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Heterocycle-containing Noyori–Ikariya catalysts for asymmetric transfer hydrogenation of ketones†

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The synthesis of a range of N-(heterocyclesulfonyl)-functionalised Noyori–Ikariya catalysts is described. The complexes were prepared through a short sequence from C2-symmetric 1,2-diphenylethylene-1,2-diamine (DPEN) and were characterised by a range of methods including X-ray crystallography. The complexes were active catalysts for the asymmetric transfer hydrogenation (ATH) of a range of acetophenone derivatives, giving products of high ee in most cases, with notably good results for *ortho*-substituted acetophenones.

Introduction

Asymmetric transfer hydrogenation (ATH) of ketones and imines can be achieved in high enantiomeric excess (ee) using [(arene)Ru(L)Cl] complexes (Noyori–Ikariya catalysts).[1–4] The bidentate ligand L is a homochiral, C2-symmetric 1,2-diamine in which one of the amines has been sulfonylated and in most cases the ligand employed is *N*-tosyl-1,2-diphenylethylene-1,2-diamine (TsDPEN), as illustrated in (R,R,S^{Ru})-**1**, the favoured diastereoisomer.[2] Under the reaction conditions, where typically either iPrOH or formic acid is used as the hydrogen source, the complex is converted *via* an unsaturated intermediate to hydride **2**, in the same favoured diastereoisomeric form.[3] Transfer of hydrogen from **2** to the substrate in a well-defined diastereoselective manner results in asymmetric reduction of the substrate with a predictable stereochemical outcome (Fig. 1).[4]

The reactivity of catalysts of this type can be moderated through a number of modifications (Fig. 2, example complexes **3–10**), including; to the diamine ligand,[5] η^6-arene[6] and through an intramolecular link from the η^6-arene to the diamine.[7] Substitution of the non-tosylated amine is also tolerated.[8] The ligand can also be modified at the sulfonamide with functional groups that can, for example, improve the solubility of the catalysts in water.[9] Although there are many other reported modifications to the sulfonamide component,[10] we were aware of very few examples of the replacement of the tosyl group with a heterocyclic sulfonamide, a modification which could potentially alter the reactivity and selectivity of the catalysts. There have been multiple reports of the application of piperidine and pyrrolidine-containing catalysts such as **8** to ATH,[11] including tethered derivatives such as **9**.[7] An imidazolium derivative **10**, has been applied to ketone ATH in ionic liquids,[12] and the use of a DPEN derivative containing a quinoline ring (also described below) has been reported in the ATH of acetophenone and propiophenone, using [(*p*-cymene)$RuCl_2]_2$ as the metal source.[13] Apart from moderating the selectivity and activity of the catalysts, heterocyclic groups may also help to facilitate the recovery of the catalysts after use, and

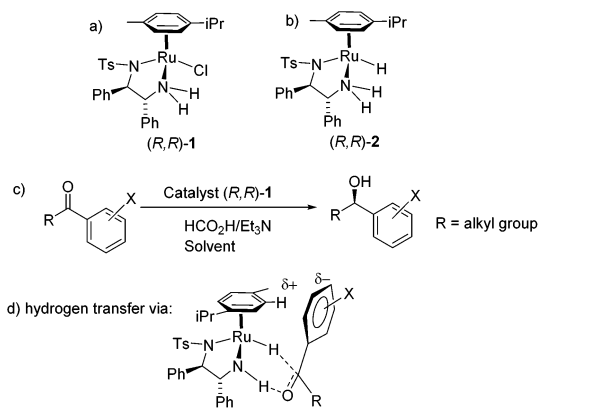

Fig. 1 (a) Noyori–Ikariya catalyst (R,R,S^{Ru})-**1** (containing (*R,R*)-TsDPEN ligand and *p*-cymene arene), (b) hydride (R,R,S^{Ru})-**2** is formed in a diastereoselective manner from (R,R,S^{Ru})-**1**, (c) asymmetric transfer hydrogenation (ATH) of ketones using Noyori–Ikariya catalysts. (d) stereochemical mode of hydride transfer from (R,R,S^{Ru})-**2** to an acetophenone derivative.

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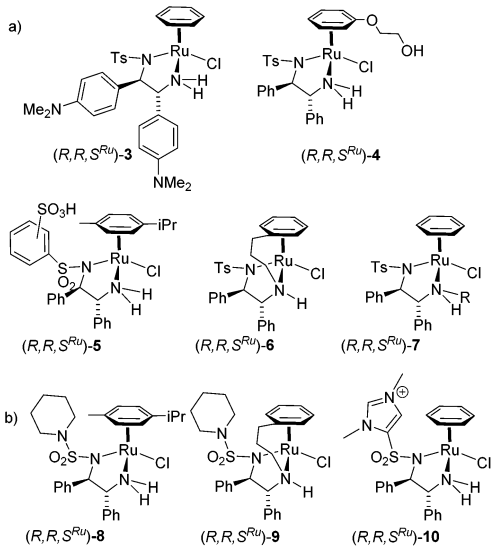


Fig. 2 (a) Examples of modifications to Noyori–Ikariya catalysts; modification to the DPEN component; modification of the η^6-arene, substitution of the sulfonamide component; introduction of a link from the diamine to the η^6-arene; additions to the non-sulfonylated nitrogen; changes to the sulfonamide component. (b) Catalysts containing heterocyclic rings in the sulfonamide unit. In all cases, the relative configuration has either been determined by X-ray crystallography or assigned by analogy as (R,R,S^{Ru}).

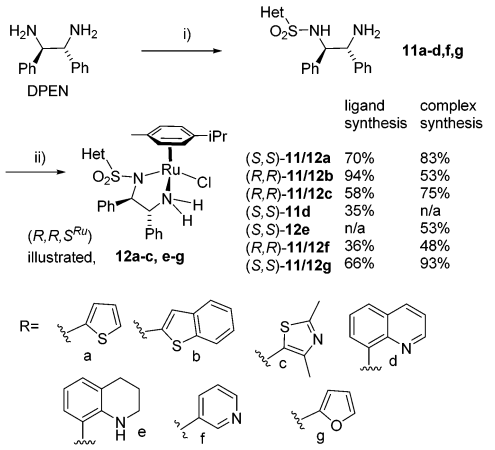


Fig. 3 Preparation of [(*p*-cymene)Ru(HetSO_2DPEN)Cl] complexes. (i) DPEN, HetSO_2Cl, Et_3N, THF, 0 °C. (ii) $[(cymene)RuCl_2]_2$, Et_3N, iPrOH, 80 °C, 1 h.

improve their solubility in specific solvents, including water, as has been the case with other modifications.[5–10]

Given their potential value, we have designed and prepared a range of heterocycle-containing Noyori–Ikariya complexes and tested them in the ATH of ketones.

Results and discussion

A series of heterocycle-containing complexes were prepared from 1,2-diphenylethene-1-2-diamine (DPEN). With aim of preparing a diverse series, the planned heterocycles included thiophene, benzothiophene, thioazole, quinoline, pyridine and furan. The first stage was formation of the ligands through direct substitution with the appropriate sulfonyl chloride to generate **11a–11d**, **11f** and **11g**, where **11d** is the previously reported quinoline derivative.[13] This was then followed by complexation with $[(p\text{-cymene})RuCl_2]_2$ dimer following the reported procedure[3a] for Noyori–Ikariya complex **1** (Fig. 3) to form the required complexes **12a–c**, **12e–g**. Some complexes were prepared from (*R*,*R*)-DPEN and others from its enantiomer, as indicated. Although the series included the reported quinoline **11d**, the other ligands and complexes are novel.

The novel complexes were formed in good yields and could be purified by column chromatography, reflecting their stability. The complexes were characterised by NMR spectroscopy, IR and MS and the X-ray crystal structures of five of the complexes were also obtained (Fig. 4, ESI†). In four cases (**12a–c**, **12g**), the complexes possessed a structure analogous to the TsDPEN-derived examples, where the relative configuration at ruthenium to that of the diamine ligand is (R,R,S^{Ru}) or (S,S,R^{Ru}). In the case of the quinoline complex, however, the reduction of the heterocyclic ring of the ligand **11d** was observed under our reaction conditions to give the tetrahydroquinoline complex **12e** as the isolated product, quinoline reductions under ATH conditions have been reported,[14] therefore this appears to be an example of self-catalysis of reduction by the catalyst as it is formed in the reaction, the hydrogen presumably coming from the isopropanol solvent. Additionally, complex **12e** was found to have with the opposite relative stereochemistry at Ru relative to the ligand to what would be expected (*i.e.* (S,S,S^{Ru}). Complex **12e** also exhibits an unusual H-bond from the NH of the isoquinoline ring to the N atom adjacent to the sulfonyl group (the total N–H–N bond length, is 3.096(8) Å). This may be the reason for the change in relative configuration for this complex, *i.e.* through stabilisation of the observed configuration. It should be noted that, in each case, the heterocycles are stacked against a DPEN phenyl group to maximize dispersion stabilization.

A comparison of key bond lengths and angles around the metal centre (Table 1, ESI†) otherwise showed only small differences between each structure. For the complexes of 'conventional' relative stereochemistry, the bond angles and lengths were very similar. In contrast, for the 'inverted' diastereoisomer (S,S,S^{Ru})-**12e**, the dimensions were slightly different, presumably due to the alternative relative positioning of groups in the complex.

Complex **12a** was first tested in the ATH of acetophenone under a variety of conditions (Table 2). In previous studies, we have typically used a 5 : 2 azeotrope of formic acid/triethylamine (FA/TEA) either neat or with a cosolvent, at rt. Under these conditions, the cosolvent-free reduction gave a product of *ca.* 97% ee, comparable to the result with catalyst **1**,[2] although the use of DCM cosolvent resulted in a slightly faster reaction and marginally higher product ee. The reduction

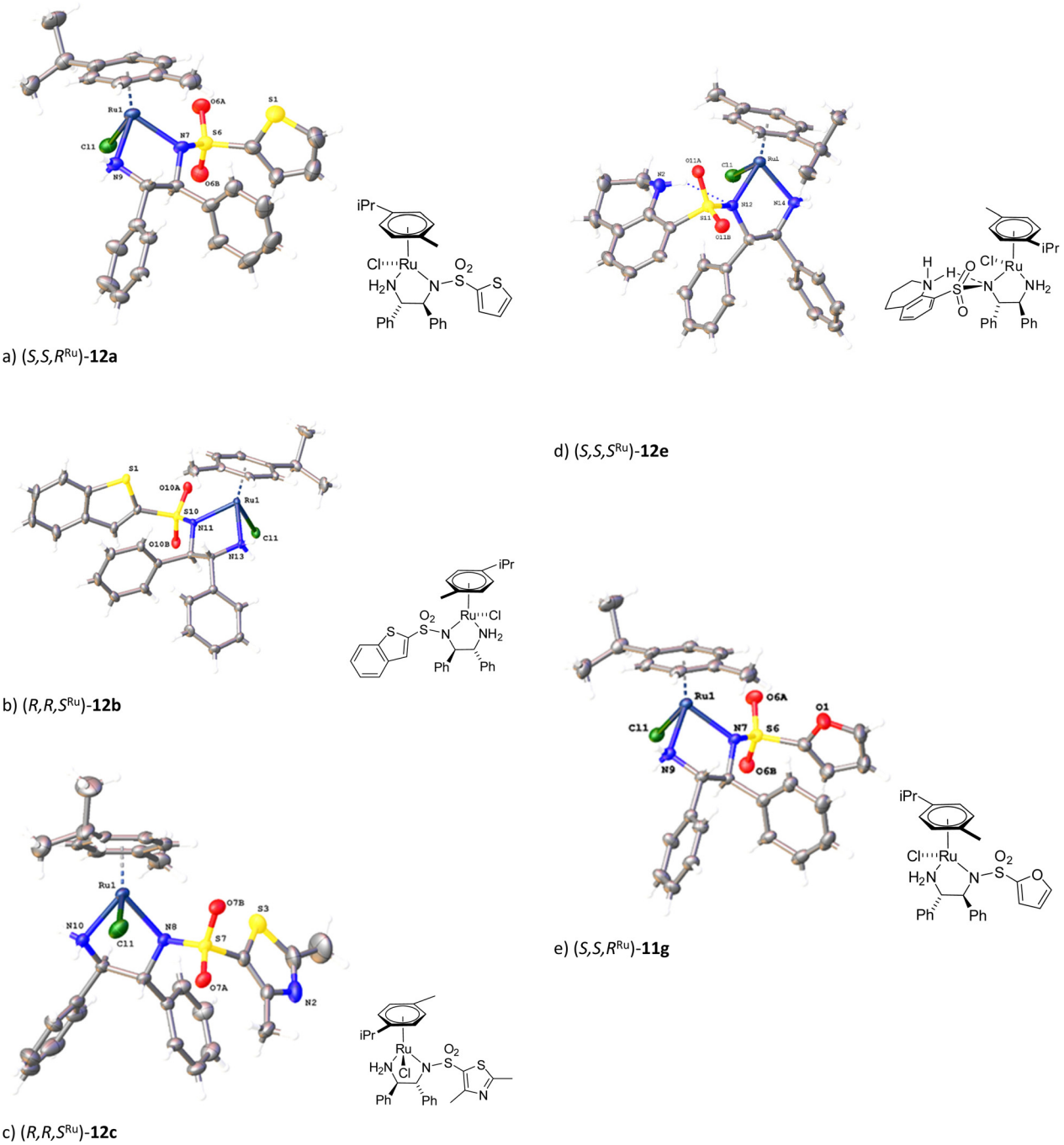


Fig. 4 X-ray crystal structures of five of the novel complexes prepared in this work.

Table 1 Key bond lengths and angles around the metal centre in complexes **12a–c**, **12e**, **12g**. Standard deviations are in brackets. Further data is in the ESI†

	(S,S,R^{Ru})-**12a**	(R,R,S^{Ru})-**12b**	(R,R,S^{Ru})-**12c**	(S,S,S^{Ru})-**12e**	(S,S,R^{Ru})-**12g**
Ru–Cl/Å	2.4292 (10)	2.4493 (13)	2.4171 (15)	2.4464 (16)	2.4312 (7)
Ru-NH_2/Å	2.117 (3)	2.127 (4)	2.113 (4)	2.134 (5)	2.117 (2)
Ru-NTs/Å	2.152 (3)	2.130 (4)	2.151 (4)	2.163 (5)	2.157 (2)
Cl–Ru-NTs/°	87.68 (10)	86.98 (13)	88.01 (11)	85.36 (14)	88.01 (7)
Cl–Ru-NH_2/°	82.20 (11)	82.37 (13)	83.40 (13)	87.09 (15)	82.30 (8)
NH_2-Ru-NTs/°	79.01 (13)	77.73 (16)	78.36 (16)	77.68 (19)	78.89 (9)
NTs-S-CHet/°	108.1 (2)	107.5 (2)	107.4 (2)	106.7 (3)	108.37 (14)

Table 2 Optimisation of ATH of acetophenone using (*S*,*S*)-**12a** [a]

Cat.	Co-solvent	*t*/h	FA : TEA	Conv./%	Ee/%	*R*/*S*
(*S*,*S*,R^{Ru})-**12a**	DCM	22	5 : 2	99	97.8	*S*
(*S*,*S*,R^{Ru})-**12a**	None	56	5 : 2	97	96.6	*S*
(*S*,*S*,R^{Ru})-**12a**	MeCN	61	5 : 2	98	96.2	*S*
(*S*,*S*,R^{Ru})-**12a**	MeOH	35	5 : 2	99	96.6	*S*
(*S*,*S*,R^{Ru})-**12a**	DCM[b]	16	5 : 2	99	96.0	*S*
(*S*,*S*,R^{Ru})-**12a**	—[c]	6	5 : 2	97	91.2	*S*
(*S*,*S*,R^{Ru})-**12a**	H_2O	56	5 : 2	66	95.4	*S*
(*S*,*S*,R^{Ru})-**12a**	DCM	26	1.2 : 1	99	96.6	*S*
(*S*,*S*,R^{Ru})-**12a**	DCM	26	0.2 : 1	97	96.4	*S*
(*S*,*S*,R^{Ru})-**1**	DCM	40	5 : 2	97	96.8	*S*

[a] Conditions; Fig. 1c summarises the transformation, 1 mmol ketone, 1% catalyst, 0.5 mL FA : TEA, 0.5 mL cosolvent where indicated, rt (*ca.* 20 °C) unless otherwise indicated, *S* = [1.0], followed by chiral GC. [b] Run at 40 °C. [c] Run at 60 °C, without DCM.

product was also formed in high ee using MeCN and MeOH as cosolvents. With DCM cosolvent, the reaction was completed more rapidly at 40 °C and after a much shorter time at 60 °C although with decreased ees of 96.0% and 91.2% respectively. The complex was also capable of catalysing ATH in water, although the activity was slightly reduced. Variation of the FA/TEA ratio (known to influence catalyst activity in some cases)[14d,15] did not significantly alter the reaction in this case, however.

The ATH of acetophenone using each of the catalysts was followed both by ^{1}H NMR and by sampling from an ongoing reaction followed by analysis by chiral GC (ESI,† Table 3). The NMR experiment allowed a comparison of the relative activities of each catalyst to be obtained, whilst the chiral GC reaction provided information about ee variation over time. In the NMR experiments, a short induction period was observed, which may reflect the formation of a ruthenium hydride at the start of the reaction. The most active catalysts were the furan **12g** and thiophene **12a**, whilst the tetrahydroisoquinoline complex **12e** was the least active. The reaction rate of the furan complex **12a** was faster than the Noyori–Ikariya catalyst **1** by a factor of 1.77, while the tetrahydroquinoline complex **12e** is slower by a factor of 0.5 than **1** under the conditions that we tested. Whilst it is difficult to make accurate comparisons, the furan and thiophene heterocycles may be slightly more active due to the smaller size of these groups. Alternatively, subtle changes to the electronic structure or conformations of the catalysts may be responsible. The tetrahydroisoquinoline complex **12e** may be less active because a proportion of the catalyst is unavailable due to stabilisation of the (presumably inactive) intramolecularly H-bond form observed in the crystal structure. However, further studies are required in order to identify the reasons for observed the rate variations.

The enantiomeric excesses remained relative constant throughout the reductions for each catalyst. In the reported application of ligand **11d**,[13a] through *in situ* formation of the catalyst, a combination of iPrOH and KOH was used as the reaction medium and reducing agent, and a product of 92.1% ee was obtained, which is similar to our result for complex

Table 3 Ketones tested for ATH using catalysts **12a–12c**, **12e–12g** [a]

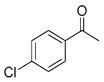
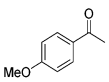
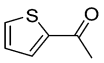
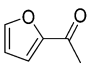
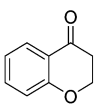
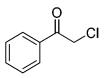
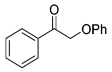
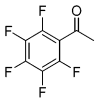
Substrate	Catalyst	*t*/h	Conv./%	Yield/%	ee/%	*R*/*S*
	(*S*,*S*,R^{Ru})-**12a**	22	100	66	97.8	*S*
	(*R*,*R*,S^{Ru})-**12b**	22	98	91	>99	*R*
	(*R*,*R*,S^{Ru})-**12c**	27	99	73	98.6	*R*
	(*S*,*S*,S^{Ru})-**12e**	49	100	77	96.8	*S*
	(*R*,*R*,S^{Ru})-**12f**	46	98	88	>99	*R*
	(*S*,*S*,R^{Ru})-**12g**	46	99	91	96.6	*S*
	(*S*,*S*,R^{Ru})-**12a**	40	100	72	94.0	*S*
	(*R*,*R*,S^{Ru})-**12b**	26	88	70	>99	*R*
	(*R*,*R*,S^{Ru})-**12c**	26	89	79	>99	*R*
	(*S*,*S*,S^{Ru})-**12e**	91	99	79	97.4	*S*
	(*R*,*R*,S^{Ru})-**12f**	47	99	92	>99	*R*
	(*S*,*S*,R^{Ru})-**12g**	48	99	93	91.2	*S*
	(*S*,*S*,R^{Ru})-**12a**	48	100	76	95.8	*S*
	(*R*,*R*,S^{Ru})-**12b**	21	100	72	96.2	*R*
	(*R*,*R*,S^{Ru})-**12c**	27	100	72	96.8	*R*
	(*S*,*S*,S^{Ru})-**12e**	161	100	80	87.4	*S*
	(*R*,*R*,S^{Ru})-**12f**	165	100	93	97.2	*R*
	(*S*,*S*,R^{Ru})-**12g**	23	100	88	96.2	*S*
	(*S*,*S*,R^{Ru})-**12a**	97	99	64	91.6	*S*
	(*R*,*R*,S^{Ru})-**12b**	111	99	71	92.0	*R*
	(*R*,*R*,S^{Ru})-**12c**	96	100	73	96.4	*R*
	(*S*,*S*,S^{Ru})-**12e**	183	30	-	89.4	*S*
	(*R*,*R*,S^{Ru})-**12f**	165	99	81	95.0	*R*
	(*S*,*S*,R^{Ru})-**12g**	96	98	71	91.2	*S*
	(*S*,*S*,R^{Ru})-**12a**	167	97	89	94.2	*S*
	(*R*,*R*,S^{Ru})-**12b**	142	98	91	98.3	*R*
	(*R*,*R*,S^{Ru})-**12c**	142	99	81	96.7	*R*
	(*S*,*S*,S^{Ru})-**12e**	167	51	44	98.9	*S*
	(*R*,*R*,S^{Ru})-**12f**	165	98	95	97.2	*R*
	(*S*,*S*,R^{Ru})-**12g**	187	96	82	93.6	*S*
	(*S*,*S*,R^{Ru})-**12a**	120	99	46	97.6	*S*
	(*R*,*R*,S^{Ru})-**12b**	120	99	41	>99	*R*
	(*R*,*R*,S^{Ru})-**12c**	120	99	59	>99	*R*
	(*S*,*S*,S^{Ru})-**12e**	145	97	65	97.6	*S*
	(*R*,*R*,S^{Ru})-**12f**	165	100	97	>99	*R*
	(*S*,*S*,R^{Ru})-**12g**	96	98	42	98.4	*S*
	(*S*,*S*,R^{Ru})-**12a**	26	93	70	99.4	*S*
	(*R*,*R*,S^{Ru})-**12b**	26	99	72	>99	*R*
	(*R*,*R*,S^{Ru})-**12c**	26	99	72	>99	*R*
	(*S*,*S*,S^{Ru})-**12e**	26	99	85	99.0	*S*
	(*R*,*R*,S^{Ru})-**12f**	22	93	70	>99	*R*
	(*S*,*S*,R^{Ru})-**12g**	23	98	81	96.4	*S*
	(*S*,*S*,R^{Ru})-**12a**	27	98	97	99.1	*S*
	(*R*,*R*,S^{Ru})-**12b**	27	99	91	>99	*R*
	(*R*,*R*,S^{Ru})-**12c**	27	99	93	>99	*R*

Table 3 *(Contd.)*

Substrate	Catalyst	*t*/h	Conv./%	Yield/%	ee/%	*R*/*S*
	(*S*,*S*,*S*^{Ru})-**12e**	27	100	90	99.3	*S*
	(*R*,*R*,*S*^{Ru})-**12f**	22	99	82	>99	*R*
	(*S*,*S*,*R*^{Ru})-**12g**	23	99	98	>99	*S*
	(*S*,*S*,*R*^{Ru})-**12a**	111	99	71	>99	*S*
	(*R*,*R*,*S*^{Ru})-**12b**	111	99	82	92.8	*R*
	(*R*,*R*,*S*^{Ru})-**12c**	160	99	82	>99	*R*
	(*S*,*S*,*S*^{Ru})-**12e**	160	99	82	99.0	*S*
	(*R*,*R*,*S*^{Ru})-**12f**	22	99	88	>99	*R*
	(*S*,*S*,*R*^{Ru})-**12g**	48	99	87	99.6	*S*
	(*S*,*S*,*R*^{Ru})-**12a**	15	100	82	99.2	*R*
	(*R*,*R*,*S*^{Ru})-**12b**	15	100	74.6	98.9	*S*
	(*R*,*R*,*S*^{Ru})-**12c**	15	100	73	>99	*S*
	(*S*,*S*,*S*^{Ru})-**12e**	15	100	86	>99	*R*
	(*R*,*R*,*S*^{Ru})-**12f**	22	100	93	98.4	*S*
	(*S*,*S*,*R*^{Ru})-**12g**	15	100	88	95.8	*R*
	(*S*,*S*,*R*^{Ru})-**12a**	23	99	91	96.8	*R*
	(*R*,*R*,*S*^{Ru})-**12b**	23	99	84	94.6	*S*
	(*R*,*R*,*S*^{Ru})-**12c**	23	99	84	98.1	*S*
	(*S*,*S*,*S*^{Ru})-**12e**	23	98	87	97.2	*R*
	(*R*,*R*,*S*^{Ru})-**12f**	22	99	93	96.2	*S*
	(*S*,*S*,*R*^{Ru})-**12g**	23	99	87	94.6	*R*
	(*S*,*S*,*R*^{Ru})-**12a**	15	100	68	8.0	*R*
	(*R*,*R*,*S*^{Ru})-**12b**	15	100	69	20.2	*S*
	(*R*,*R*,*S*^{Ru})-**12c**	15	100	74	33.8	*S*
	(*S*,*S*,*S*^{Ru})-**12e**	15	100	78	9.8	*R*
	(*R*,*R*,*S*^{Ru})-**12f**	22	100	82	35.2	*S*
	(*S*,*S*,*R*^{Ru})-**12g**	15	100	76	1.2	*R*

[a] Conditions; 1 mmol ketone, 1% catalyst, 0.5 mL FA : TEA, 0.5 mL DCM, *S* = [1], rt. Product configurations assigned by comparison to the literature data. Conv. = conversion by GC, yield = isolated product yield. ee determined by chiral GC. Where >99% ee is shown, a minor HPLC peak was not observed.

12e. Under the iPrOH/KOH conditions, the quinoline ring may have remained unreduced, or **12e** may have been formed *in situ*.

The new complexes proved to be effective in the ATH of a range of ketone substrates (Table 3). In many cases, the results were excellent, with products of high ee formed. For relatively unhindered ketones such as acetophenone, *para*-substituted acetophenones, and heterocyclic analogues containing furan and thiophene rings, several of the catalysts gave alcohols in high yields and very high ee. Across this class, catalysts **12b** and **12c** gave the most consistently high product ee, although other catalysts also performed well. In one case, catalyst **12e** gave significantly lower than 100% conversion for electron-rich *para*-methoxyacetophone. Notably, complex (*S*,*S*,*S*^{Ru})-**12a** gave the same configuration of alcohol as other complexes derived from (*R*,*R*)-DPEN, despite the alternative relative configuration at Ru, indicating a similar mode of hydride transfer (Fig. 1c). Examples of fused-ring ketones, *i.e.* 4-chromanone and tetralone, were also reduced in very high ee; these compounds are known to be very compatible with ATH using Noyori–Ikariya catalysts.[2,5–10,16] In addition, substrates containing substituents at the α-position to the ketone, including chloro and phenoxy, were also compatible substrates. The ATH of the pentafluorophenyl analogue of acetophenone is known to be difficult to achieve in high ee due to the electron-poor nature of the aromatic ring,[4d] but could be reduced in up to *ca*. 34% ee by catalyst **12c**, which was the best of those tested. It is was also demonstrated that the ATH of ketones can also be achieved through *in situ* formation of the catalysts; using (*R*,*R*)-**12f** with [(*p*-cymene)RuCl$_2$]$_2$ in FA/TEA/DCM as before resulted in reduction of acetophenone in equivalent ee to that achieved using the preformed catalyst.

In the case of challenging *ortho*-substituted acetophenones, specifically *ortho*-chloro (up to 97.2% ee) and *ortho*-methoxy acetophenone (up to 96.4% ee), the product ees and rates were high, and better than for several established Noyori–Ikariya ATH catalysts which have commonly been employed, including tethered derivatives.[7] Under the conditions in Table 3, *ortho*-methoxyacetophenone was reduced in 91.4% ee but at only 80.4% conversion after 170 h using catalyst (*R*,*R*)-**1**. Tethered catalyst (*R*,*R*)-**6** is reported to give a product of 70% ee for the same substrate,[17] although a derivative containing a OMe group on the η^6-arene ring gave a product of 96% ee.[18] Since *ortho*-phenyl substituted ketones were found to be particularly good substrates, other ketones with *ortho*-substituents were investigated with two of the most effective catalysts and these also gave products of high ee, in high conversions and good yields (Fig. 5), underlining the versatility of the catalysts, and opening possibilities for the asymmetric synthesis of otherwise challenging products of this type. The ATH reaction of (*ortho*-OiPr)acetophenone was successful but the enantiomers could not be resolved by chiral GC or HPLC.

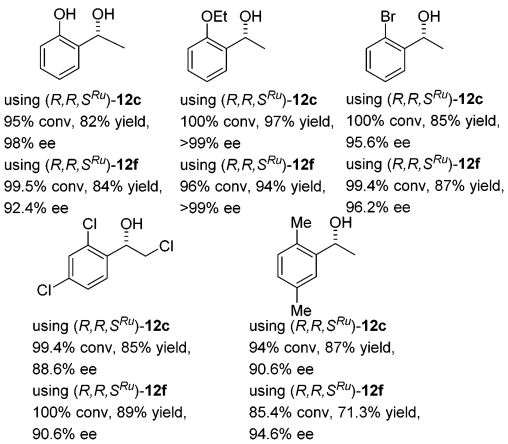


Fig. 5 Further *ortho*-substituted products of ATH using the thioazole (**12c**) and 3-pyridyl (**12f**) catalysts. Configurations assigned by analogy with 2-methoxyacetophenone reduction.

Conclusions

In conclusion, we report the results of the first comprehensive study of the preparation and applications to ATH of ketones of a series of DPEN-derived catalysts containing heterocyclic sulfonamide groups. The catalysts proved to be robust, readily characterised and highly active in the ATH of a series of ketones, giving alcohols in high conversion and enantiopurity. In some cases, the observed product ees exceeded those for established catalysts of this class. Although each catalyst generated an ATH product of similar ee in most cases, several variations were noted, suggesting the involvement of secondary directing effects. Although the precise nature of these effects cannot be fully identified at this point, these and further applications remain the subject of ongoing studies.

Data availability

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

Author contributions

The manuscript was written through contributions of all authors. MW planned the investigation, provided supervision, analyzed the data and wrote the manuscript. NK planned the investigation, carried out the practical work, analyzed the data and wrote the manuscript. GJC carried out the X-ray crystal structure analyses and provided the data for the paper.

Conflicts of interest

There are no conflicts to declare.

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