 'benzyl-linked' **4**,[1b] 'OMe-substituted' **5**[1b] and the untethered catalyst **6**.[1] The (*R,R*)- form of the catalysts **2**, **4** and **5** were used, however the (*S,S*)- enantiomer of **6** was employed. As substrates, we selected ketones where Ar = Ph, *o*-(MeO)C$_6$H$_4$ (oOMe), *o*-(Me)C$_6$H$_4$ (oMe), *o*-(Br)C$_6$H$_4$ (oBr), *o*-(Br)C$_6$H$_4$ (oCl) and α-naphthyl (Np) versus Het = 2-furyl (Fu), 2-thienyl (Thio), 2-*N*-methylimidazole (Im) and 2-*N*-methylpyrrole (PyMe) (Figure 4), these being designed to test the effect of aromatic ring size and heterocycle type across a range of substrates. The ketones were prepared either by the addition of a Grignard reagent to the corresponding aldehyde followed by oxidation or by acylation of N–methylimidazole (Supporting Information). Products **7** – **19**, formed from the ATH reactions are shown in Figure 4 (for reductions with (*R,R*(-**2**) / Table 1 (for reductions with other catalysts). Conversion and ee vs time graphs for several reductions are given in the Supporting Information. Reactions were consistently carried out at loadings of 1 mol% catalyst in FA:TEA (5:2 azeotropic mixture) as the hydrogen source and DCM (due to the limited solubility of the substrates in pure FA/TEA), at room temperature.

Substrates containing furan, thiophene and methylimidazole groups were all reduced with one or more of the catalysts however there was a significant variation in both the activity and the enantioselectivity. The 3C tethered complex (*R,R*)-**2** proved to be the most enantioselective catalyst for most substrates, also delivering products in almost quantitative conversions at rt in most cases. This catalyst was therefore used as for reduction of each substrate we tested, to provide a comparison of activity and enantioselectivity between substrates.

The more electron-rich OMe-substituted catalyst (*R,R*)-**5** was much less active and the benzyl-tethered (*R,R*)-**4** was of intermediate activity. All tethered catalysts were more active or comparable to the non-tethered catalyst (*S,S*)-**6**, which gave products of opposite configuration to the other catalysts, i.e. indicating that a common mechanism is operating between all catalysts.[1] The pyrrole-containing substrate **20** was not reduced by any catalysts however, or even when 5 mol% of catalyst (*R,R*)-**2** was used. Ketone **21** (Figure 4), designed to be less electron rich, was also not reduced using (*R,R*)-**2**.
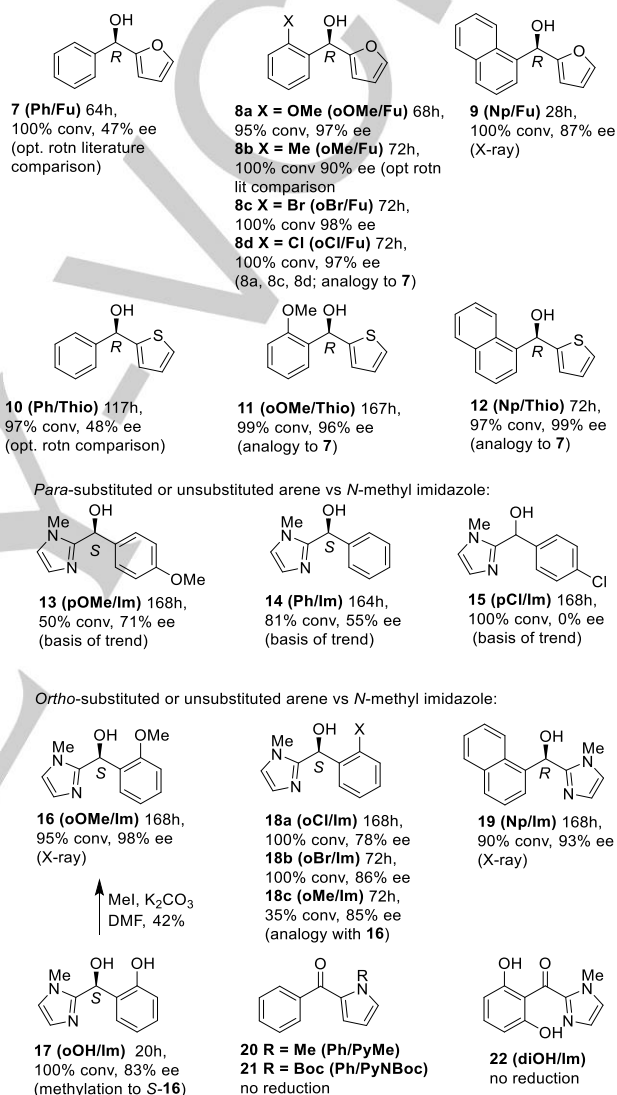
Figure 4. Products of ATH formed in this study using catalyst (*R,R*)-**2**, and ketones which were not reduced. Products have configuration either known or speculated to be formed. The method used for determination of the absolute configuration is given in brackets. Products are depicted with the group speculated to be closest to the catalyst η^6-arene ring during the hydrogen transfer (Figure 2C) on the right-hand side. Table 1 illustrates the results of reductions using alternative catalysts, where studied.

Table 1. ATH of aromatic/heterocyclic substrates; results not illustrated in Figure 4.*

ATH product	Catalyst	Temp./°C	time/h	Conv./%	ee/%
7 Ph/Fu [a]	(*R,R*)-**4**	rt	158	100	61 (*R*)
"	(*R,R*)-**5**	rt	120	100	27 (*R*)
"	(*S,S*)-**6**	rt	163	99	43 (*S*)
8a oOMe/Fu [c]	(*R,R*)-**4**	rt	164	99	89 (*R*)
"	(*R,R*)-**5**	rt	164	28	56 (*R*)
"	(*S,S*)-**6**	rt	159	58	88 (*S*)
9 Np/Fu [b][c]	(*R,R*)-**4**	rt	47	100	91 (*R*)
"	(*R,R*)-**5**	rt	76	27	31 (*R*)
"	(*S,S*)-**6**	rt	144	47	94 (*S*)
10 Ph/Thio [a]	(*R,R*)-**4**	rt	160	97	69 (*R*)
"	(*R,R*)-**5**	rt	187	39	25 (*R*)
"	(*S,S*)-**6**	rt	160	30	28 (*S*)
11 oOMe/Thio [c]	(*R,R*)-**4**	rt	186	62	88 (*R*)
"	(*R,R*)-**5**	rt	189	98	48 (*R*)
"	(*S,S*)-**6**	rt	217	37	89 (*S*)
12 Np/Thio [c]	(*R,R*)-**4**	rt	162	99	99 (*R*)
"	(*R,R*)-**5**	rt	165	0	-
"	(*S,S*)-**6**	rt	165	90	97 (*S*)
12 Np/Thio [c]	(*R,R*)-**2**	38	16	100	96 (*R*)
12 Np/Thio [c][e]	(*R,R*)-**2**	40	16	100	98 (*R*)
12 Np/Thio [c][f]	(*R,R*)-**2**	40	16	88	95 (*R*)
12 Np/Thio [c][e]	(*R,R*)-**2**	60	4	100	95 (*R*)
12 Np/Thio [c][f]	(*R,R*)-**2**	60	6	100	94 (*R*)
12 Np/Thio [c][e]	(*R,R*)-**4**	40	16	100	97 (*R*)
12 Np/Thio [c][e]	(*R,R*)-**5**	40	16	55	80 (*R*)
12 Np/Thio [c][e]	(*R,R*)-**6**	40	16	28	94 (*R*)
13 pOMe/Im [c]	(*S,S*)-**6**	rt	168	6	14 (*R*)
14 Ph/Im [c]	(*R,R*)-**4**	rt	165	30	50 (*S*)
"	(*R,R*)-**5**	rt	168	14	13 (*S*)
"	(*S,S*)-**6**	rt	168	6	48 (*R*)
15 pCl/Im [c]	(*S,S*)-**6**	rt	168	22	43 (*R*)
15 pCl/Im [c][e]	(*R,R*)-**2**	40	16	100	14 (*S*)
15 pCl/Im [c][e]	(*R,R*)-**6**	40	16	10	38 (*S*)
16 oOMe/Im [b][d]	(*R,R*)-**4**	rt	169	68	93 (*S*)
"	(*R,R*)-**5**	rt	168	61	91 (*S*)
"	(*S,S*)-**6**	rt	169	5	42 (*R*)
16 oOMe/Im [b][d][e]	(*R,R*)-**2**	40	16	100	57 (*S*)
18a oCl/Im [d]	(*S,S*)-**6**	rt	168	14	93 (*R*)
18c oMe/Im [d][e]	(*R,R*)-**2**	40	16	31	81 (*S*)
19 Np/Im [b][d]	(*R,R*)-**4**	rt	168	60	93 (*R*)
"	(*R,R*)-**5**	rt	168	26	85 (*R*)
"	(*S,S*)-**6**	rt	168	8	18 (*S*)
19 Np/Im [b][d][e]	(*R,R*)-**2**	40	16	98	89 (*R*)

*Reaction conditions are as given in Figure 3, at rt (ca. 20 °C) in FA/TEA/DCM unless otherwise stated. [a] Configuration confirmed by comparison of optical rotation to that reported. [b] Configuration established by X-ray crystallography. [c] reported in racemic form/configuration not previously established. [d] novel [e] reaction in FA/TEA alone. [f] reaction in 1,2-dichloroethane (DCE).

In the following discussion, the focus will be on the results from the use of (*R,R*)-**2**, with others described if they gave superior results. Taking the reductions of the furan- and thiophene- containing substrates first, the configuration (*R*) of the products **7 (Ph/Fu)** and **10** (**Ph/Thio**) (Figure 4) were assigned by comparison of the sign of their optical rotations with those previously reported. Based on the model for ATH reductions with this class of catalyst (Figure 2C and Figure 7),

this suggests a slight preference for the furan or thiophene to adopt the position proximal to the η⁶-arene in the complex. Introduction of an *ortho*-methoxy group to the aromatic ring in the substrate provided a route to products **8a (oOMe/Fu)** and **11 (oOMe/Thio)** in higher ees of 97% and 96% respectively. Although the configurations could not be proven unambiguously, we tentatively assign *R*- configuration to these products by analogy with the non-methoxylated products and would suggest that the higher ee arises from increased hindrance placing the aromatic ring in the position distal from the η⁶-arene, i.e. following on from previous observations (Figure 2C).[5,6] The structurally-related products **8b-8d** were also formed in very high ee (90-98% ee), indicating a useful level of generality. Continuing this trend and using catalyst (*R,R*)-**2**, products **9** (**Np/Fu**) and **12** (**Np/Thio**) were also formed in excellent ees of 87% and 99% respectively. The absolute configuration of the major **9** (**Np/Fu**) product was confirmed by X-ray crystallographic analysis (Figure 6A) and that of **12** (**Np/Thio**) was assigned by analogy with this. Again, these results fit the accepted model for hydrogen transfer (Figure 7A), with more hindered substrates giving products of highest ee. The sense of reduction for the furan and thiophene-containing substrates aligns with that reported in precedents (Figure 2) which the more electron-rich heterocycle adopts the position adjacent to the η⁶-arene of the catalyst as illustrated in Figure 7A and 7B. For the 1-Np products **9** and **12**, there is precedent in the reported ATH of PhCO(1-Np) using a closely-related *ansa*-Ru sulfamoyl-(S,S)-DPEN catalyst (Figure 7E).[2e] In this example, the Np ring adopts the position distal to the η⁶-arene of the catalyst. This is in contrast to the reduction mode of 1-acetylnapthylene (Figure 7F) in which the Np ring occupies the expected position adjacent to the η⁶-arene of the catalyst during the reduction. Notably, catalyst (*R,R*)-**4** gave **7 (Ph/Fu)** and **9 (Np/Fu)** in slightly higher 61% ee and 91% ee respectively, and full conversion. Catalyst (*S,S*)-**6** gave **9 (Np/Fu)** in 94% ee, which was the highest for this product, but only 47% yield. Surprisingly, catalyst (*R,R*)-**5** did not give any **12 (Np/Thio)**, possibly due to a specific destabilising effect involving the methoxy substituent. However the catalyst proved to be effective at slightly elevated temperature (see below).

Although the reductions of **7-12** proceeded to complete or almost complete conversion, we investigated the formation of **12** (Np/Thio), as a representative substrate, at slightly elevated temperature. ATH reactions at temperatures of 40 and 60 °C have been reported to proceed successfully with minimal loss of enantioselectivity.[1-6] Using catalyst (*R,R*)-**2**, using the standard reaction conditions at 38 °C led to full reduction in 16h, as did the reduction at 40 °C in only FA/TEA. Using DCE as a solvent at 40 °C gave 88% conversion after 16h. In these cases, the products were formed in 96, 98 and 95% ee respectively, i.e. slightly lower than at rt. At a higher temperature of 60 °C, in FA/TEA alone, 100% reduction was achieved in 4h (95% ee) and in 6h when DCE was used as cosolvent at 60 °C (94% ee). Extending the 40 °C, cosolvent-free conditions to the other catalysts gave, in 16h, full conversion (97% ee) using **4**, 55% conversion (80% ee) with **5** and 28% conversion (94% ee) with **6**. The result with **5** was particularly significant as the rt reaction had given no conversion, even over an extended reaction time, for this sluggish substrate/catalyst combination. Hence, slightly higher temperatures can accelerate the reactions, with slight

loss of enantioselectivity, and hence the conditions can be selected for optimisation of rate or ee.

The pattern of results for the methylimidazole series was more complicated. Three alcohols (**13-15**), containing a *para*-substituted or unsubstituted aromatic ring, were formed in 0% - 70% ee. Since the more electron-rich (OMe substituted) substrate gave the highest ee product, and the electron-poor (Cl substituted) the lowest, it is speculated that *S*- configuration products were formed, via an approach of substrate to catalyst in which the aromatic group is proximal to the η^6-arene of the catalyst (Figure 7C). Catalyst (*S,S*)-**6** gave **15 (pCl/Im)** in an improved ee of 43% but just 22% conversion. The racemic reduction using catalyst **2** at rt was improved at 40 °C in FA/TEA alone; 100% conversion in 16h but still only 14% ee, In this case, catalyst **6** gave just 10% conversion in 16h at 40 °C vs 22% at 168h at rt. *ortho*-Methoxyphenyl-substituted product **16 (oOMe/Im)** was formed in a very high ee of 98% at rt, and *S*-configuration, as confirmed by X-ray crystal structure analysis (Figure 6B). At 40 °C, full conversion was obtained in 16h but in just 57% ee, representing a sharp drop relative to the rt reaction. This was also supported by the formation of *S*-**17 (oOH/Im)** under the same conditions, which, upon methylation was converted to *S*-**16 (oOMe/Im)**. It has been demonstrated that *ortho*-hydroxyphenyl groups have a strong propensity to occupy the position near the catalyst η^6-arene during ketone reduction (Figure 2C),[11] and the same selectivity is likely operating here. In contrast, ATH of substrate **22** containing two *ortho*-hydroxy groups failed (Figure 4). Products **18a-18c,** containing *ortho*-chloro, bromo and methyl groups respectively, were also formed in high ee (78%, 85%, 85% respectively) and were tentatively assigned *S* configuration by analogy with **16 (oOMe/Im)**. The ee of **18c (oMe/Im)** dropped slightly, to 81%, but with 100% conversion in 16h, at 40 °C. Product **19 (Np/Im)**, was formed in 93% ee at rt (90% conv in 168h) and this dropped slightly to 89% ee when the reaction was run in FA/TEA at 40 °C (98% conversion in 16h), However its X-ray crystal structure revealed an unexpected switch to the *R*-configuration (Figure 6C). This suggests that the *N*-methylimidazole group occupies the position near the η^6-arene of the catalyst during the reduction (Figure 7D). Hence, how to explain the apparent switch in selectivity? The *N*-methyl imidazole is likely to be protonated under the mildly acidic reaction conditions; attempted ATH to form **16 (oOMe/Im)** under neutral conditions in iPrOH/KOH gave no product formation. In addition, the *N*-methyl substituent will create further steric hindrance which may favour its positioning as indicated in Figure 7C for the formation of **13, 14, 16, 17, 18a-18c** and **17**. However the bulkier Np structure may overwhelm this preference when **19** is formed, as observed for the reduction of PhCO(1-Np) (Figure 7E).[2e] It would appear that the Ph ring opposing the 1-Np group prevents this substrate from adopting a conformation which allows the 1-Np to adopt the position observed for less-hindered substrates (Figure 7F). In the reduction to form **19**, we hypothesise that the protonated methylimidazole, whilst likely to be less electron-rich, controls the conformation of the substrate in a similar manner and this leads to an analogous directing effect (Figure 7D). It is also noteworthy that the ees were moderated by other catalysts, indicating that some important, and more subtle, secondary control factors also influence the reduction enantioselectivity.

An X-ray crystallographic structure of the ketone precursor of **12 (Np/Thio)** revealed the naphthyl ring to be out of plane

with the carbonyl group (Figure 6D). This would be in accordance with the general suggestion that bulky aromatic groups create a high level of steric hindrance which favours their positioning distal to the η^6-arene in most cases (Figure 2).
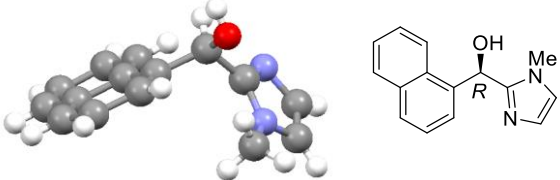
A. X-ray structure of 9 (Np/Fu), CCDC 2071155
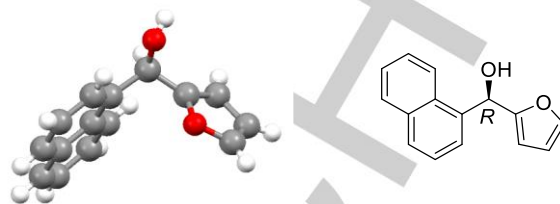
B. X-ray structure of 16 (oOMe/Im), CCDC 2071157.
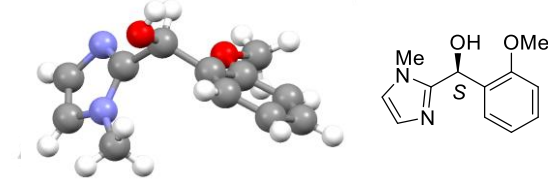
C. X-ray structure of 19 (Np/Im), CCDC 2071158.

D. Np/Thio ketone precursor. CCDC 2071156.
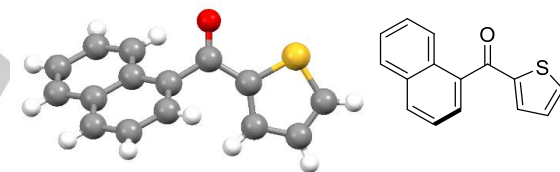
Figure 6. X-ray crystal structures of major enantiomer of alcohols formed by reduction with (*R,R*)-catalyst and one ketone precursor.

Proposed favoured modes of hydrogen transfer:

A. Proposed Ar/Fu and Ar/Thio reduction
B. Proposed Ar/Fu and Ar/Thio reduction
C. Proposed 'default' Ar/Im reduction

Relevant literature precedents[2e]:

D. Proposed Np/Im reduction
E. Reduction of PhCO(1-Np)
F. Reduction of MeCO(1-Np)
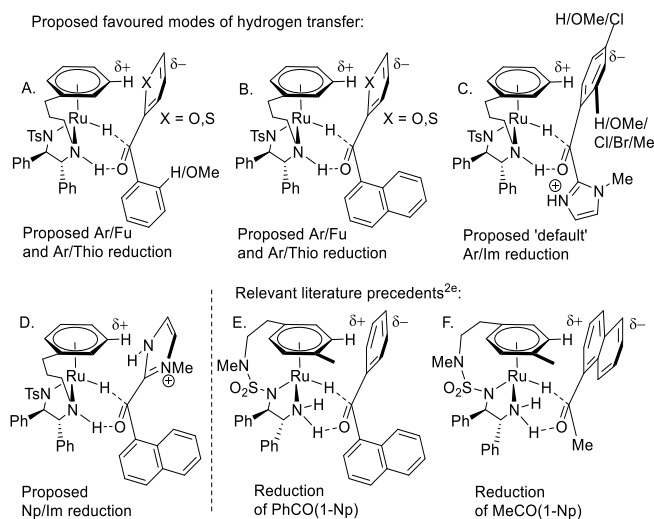
Figure 7. Reduction modes using catalyst (*R,R*)-**2**; A, B. Furan/thiophene generally adopts the position adjacent to the η^6-arene group. C, D. The *N*-

methylimidazole series exhibits a more complex balance of selectivities depending on the nature of the aromatic group on the opposing side of the ketone. E,F. favoured modes of reduction of related 1-Np ketones. In the original paper, the (*S,S*)-catalyst was employed however the sense of reduction using the (*R,R*)-catalyst is illustrated for ease of comparison.[2e]

Conclusion

In conclusion, a series of hindered ketones flanked by a combination of aromatic and heterocyclic groups have been reduced efficiently by ATH using Ru(II) Noyori-Ikariya type catalysts. In the case of furan and thiophene-containing substrates, the products follow a selectivity which has been established in previous studies in this area, for related ketones. The ATH of *N*-methylimidazole-containing ketones, where the heterocyclic group is likely protonated under the reaction conditions, follows a more complex pattern of selectivity. This is speculated to be due to a closer balance of steric and electronic control factors, although most products were formed in good-excellent ee. The heterocyclic alcohol products are of interest and value to the asymmetric synthesis of challenging heterocyclic targets, notably pharmaceutical molecules. The formation of number of novel alcohols which may otherwise be challenging to prepare, are reported, using a practical and accessible catalyst system.

Experimental Section

General experimental details.

Reagents and solvents were used as purchased and without further purification. Reactions were carried out under a nitrogen atmosphere unless otherwise specified. Reactions at elevated temperature were maintained by thermostatically controlled oil-baths or aluminium heating blocks. A temperature of 0 °C refers to an ice slush bath, -78 °C to a dry ice acetone bath. NMR spectra were recorded on a Bruker AV (250 MHz), Bruker DPX (300 or 400MHz) or Bruker DRX (500 MHz). Chemical shifts are rounded to the nearest 0.01 ppm for ^{1}H spectra and the nearest 0.1 ppm for ^{13}C spectra and are referenced to the solvent chemical shift. Coupling constants are rounded to the nearest 0.1 Hz. Mass spectra were recorded on an Esquire 2000 and high-resolution mass spectra were recorded on a Bruker Micro ToF or MaXis. IR spectra were recorded on a PerkinElmer spectrum100 and peaks are reported in wavenumbers. Optical rotations were measured on an Optical Activity Ltd. AA-1000 Polarimeter and are reported in deg dm^{-1} cm^3 g^{-1}. The chiral GC measurements were performed using a Hewlett-Packard 1050 instrument linked to a PC running DataApex Clarity software. HPLC measurements were performed out using a Hewlett Packard 1050 Series with a quaternary pump, autosampler and variable wavelength detector linked to a PC running DataApex Clarity software. Melting points were determined on a Stuart scientific melting point apparatus and are uncorrected. Flash column chromatography was performed using silica gel of 230-400 mesh size. Thin layer chromatography was carried out on aluminium backed silica gel 60(F254) plates, visualised using 254nm UV light, potassium permanganate or cerium ammonium molybdate (CAM). Column chromatography was performed either by gradient elution (reported as a range, eg EtOAc/Petroleum ether (2-12%), or by isocratic elution.

Furan-2-yl(phenyl)methanone. This compound has been reported and fully characterized.[12] To a solution of furan-2-yl(phenyl)methanol **7** (424 mg, 2.44 mmol) in DCM (10 mL) at rt was added manganese dioxide

(3.18 g, 36.6 mmol). The reaction mixture was left to stir under a nitrogen atmosphere overnight. TLC (9:1 hexane: EtOAc) after this time indicated full conversion. The solids were removed by gravity filtration and washed with DCM. The combined solvent was removed to give the product as a yellow oil (369 mg, 2.15 mmol, 88%). TLC: Rf ca 0.30 (9:1 hexane: EtOAc), strong UV and KMnO$_4$; ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.97 (d, $^3J_{H,H}$=7.3 Hz, 2H; Ar-H), 7.71 (s, 1H; Ar-H), 7.59 (t, $^3J_{H,H}$=7.4 Hz, 1H; Ar-H), 7.49 (t, $^3J_{H,H}$=7.7 Hz, 2H; Ar-H + C$_4$H$_3$O), 7.23 (d, $^3J_{H,H}$=3.5 Hz, 1H; C$_4$H$_3$O), 6.60-6.59 ppm (m, 1H; C$_4$H$_3$O); ^{13}C NMR (125 MHz, CDCl$_3$): δ=182.60 (C), 152.31 (C), 147.14 (CH), 137.28 (C), 132.60 (CH), 129.30 (CH), 128.44 (CH), 120.59 (CH), 112.23 ppm (CH). Data matched that reported.

Furan-2-yl(phenyl)methanol 7 (Ph/Fu). This compound has been reported and fully characterized.[13,14] Furan-2-carbaldehyde (250 mg, 2.60 mmol) was added to a flask, followed by THF (2.5 mL) and the flask was placed into an ice bath and cooled to 0°C, with stirring under a nitrogen atmosphere. Phenyl magnesium bromide (0.950 ml, 3.0 M in diethyl ether, 2.85 mmol) was added dropwise and the reaction was stirred under the nitrogen atmosphere at rt overnight. The reaction was followed by TLC (9:1 hexane: EtOAc). After 17 hours, the reaction was quenched by the addition of distilled water (20 mL), extracted with EtOAc (3 × 20 ml), and the organic extracts were dried with MgSO$_4$. The solvent was removed under vacuum to give the product as a yellow oil (423 mg, 2.43 mmol, 92%). TLC: Rf ca 0.20 (9:1 hexane: EtOAc), strong UV and KMnO$_4$; ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.45-7.33 (m, 6H; Ar-H + C$_4$H$_3$O), 6.32 (dd, $^3J_{H,H}$=3.0 Hz, 1.5 Hz, 1H; C$_4$H$_3$O), 6.12 (d, $^3J_{H,H}$=3.0 Hz, 1H; C$_4$H$_3$O), 5.84 (d, $^3J_{H,H}$=4.0 Hz, 1H; Ar*CH*OH), 2.40 ppm (d, $^3J_{H,H}$=4.0 Hz, 1H; OH); ^{13}C NMR (125 MHz, CDCl$_3$): δ=155.94 (C), 142.59 (CH), 140.80 (C), 128.50 (CH), 128.11 (CH), 126.61 (CH), 110.25 (CH), 107.47 (CH), 70.17 ppm (CH). Data matched that reported. The enantiomeric excess and conversion were determined by HPLC analysis (Chiralcel ODH, 30 cm x 6mm column, hexane:iPrOH 97:3, 1.0 mL/min, T = 25°C) ketone 12.7 min, *S* isomer 25.5 min, *R* isomer 29.7 min ((*S,S*)-Noyori Ru(II)-TsDPEN catalyst), or *S* isomer 33.1 min , *R* isomer 40.1 min ((*R,R*)-benzyl-tethered Ru(II)-TsDPEN catalyst), or *S* isomer 29.6 min, *R* isomer 34.7 min ((*R,R*)-3C-tethered, 4-methoxy-Ru(II)-TsDPEN catalyst and (*R,R*)-3C-tethered Ru(II)-TsDPEN catalyst).

ATH of furan-2-yl(phenyl)methanone: Catalyst (0.00233 mmol, 1.0 mol%) was added to FA: TEA (5:2 azeotropic mixture, 0.18 mL) at rt and the mixture was stirred at rt under a nitrogen atmosphere for 10-15 minutes; after which a solution of furan-2-yl(phenyl)methanone (40 mg, 0.233 mmol) in DCM (0.25 mL) was added, and the reaction mixture was stirred at rt, followed by TLC (9:1 hexane: EtOAc). After 64 hours, the reaction was quenched by saturated NaHCO$_3$ solution (20 mL). EtOAc (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried (MgSO$_4$) and filtered. The solvent was removed under vacuum to give the crude product. The product was isolated via flash chromatography on silica eluted with 0-20% EtOAc in hexane to give furan-2-yl(phenyl)methanol **7** (13.9 mg, 0.080 mmol, 34%; (*R,R*)-3C-tethered Ru(II)-TsDPEN catalyst example). The reaction was also followed by HPLC (Chiralcel ODH, 30 cm x 6mm column, hexane:iPrOH 97:3, 1.0 mL/min, T = 25°C); (*R,R*)-3C-tethered Ru(II)-TsDPEN catalyst: [α]$_D^{23}$ +2.35 (c 0.5 in CHCl$_3$) 99.9% conversion (HPLC calibration: 1:1 furan-2-yl(phenyl)methanone: furan-2-yl(phenyl)methanol gives 25.3:1 ratio of absorption at 254 nm); 47% ee (*R*) (lit.[14] [α]$_D^{20}$ -1.4 (c 0.15 in CHCl$_3$) 20% ee (*S*)).

Phenyl(thiophen-2-yl)methanone. This compound has been reported and fully characterized.[15] To a solution of phenyl(thiophen-2-yl)methanol **10** (360 mg, 1.89 mmol) in DCM (10 mL) at rt was added manganese dioxide (2.47 g, 28.4 mmol). The reaction mixture was left to stir under a nitrogen inert atmosphere overnight; TLC (9:1 hexane: EtOAc) after this time indicated full conversion. The remaining manganese dioxide was removed by gravity filtration. The solids were removed by gravity filtration and washed with DCM. The combined solvent was removed to give the

product as a white solid (260 mg, 1.38 mmol, 73%). TLC: Rf ca 0.30 (9:1 hexane: EtOAc), strong UV and KMnO$_4$; m.p. 54°C; ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.87 (d, $^3J_{H,H}$=7.2 Hz, 2H; Ar-H), 7.73 (d, $^3J_{H,H}$=4.7 Hz, 1H; Ar-H), 7.65 (d, $^3J_{H,H}$=3.3 Hz, 1H; Ar-H), 7.59 (t, $^3J_{H,H}$=7.5 Hz, 1H; Ar-H), 7.50 (t, $^3J_{H,H}$=7.5 Hz, 2H; C$_4$H$_3$S), 7.17 ppm (t, $^3J_{H,H}$=5.0 Hz, 1H; C$_4$H$_3$S); ^{13}C NMR (125 MHz, CDCl$_3$): δ=188.27 (C), 143.66 (C), 138.16 (C), 134.88 (CH), 134.24 (CH), 132.29 (CH), 129.19 (2×CH), 128.43 (2×CH), 127.98 ppm (CH). Data matched that reported.

Phenyl(thiophen-2-yl)methanol 10 (Ph/Thio). This compound has been reported and fully characterized.[14,16] Thiophene-2-carbaldehyde (250 mg, 2.23 mmol) was added to a flask, THF (2.5 ml) was added and the flask was placed into an ice bath to cool down to 0°C, and the reaction was stirred under a nitrogen atmosphere. Phenyl magnesium bromide solution (0.813 ml, 3.0M in diethyl ether, 2.44 mmol) was added dropwise and the reaction was stirred under a nitrogen atmosphere at rt overnight. TLC (9:1 hexane: EtOAc) after this time indicated full conversion. After 17 hours, distilled water (20 mL) was added, and the mixture was extracted with EtOAc (3 × 20ml), the combined extracts were dried with MgSO$_4$, and the solvent was removed under vacuum to give the product as a yellow solid (407.5 mg, 2.14 mmol, 96.1%). TLC: Rf ca 0.20 (9:1 hexane: EtOAc), strong UV and KMnO$_4$; m.p. 62°C; ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.35 (d, $^3J_{H,H}$=7.5 Hz, 2H; Ar-H), 7.28 (t, $^3J_{H,H}$=7.4 Hz, 2H; Ar-H), 7.21 (t, $^3J_{H,H}$=7.2 Hz, 1H; Ar-H), 7.16 (d, $^3J_{H,H}$=5.6 Hz, 1H; C$_4$H$_3$S), 6.90-6.81 (m, 1H; C$_4$H$_3$S), 6.79 (d, $^3J_{H,H}$=3.2 Hz, 1H; C$_4$H$_3$S), 5.96 (d, $^3J_{H,H}$=3.4 Hz, 1H; ArCHOH), 2.31 ppm (d, $^3J_{H,H}$=3.8 Hz, 1H; OH); ^{13}C NMR (125 MHz, CDCl$_3$): δ=148.13 (C), 143.12 (C), 128.57 (CH), 128.04 (CH), 126.68 (CH), 126.31 (CH), 125.46 (CH), 124.92 (CH), 72.46 ppm (CH); m/z (ES-API+) 190.8 (M+, 100%). Data matched that reported. Enantiomeric excess and conversion determined by GC (Chrompac cyclodextrin-β-236M-19 50m × 0.25mm × 0.25μm, column head pressure: 15psi, carrier gas: hydrogen, oven temperature: 140 °C, injection temperature: 220 °C, FID detector temperature: 250 °C) ketone 66.7 min, *S* isomer 98.6 min., *R* isomer 100.2 min.

ATH of phenyl(thiophen-2-yl)methanone. Catalyst (0.00213 mmol, 1 mol%) was added to FA: TEA (5:2 azeotropic mixture, 0.18 mL) at rt and the mixture was stirred under a nitrogen atmosphere for 10-15 minutes; after which a solution of phenyl(thiophen-2-yl)methanone (40 mg, 0.213 mmol) in DCM (0.25 mL) was added. The reaction mixture was stirred at rt, followed by TLC (9:1 hexane: EtOAc). After 117 hours, the reaction was quenched using saturated NaHCO$_3$ solution (20 mL). EtOAc (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried (MgSO$_4$) and filtered. The solvent was removed to give the crude product. The product was isolated via flash chromatography on silica eluted with 0-20% EtOAc in hexane to give phenyl(thiophen-2-yl)methanol **10** (32.0 mg, 0.168 mmol, 79%; (*R,R*)-3C-tethered Ru(II)-TsDPEN catalyst example). The reaction was also followed by GC (Chrompac cyclodextrin-β-236M-19 50m × 0.25mm × 0.25μm, column head pressure: 15psi, carrier gas: hydrogen, oven temperature: 140 °C, injection temperature: 220 °C, FID detector temperature: 250 °C); (*R,R*)-3C-tethered Ru(II)-TsDPEN catalyst: 97% conversion; [α]$_D^{23}$ -2.034 (c 0.0885 in CHCl$_3$) 48% ee (*R*) (lit.[14] [α]$_D^{20}$ -1.7 (c 0.3 in CHCl$_3$) 19% ee (*R*)).

(2-Methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanone. This compound is novel. To a solution of 1-methylimidazole (250 mg, 3.05 mmol) in MeCN (9 mL) at 0 °C was added 2-methoxybenzoyl chloride (780 mg, 4.58 mmol), followed by the addition of Et$_3$N (462 mg, 4.58 mmol). The reaction mixture was stirred under a nitrogen atmosphere overnight; and the conversion was monitored by TLC (1:1 hexane: EtOAc). The mixture was quenched by dropwise addition of water (20 mL). EtOAc (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (MgSO$_4$) and filtered. The solvent was removed to give the crude product. The product was isolated via flash chromatography on silica eluted with 50-100% EtOAc in hexane to give

(2-methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanone as a white solid (292 mg, 1.35 mmol, 44%). TLC: Rf ca 0.20 (1:1 hexane: EtOAc), strong UV and KMnO$_4$; m.p. 74°C; ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.53 (dd, $^3J_{H,H}$=7.5 Hz, 1.5 Hz, 1H; Ar-H), 7.48-7.43 (m, 1H; Ar-H), 7.16 (s, 1H; Ar-H), 7.07-7.00 (m, 3H; Ar-H + NCHCHN), 4.11 (s, 3H; OCH$_3$), 3.80 ppm (s, 3H; NCH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ=186.19 (C), 157.79 (C), 143.84 (C), 132.20 (CH), 130.22 (CH), 129.76 (CH), 128.48 (CH), 126.79 (CH), 120.10 (CH), 111.79 (CH), 55.89 (CH$_3$), 36.25 (CH$_3$); IR: v̄=3116, 3067, 1648 (C=O), 1596, 1437, 1392, 1282, 1238, 1020, 753 cm^{-1}; m/z (ES-API+) 239.2 (M$^+$ + 23, 100%); HRMS: (found (ESI+): [M+H]+, Calcd for C$_{12}$H$_{13}$N$_2$O$_2$ 217.0967; Found 217.0972; 1.9 ppm error).

(2-Methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanol 16 (oOMe/Im). This compound is novel. To a solution of (2-methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanone (200 mg, 0.93 mmol) in MeOH (5 mL) was added sodium borohydride (70.4 mg, 1.85 mmol). The reaction was stirred for 4 hours. TLC (1:1 hexane: EtOAc) after this time indicated full conversion. Distilled water (20 mL) was added, and the mixture was extracted with EtOAc (3 × 20ml), dried with MgSO$_4$, and the solvent was removed under vacuum to give (2-methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanol **16** as a white solid (167 mg, 0.766 mmol, 83%). TLC: Rf ca 0.20 (1:1 hexane: EtOAc), strong UV and KMnO$_4$; m.p.133°C; ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.29-7.26 (m, 1H; Ar-H), 7.15 (d, $^3J_{H,H}$=7.5 Hz, 1H; Ar-H), 6.97-6.90 (m, 3H; Ar-H + NCHCHN), 6.82 (s, 1H; NCHCHN), 6.20 (s, 1H; ArCHOH), 3.86 (s, 3H; OCH$_3$), 3.50 ppm (s, 3H; NCH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$): δ=156.68 (C), 148.78 (C), 129.33 (C), 129.11 (CH), 127.87 (CH), 126.96 (CH), 121.58 (CH), 121.06 (CH), 110.82 (CH), 64.19 (CH), 55.66 (CH$_3$), 32.83 ppm (CH$_3$); IR: v̄=3037 (br), 2970, 2839, 1600, 1489, 1243, 1041, 747, 716 cm^{-1}; m/z (ES-API+) 219.2 (M$^+$ + 1, 100%); HRMS: (found (ESI+): [M+H]+, Calcd for C$_{12}$H$_{15}$N$_2$O$_2$ 219.1128; Found 219.1128; 0.1 ppm error). Enantiomeric excess and conversion determined by HPLC analysis (Chiralcel ODH, 30 cm x 6mm column, hexane:iPrOH 9:1, 0.8 mL/min, T = 25°C) ketone 33.9 min, *R* isomer 19.5 min and *S* isomer 29.3 min. The configuration was assigned by X-ray crystallographic analysis of the ATH product.

ATH of (2-methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanone. Catalyst (0.00185 mmol, 1 mol%) was added to FA: TEA (5:2 azeotropic mixture, 0.18 mL) at rt and the mixture was stirred under a nitrogen atmosphere for 10-15 minutes; after which a solution of 2-methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanone (40 mg, 0.185 mmol) in DCM (0.25 mL) was added. The reaction mixture was stirred at rt, followed by TLC (1:1 hexane: EtOAc). After 168 hours, the reaction was quenched using saturated NaHCO$_3$ solution (20 mL). EtOAc (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried (MgSO$_4$) and filtered. The solvent was removed to give the crude product. The product was isolated via flash chromatography on silica eluted with 50%-100% ethyl acetate in hexane to give (2-methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanol **16** (17.4 mg, 0.0798 mmol, 43%; (*R,R*)-3C-tethered Ru(II)-TsDPEN catalyst example). The reaction was also followed by HPLC (Chiralcel ODH, 30 cm x 6mm column, hexane:iPrOH 9:1, 0.8 mL/min, T = 25°C); (*R,R*)-3C-tethered Ru(II)-TsDPEN catalyst: 95% conversion (HPLC calibration: 1:1 (2-methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanone: (2-methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanol gives 7.62:1 ratio of absorption at 254 nm) [α]$_D^{26}$ +21.6 (c 0.03 in CHCl$_3$) 98% ee (*S*).

(2-Hydroxyphenyl)(1-methyl-1*H*-imidazol-2-yl)methanone. This compound is novel. To a solution of 2-(hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl)phenol **17** (94 mg, 0.461 mmol) in DCM (5 mL) at rt was added manganese dioxide (601 g, 6.92 mmol). The reaction mixture was left to stir under a nitrogen atmosphere overnight. TLC (19:1 DCM: MeOH) after this time indicated full conversion. The solids were removed by gravity filtration and washed with DCM. The combined solvent was removed to give the product as a yellow solid (58.6 mg, 0.290 mmol, 63%). TLC: Rf ca 0.80 (19:1 DCM: MeOH), strong UV and KMnO$_4$; m.p. 62.5°C; ^{1}H

NMR (500 MHz, CDCl₃): δ=13.25 (s, 1H; ArOH), 8.64 (dd, $^3J_{H,H}$=8.2 Hz, 1.7 Hz, 1H; Ar-H), 7.48 (ddd, $^3J_{H,H}$=8.6 Hz, 1.7 Hz, 1.7 Hz, 1H; Ar-H), 7.32-7.18 (m, 1H; Ar-H), 7.13 (s, 1H; Ar-H), 7.02 (dd, $^3J_{H,H}$=8.3 Hz, 0.9 Hz, 1H; NCH=CH), 6.98-6.89 (m, 1H; NCH=CH), 4.07 ppm (s, 3H; NCH₃); ¹³C NMR (125 MHz, CDCl₃): δ=185.10 (C), 161.97 (C), 142.79 (C), 136.09 (CH), 133.79 (CH), 128.19 (CH), 127.07 (CH), 120.93 (C), 118.99 (CH), 36.87 ppm (CH₃); IR: $\tilde{v}$=3141, 3125, 3058, 3016, 1768 (C=O), 1621, 1595, 1457, 1407, 1392, 1298, 1277, 948, 816, 790, 751 cm⁻¹; m/z (ES-API+) 225.2 (M⁺ + 23, 100%); HRMS: (found (ESI+): [M+H]+, Calcd for C₁₁H₁₁N₂O₂ 203.0818; Found 203.0815; -1.3 ppm error).

Racemic and *S*-2-(Hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl)phenol 17 (oOH/Im). This compound is novel. To a solution of 2-(((tert-butyldimethylsilyl)oxy)(1-methyl-1*H*-imidazol-2-yl)methyl)phenol (210 mg, 0.660 mmol) in THF (10.5 mL) was added a solution of *Tetra*-n-butylammonium fluoride (TBAF) (0.990 mL, 1.0M in THF, 0.990 mmol) at rt. The reaction mixture was left stirring under the nitrogen atmosphere and followed by TLC (19:1 DCM: MeOH). Solvent was removed to give the crude product. The product was isolated via flash chromatography on silica eluted with 0-50% MeOH in DCM to give 2-(hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl)phenol 17 as a white solid (85.3 mg, 0.418 mmol, 63.3%). m.p. 40°C; TLC: Rf ca 0.20 (19:1 DCM: MeOH), strong UV and KMnO₄; ¹H NMR (500 MHz, CDCl₃): δ=7.24-7.12 (m, 1H; Ar-H), 6.95 (d, $^3J_{H,H}$=8.1 Hz, 1H; Ar-H), 6.91-6.83 (m, 2H; Ar-H), 6.85-6.71 (m, 2H; NCH=CHN), 5.89 (s, 1H; Ar*CH*OH), 3.63 ppm (s, 3H; NCH₃); ¹³C NMR (125 MHz, CDCl₃): δ=158.11 (C), 148.81 (C), 129.81 (CH), 128.06 (CH), 125.85 (CH), 125.05 (C), 122.12 (CH), 119.82 (CH), 119.03 (CH), 69.39 (CH), 33.31 ppm (CH₃); IR: $\tilde{v}$=3344 (br), 3113, 3042, 2952, 2871, 1595, 1490, 1453, 1390, 1277, 1233, 1137, 937, 748, 706 cm⁻¹; m/z (ES-API+) 227.2 (M⁺ + 23, 100%); HRMS: (found (ESI+): [M+H]+, Calcd for C₁₁H₁₃N₂O₂ 205.0972; Found 205.0972; -0.1 ppm error). Enantiomeric excess and conversion determined by HPLC analysis (Chiralpak IG, 30 cm x 6mm column, hexane:iPrOH 90:10, 1.0 mL/min, T = 25°C) ketone 13.6 min, *R* and *S* isomer 15.1 min and 22.9 min, configuration *S* assigned by methylation to OMe/Im previously characterized by X-ray.

ATH of (2-Hydroxyphenyl)(1-methyl-1*H*-imidazol-2-yl)methanone. Catalyst (0.00198 mmol, 1 mol%) was added to FA: TEA (5:2 azeotropic mixture, 0.18 mL) at rt and the mixture was stirred under a nitrogen atmosphere for 10-15 minutes; after which a solution of (2-hydroxyphenyl)(1-methyl-1*H*-imidazol-2-yl)methanone (40 mg, 0.198 mmol) in DCM (0.25 mL) was added. The reaction mixture was stirred at rt overnight (20 h). The reaction was followed by TLC (19:1 DCM: MeOH). Then the reaction was quenched using saturated NaHCO₃ solution (20 mL). EtOAc (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried (MgSO₄) and filtered. The solvent was removed to give the crude product. The product was isolated via flash chromatography on silica eluted with 0-10% MeOH in DCM to give 2-(hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl)phenol 17 (20.3 mg, 0.0995 mmol, 50.3%; (*R,R*)-3C-tethered Ru(II)-TsDPEN catalyst example). The reaction was also followed by HPLC analysis (Chiralpak IG, 30 cm x 6mm column, hexane:iPrOH 90:10, 1.0 mL/min, T = 25°C); (*R,R*)-3C-tethered Ru(II)-TsDPEN catalyst: α]ᴅ²¹ -18.5 (c 0.0600 in CHCl₃) 83% ee (*S*).

Formation of *S*-(2-methoxyphenyl)(1-methyl-1*H*-imidazol-2-yl)methanol 16 by methylation of *S*-2-(hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl)phenol 17 to compare with ATH of (2-methoxyphenyl)(1-methyl-1*H*-imidazol-2-yl)methanone. To a solution of asymmetric *S*-(2-methoxyphenyl)(1-methyl-1*H*-imidazol-2-yl)methyl)phenol 16 (20 mg, 0.0980 mmol) in DMF (0.98 mL) was added potassium carbonate (13.6 mg, 0.118 mmol) and iodomethane (13.9 mg, 0.0980 mmol) at rt. The mixture was stirred under a nitrogen atmosphere overnight. TLC (19:1 DCM: MeOH) after this time indicated full conversion. Then the reaction was quenched using distilled water (20 mL). EtOAc (20 mL) was added and the organic layer was separated.

The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried (MgSO₄) and filtered. The solvent was removed to give the crude product. The product was isolated via flash chromatography on silica eluted with 0-10% MeOH in DCM to give asymmetric (2-methoxyphenyl)(1-methyl-1*H*-imidazol-2-yl)methanol **17** as a colorless oil (8.90 mg, 0.0408 mmol, 41.6%). The reaction also followed by HPLC analysis (Chiralcel ODH, 30 cm x 6mm column, hexane:iPrOH 9:1, 0.8 mL/min, T = 25°C): 82% ee.

Acknowledgements

Supporting Information

The Supporting Information contains details of the remaining experimental procedures, NMR spectra, chiral HPLC spectra, X-ray crystallographic data for structures CCDC 2071155 – 2071158 and conversion and ee vs time graphs.

Author Contributions

YZ, JM-A and MK carried out the experimental work, MW was supervisor to YZ and MK and LCAB was supervisor to JAM-A. YZ, JM-A, MK, LCAB and MW contributed to the design and planning of the investigation. GJC carried out the X-ray crystallographic analyses.

Conflicts of interest

There are no conflicts to declare.

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Data sharing statement

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

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Entry for the Table of Contents

Products formed by ketone reduction using (*R,R*)- Ru(II) ATH catalysts:

Ph/Fu
up to 61% ee

oOMe/Fu
up to 97% ee

Np/Fu
up to 94% ee

oOMe/Im
up to 98% ee

Np/Im
up to 93% ee
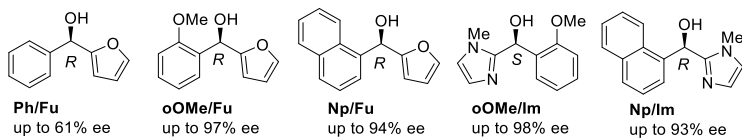
A systematic study of the asymmetric transfer hydrogenation (AH), using [arene/Ru(II)/TsDPEN] pre-catalysts, of a range of heterocyclic ketones is described. The products are formed in very high ee in cases where an *ortho*-substituted aromatic ring opposes the heterocycle on the ketone group. This provides a practical and selective access to a range of hetereocyclic alcohols in high ee, for the by ATH using Noyori-Ikariya catalysts.

Institute and/or researcher Twitter usernames: ((optional))