Tethered ruthenium(II) η^6-arene complexes: assessing the potential of benzylic substituents to control metal-centred chirality, and applications in asymmetric transfer hydrogenations of ketones.

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Abstract

The synthesis and characterisation of a small series of tethered ruthenium(II) η^6-arene complexes is described, where a single benzylic substituent is examined as a route to enforcing chirality at the metal centre upon ligation of a tethered bidentate ligand. The application of these complexes as catalysts in the asymmetric transfer hydrogenation of ketones is described, with moderate enantioselectivities confirming the validity of the approach.

Keywords: chiral-at-metal, ruthenium, asymmetric transfer hydrogenation, half-sandwich complexes.

1. Introduction

Numerous reports have detailed the synthesis of chiral-at-metal ruthenium(II) half-sandwich complexes with applications focused predominantly on enantioselective catalysis [1-3], as well as evaluation in a number of studies focused on bioinorganic aspects [4-6].

Synthetic approaches to chiral-at-metal ruthenium(II) half-sandwich complexes have taken a variety of routes, including via the use of achiral ligands, chiral monodentate ligands, chiral bidentate ligands, and arene ligands tethered to functionalities able to coordinate to the metal [1-3]. For ruthenium(II) half-sandwich complexes bearing monodentate ligands, there is a low barrier to inversion of the coordinatively unsaturated two-legged species formed as intermediates or transition states during catalysis and bioinorganic applications [7]. This has resulted in complexes bearing bidentate ligands being favoured due to the greater control of stereochemistry enforced at the metal centre during the course of a reaction. The use of a chiral bidentate ligand to yield a chiral-at-metal complex is well exemplified by examples reported by Noyori incorporating a bidentate (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine ((*S*,*S*)- or (*R*,*R*)-TsDPEN) ligand coordinated to a Ru(η^6-arene)Cl moiety (e.g. Fig. 1 - left) [8]. These complexes have been extensively utilised in the asymmetric transfer hydrogenation of ketones [8, 9]; within these complexes it is the chirality of the TsDPEN ligand which determines the configuration at the ruthenium centre [10]. More recent work by various research groups has focused on the incorporation of tethers into ruthenium(II) half-sandwich complexes. In one approach, chiral-at-metal piano-stool ruthenium complexes were obtained via the use of a meta-substituted η^6-benzene ligand bearing a pendant phosphine and pendant pyrazole group [11]. The coordination of both pendant coordinating groups to the ruthenium ion established a chiral-at-metal centre where the configuration at the metal is dictated by the planar chirality of the complex. Each diastereoisomer (the pyrazole functionality also acted as a chiral auxilliary) was accessed and the complexes were found to be configurationally

stable on heating and irradiation. Other approaches have utilized a single tether in complexes analogous to the Noyori asymmetric transfer hydrogenation catalysts, including the tethering of the arene to the metal centre [12], and the connecting of the η^6-arene and the chiral bidentate ligand (e.g. Fig. 1 – centre) [13-15]. The latter systems, where the ligand is attached to the metal at three points, are of note due to their increased stability and greater reactivity in asymmetric transfer hydrogenation reactions compared to the original Noyori catalysts [14-16].

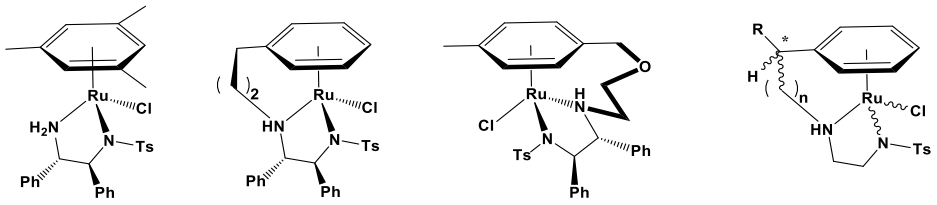


Figure 1: Chiral-at-metal ruthenium(II) half-sandwich complexes incorporating a chiral bidentate ligand [8] (left), and examples bearing a tether between the arene ligand and the TsDPEN moiety [14,15] (centre). Target structure for the current work (right).

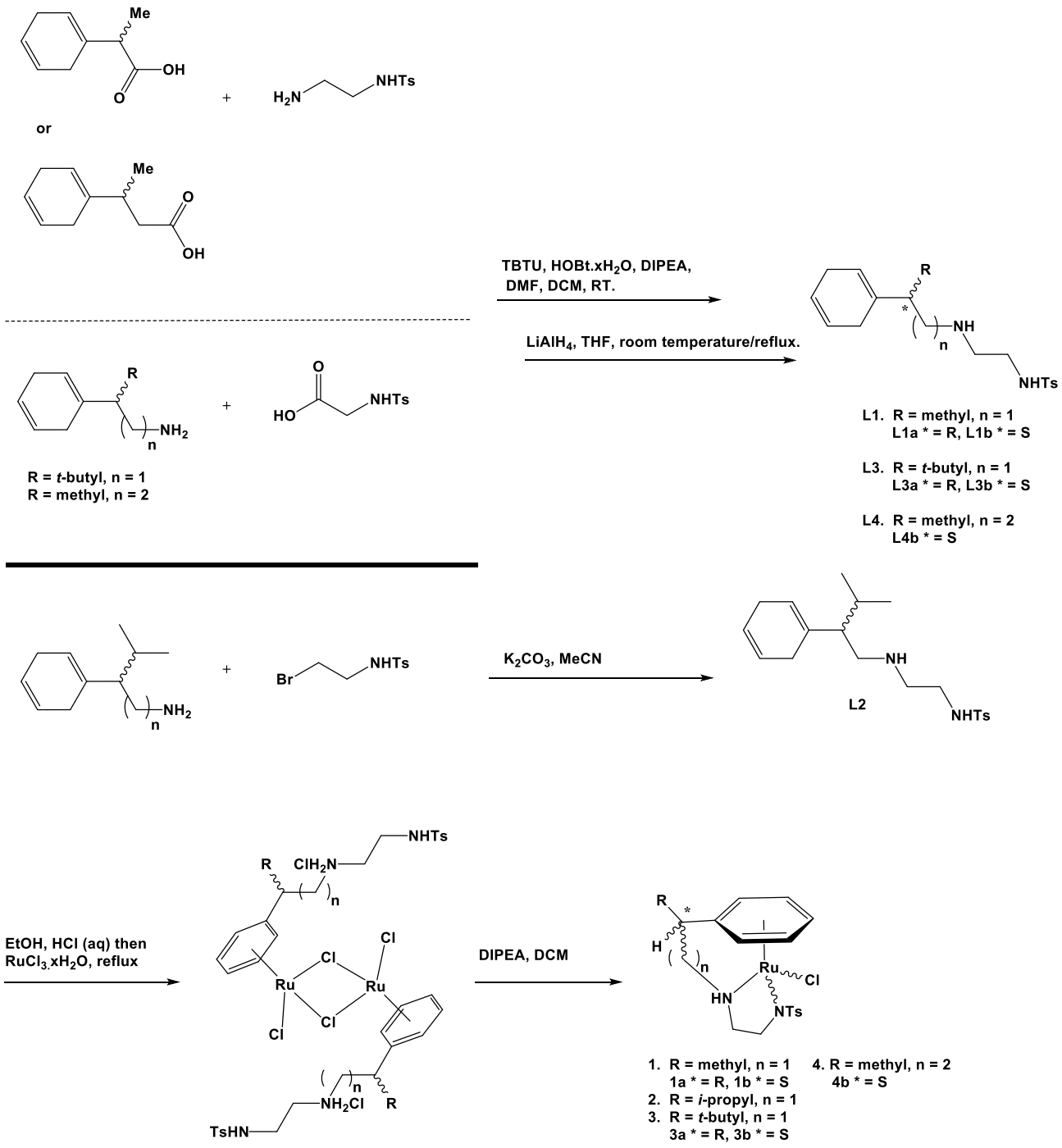
With this background in mind, and as an extension of the tethered structures introduced by Wills and Ikariya [12-15], we postulated that the introduction of functionality of moderate steric bulk at the benzylic position of the arene ligand of a ruthenium(II) half-sandwich complex of the type shown in Figure 1 (right) would result in a degree of control over the stereochemical configuration at the ruthenium ion upon ligation of the tethered bidentate ligand. Such complexes would provide an alternative route to control metal-centred stereochemistry in half-sandwich systems that is commonly achieved through the use of chiral bidentate ligands. In addition, the steric demands of the benzylic substituent coupled with the position of the tether may provide a degree of control over the interactions of substrates with the complex, potentially restricting substrate approach to the complex to be limited to a defined segment of the coordination sphere.

Herein we report the synthesis of a series of tethered Ru(II)-η^6-arene compounds bearing functionality (methyl, *i*-propyl and *t*-butyl) at the benzylic position of the tether, including examples formed from enantiopure ligands. The influence of the benzylic substituent on the stereochemical configuration at the metal centre is probed by NMR spectroscopy and single crystal X-ray crystallography. The ability of the complexes to reduce ketones in an enantioselective manner is also reported.

2. Results and Discussion

2.1 Synthesis and Characterisation

The tethered complexes **1**-**4** were each prepared in a similar manner (Scheme 1), commencing with the Birch reduction of an appropriate arene ligand. For complexes **1a** and **1b**, the Birch reduction of commercially available (*R*)-(-)-2-phenylpropionic acid or (*S*)-(+)-2-phenylpropionic acid respectively yielded the corresponding diene. Amide formation between the pendant acid group of the diene and *N*-tosylethylenediamine, followed by reduction with $LiAlH_4$, afforded the target ligands **L1a** and **L1b**. An analogous route was used to access racemic **4**, whilst the enantiopure ligand (*S*)-3-phenylbutan-1-amine was converted to the diene, then utilised in the amide formation with *N*-(*p*-toluenesulfonyl)glycine followed by reduction to the amine using $LiAlH_4$ to yield the enantiopure diene ligand **L4b**.



Scheme 1: Synthesis and numbering scheme of the tethered Ru(II)-η^6-arene compounds bearing benzylic functionality.

For the racemic *i*-propyl analogue **2** the synthetic route commenced with the reduction of commercially available 3-methyl-2-phenylbutyronitrile using $LiAlH_4$. The resulting arene bearing a pendant amine was converted to the corresponding diene via Birch reduction, followed by its reaction (in excess) with *N*-(2-bromoethyl)-4-methylbenzenesulfonamide to afford the target diene ligand **L2**.

The synthesis of the *t*-butyl analogues, **3**, **3a** and **3b**, commenced with the synthesis of 3,3-dimethyl-2-phenylbutan-1-amine via the addition of *t*-butylmagnesium chloride to *trans*-β-nitrostyrene. The nitro group was reduced using a mixture of iron powder and NH_4Cl in EtOH/H_2O, then the intermediate amine was separated into its constituent enantiomers by fractional crystallisation of the salt formed with (*S*)-mandelic acid, followed by Birch reduction of the arene. The resulting diene was coupled with *N*-(*p*-toluenesulfonyl)glycine then reduced to the amine using $LiAlH_4$ to yield ligand **L3,** and the enantiopure ligands, **L3a** and **L3b**, for the synthesis of **3**, **3a** and **3b** respectively. An analogous complex to **1a**, **5**, bearing a tether without the extended diamine component, was accessed via the Birch reduction of (*R*)-2-phenyl-1-propylamine to yield the target ligand, **L5**.

In each case the target complex was accessed via dissolution of the respective diene ligand in ethanol, followed by the addition of HCl, then reflux in the presence of $RuCl_3.xH_2O$ to yield the chloride-bridged half-sandwich Ru(II) complex. The target mononuclear complexes were then accessed by deprotonation of the ligand using DIPEA, followed by purification using silica gel column chromatography. Full details of the synthesis of all complexes, including precursors, are given in the Supporting Information.

2.2 NMR Spectroscopy Studies

^{1}H NMR spectra of **1**-**4** revealed the presence of two distinct sets of arene signals for each complex, indicating the presence of a pair of diastereoisomers in solution (confirmed by X-ray diffraction studies, see later discussion). Each set of arene signals consisted of five unique resonances, highlighting the non-equivalence of the five arene protons within each isomer due to the restricted rotation of the tethered arene ligand and the chiral metal centre. For complexes constructed from a racemic arene ligand, each diastereoisomer will be present as racemic mixtures of both possible enantiomers.

For **1a** and **1b**, the two major configurational isomers were obtained, following column chromatography, in a ratio of ~0.5:1. The structure of these diastereoisomers were assigned to **B** and **A** respectively (Fig. 2), based on crystallographic data and comparison with the NMR and structural data collected for both enantiomers of a diastereoisomer of **2** (see discussion later). On standing of solutions of **1a** in $CDCl_3$ at 25°C the two isomers were in slow exchange with one another, reaching a constant ratio of 1:1 after 60 h. Further heating of the sample at 40°C for 24 h did not lead to additional changes to the ratio of isomers in solution.

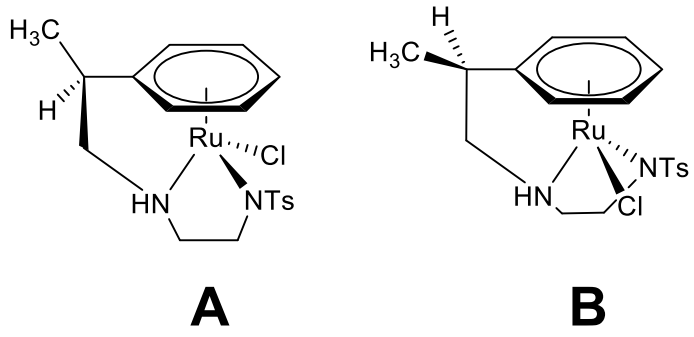


Figure 2: The structures of the two diastereoisomers of **1b** observed in ^{1}H NMR studies, as assigned based on crystallographic studies and comparison with NMR and structural data obtained for **2**. The two diastereoisomers observed for **1a** are assigned to the respective mirror image structures.

For **2** a similar observation was made, with two major sets of arene signals seen in solution in a ratio of 0.25:1 (each set corresponding to one diastereoisomer as a racemic mixture of both enantiomers) following isolation of the complex by column chromatography. With this complex it was possible to isolate one diastereoisomer (as a racemic mixture of the two enantiomers) in >94% excess by further recrystallisation from ethanol (solid state structure discussed later). On standing of a sample of this complex in $CDCl_3$ at 25°C interconversion of the two diastereoisomers was observed, reaching a ratio of 0.35:1 after 7 days, however equilibrium was not yet reached at this point. Close inspection of the NMR spectra of **1a**/**1b** and **2** also revealed the presence of a further minor (circa 2%) set of arene peaks, indicative of a third isomer. The identity of this species was not determined. The analogous complexes bearing a *t*-butyl substituent at the benzylic position were also isolated as a pair of configurational isomers. Like with **1** and **2**, the NMR spectra of **3** (formed with the racemic ligand) indicated the major isomer which initially formed related to the structure of type **A** (Fig. 2), where the benzylic substituent is approximately perpendicular to the plane of the arene ligand. Presumably for isomers of the type **B** (Fig. 2), where the benzylic substituent nears the plane of the arene ligand, the greater steric hindrance between the benzylic substituent and the arene leads to the lesser degree of initial formation of this isomer. For **4** two sets of arene signals were observed in the ^{1}H NMR spectrum, these being found in a ratio of 1:1, reflecting the increased length of the tether which clearly allows for equal formation of each diastereoisomer. The ^{1}H NMR spectrum for **5** was much simpler, with a single set of arene resonances consisting of five signals being observed. This again reflects the non-equivalence of the arene protons due to the tether restricting the rotation of the arene ligand.

2.3 X-ray Diffraction Studies

The molecular structures of **1a**, **1b**, **2**, **4** and **5** were determined by single crystal X-ray crystallography. Crystals were all grown by the slow evaporation of a solution of the complex in ethanol. Structural data for **1b** show it crystallises in the chiral space group $P2_12_12_1$ with two diastereoisomers of **1b** in the asymmetric unit, related by a pseudo-inversion centre, differing from one another in the stereochemical configuration at the ruthenium centre (Fig. 3, left). In one diastereoisomer the methyl group was found to reside above the plane of the arene ligand with the benzylic carbon-methyl bond approximately perpendicular to this plane. The tether coordinates to the ruthenium ion through both N-atoms yielding the *R* configuration at Ru(II) [17]. The structure of the alternative diastereoisomer differed in that the benzylic carbon-methyl bond lies in the same plane as the arene moiety, with the bending of the arene-benzyl carbon bond resulting in the methyl carbon residing just below this plane. Consequently, the amine group of the tether is found positioned directly under the arene carbon from which the tether emanates, and the stereochemical configuration at the ruthenium ion in this case is *S*. The difference is most easily discernable by viewing the molecules down the bonds C1-C7 and C21-C27 towards the arene (Fig. S2). The crystal structure of **1a** is centrosymmetric and contains a pair of structures related by a strict centre of inversion, meaning both configurations at the ruthenium ion are observed. There is disorder at the stereogenic centre at C7 such that both configurations are present in equal amount in the crystal as a whole, meaning that the four possible stereoisomers of this complex are observed**.‡**

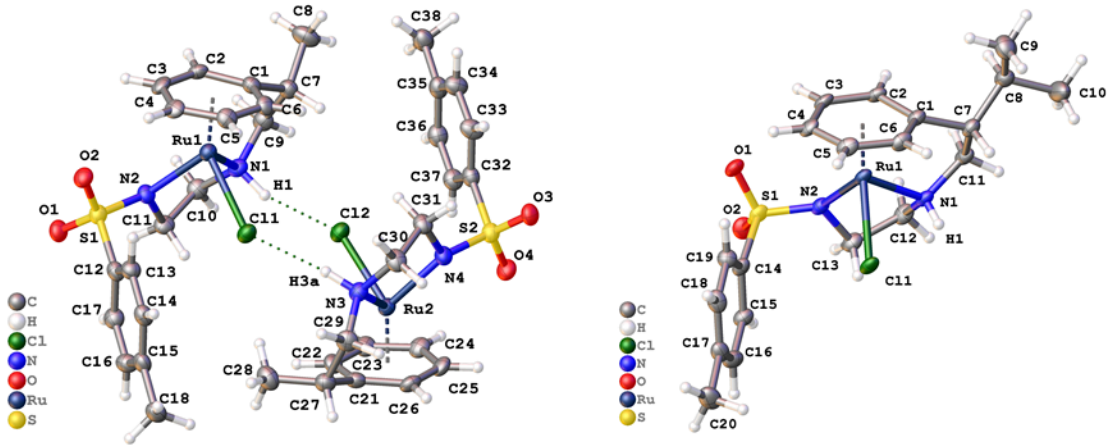


Figure 3: Asymmetric unit of **1b** with atoms show as 50% probability elipsoids (left) and complex **2** (right)

The crystals obtained of **2**, isolated following repeated recrystallisation, were predominantly of a single diastereoisomer (as a racemic mixture of both its enantiomers due to the racemic ligand used in the synthesis of the complex), as assessed by ^{1}H NMR spectroscopy (obtained in >94% excess). Within the structure determined from diffraction data, as in structures of **1a** and **1b**, there was a noticeable bend of the benzylic carbon-arene bond resulting in the benzylic carbon residing in a position under the plane of the arene ligand (Fig. 3, right). The *i*-propyl substituent was observed to reside above the arene ligand, where the bond between the benzylic carbon and *i*-propyl group was at 90° to the plane of the arene. The tether then coordinated to the metal centre via both nitrogen atoms to establish the *R* configuration at the ruthenium ion with a configuration at the benzylic position of *S*, or vice versa.

Structural data obtained for **4** related to only one of the two diastereoisomers (present as a racemic mixture of both its enantiomers due to the racemic ligand used in the synthesis) seen in the solution state (Fig. 4, left). The decreased strain due to the longer tether is seen through the arene and benzylic carbon atoms residing in the same plane, whereas in the shorter chain analogues the benzylic carbon resides below the plane of the arene ligand. In the structure of **4** represented in Fig. 4, the methyl substituent, with *R* configuration at the benzylic stereocentre, was able to reside above the plane of the arene ligand, with the tether coordinating to the metal ion in a bidentate manner resulting in a *S* configuration at this stereocentre. Based on this data, it would be expected the alternative diastereoisomer, with *R* configuration at the metal centre, would be readily formed with only a relatively modest rotation of the arene-benzylic carbon bond being required, as opposed to the more dramatic changes in structure seen between the diastereoisomers observed for **1b**. The relatively unconstrained nature of this system is reflected by the equimolar ratio of diastereoisomers observed by ^{1}H NMR spectroscopy in solution.

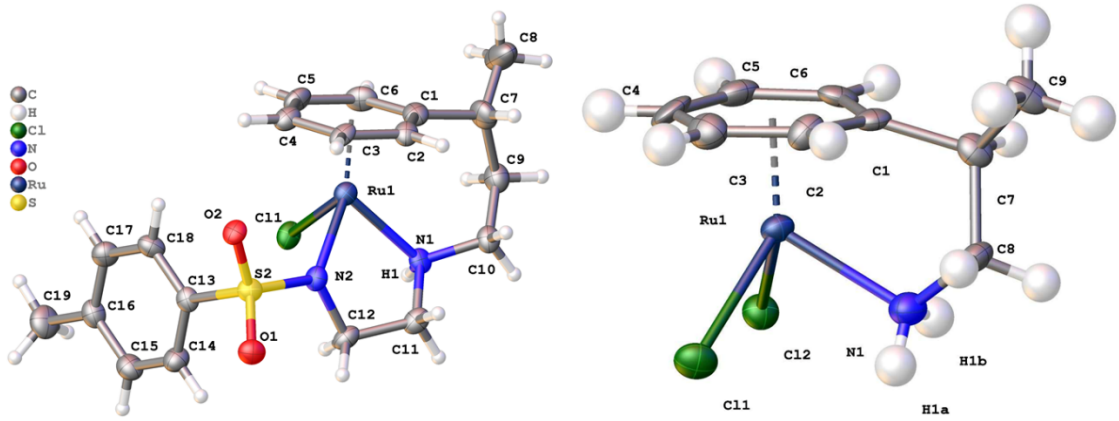


Figure 4: The molecular structures of **4** (left) and **5** (right) as determined by X-ray diffraction.

The structure of **5** (Fig. 4, right) is non-centrosymmetric and contains a non-chiral metal centre. However, there are four unique conformers of **5** observed in the asymmetric unit (Fig. S8), in each case the chelated structure is relatively strained, apparent from the bending of the arene-benzylic carbon bond to result in the benzylic carbon residing below the plane of the arene ligand. The configuration at the benzylic stereocentre was confirmed as *R*, as expected from the *R* configuration of the starting ligand.

2.4 Asymmetric Transfer Hydrogenation Studies

Given the interesting distributions of configurational isomers seen for these complexes in the solution and solid state they were evaluated for their ability to effect asymmetric transfer hydrogenation (ATH) of ketones in formic acid/triethylamine (Table 1). **1b** (0.5 mol%) was employed in the reduction of acetophenone to yield the product with 22% conversion and 20% ee (*S*) after 24 h at 40°C, whilst **1a** yielded the product in 23% yield and 18% ee (*R*). The product enantiomer observed in excess in each case is that predicted to be formed by the hydride derivative of the major diastereoisomer of **1a**/**1b** observed at earlier time points in NMR studies, assuming the mode of action remains the same as for previously reported tethered compounds incorporating a tosyl-diphenylethylenediamine moiety [18].

1a was utilised in the reduction of a series of ketones, yielding product alcohols in a similarly modest range of ee's, although conversions remained low. As with acetophenone, for further ketones containing an aryl group the stereochemical configuration of the product alcohols formed in excess matches, in each case, what would be expected with the hydride derivative of the major diastereosiomer observed in NMR studies. The exceptions to this were isobutyrophenone, which was reduced in too low a yield for the enantioselectivity to be assessed, 2-acetylpyridine, which was not reduced, and α,α,α-trifluoroacetophenone, which was reduced in good yield (88%) but for which the ee was very low (2% (*S*)). This substrate has been reported in the literature to be reduced with relatively low enantioselectivity by structurally related catalysts due to competition between the two ketone substituents for occupation of space adjacent to the η^6-arene ligand in the transition state [19, 20]. This explanation is likely to hold for the present complexes, and explains the lower ee on reduction of α,α,α-trifluoroacetophenone relative to the other ketones.

Due to low quantities of material obtained, single ATH experiments were performed with **3a** and **3b**, the *t*-butyl analogues of **1a** and **1b**, and acetophenone. Both reductions were found to proceed with low yield (<7%), but the enantiomers formed in excess were (*R*)-phenylethan-1-ol (31%

ee) and (*S*)-phenylethan-1-ol (34% ee) respectively, agreeing with the order of enantioselectivities found with **1a** and **1b**.

With **4b** a single ATH experiment was performed, reduction of acetophenone proceeded in 99% yield and 18% ee (*S*). Again, assuming the interaction of the substrate and complex is governed by a C-H···π interaction, the enantiomer of the product alcohol formed in excess is what would be expected from the hydride derivative of the diastereoisomer with *R* configuration at ruthenium. This suggests, given that room temperature NMR studies in $CDCl_3$ show both diastereoisomers of **4b** being present in a 1:1 ratio, the active catalyst derived from the diastereoisomer of **4b** with *R* configuration at the metal centre is dominant/possesses the greatest activity under the reaction conditions. The achiral-at-metal complex, **5** was also screened for its ability to reduce acetophenone. The almost negligible conversion of 2% and ee of 7% (*S*) highlighted the poor activity of this complex.

catalyst	Time, h	ketone	Yield[a] (%)	alcohol ee[b] (%)	alcohol configuration[b]
1a	24	acetophenone	23 ± 6	18 ± 3	R
1b	24	acetophenone	22 ± 1	20 ± 2	S
3a	24	acetophenone	4	31	R
3b	24	acetophenone	7	34	S
4b	24	acetophenone	99	18	S
5	24	acetophenone	2 ± 0	7 ± 1	S
1a	24	1-(4-chlorophenyl)ethanol	21 ± 6	15 ± 1	R
1a	24	4′ -methylacetophenone	9 ± 1	19 ± 0	R
1a	24	propiophenone	8 ± 0	16 ± 2	R
1a	24	1-cyclohexylethan-1-one	7 ± 2	13 ± 1	R
1a	24	isobutyrophenone	1 ± 0	-	-
1a	24	pinacolone	6 ± 2	-	-
1a	24	α,α,α-trifluoroacetophenone	88 ± 7	2 ± 0	S
1a	24	2-acetylpyridine	-	-	-

Table 1: Data for the ATH of ketones in formic acid/triethylamine, catalysed by tethered ruthenium(II) η^6-arene complexes bearing a benzylic substituent. Reactions were performed at 40°C for 24 h in a 2 M solution of the ketone, 0.5 % catalyst loading, in a formic acid/triethylamine (5:2) mixture. [a] Yields are those following column chromatography and determined by ^{1}H NMR analysis (average of three replicates except entries 3-5 which are results from a single experiment) [b] Determined by capillary GLC analysis using a chiral Restek RT-βDEXsm, 30 m x 0.25 mm x 0.25 µm column (ee values reported are the average of three replicates except entries 3-5 which are obtained from a single experiment). Where yield and/or ee entries are blank, the degree of conversion was insufficient to allow these values to be determined.

These results demonstrate that enantiocontrol in transfer hydrogenation reactions in formic acid/triethylamine can be achieved using complexes of the type reported herein. As seen with most ketone substrates, the product alcohol produced in excess is the one which would be expected to be formed from the active catalyst derived from the diastereoisomer of the complex with structure of type **A** (Fig. 2). Given that each complex was found to be present as a mixture of diastereoisomers, for which the hydride derivatives of each may be able to effect the transfer of hydrogen to a ketone

substrate, we postulate the origins of the formation of this alcohol enantiomer in excess may be related to several different factors. The first is that the active catalytic species derived from the diastereoisomer of the complex seen in excess in NMR studies in $CDCl_3$, and which would be expected to yield the alcohol enantiomer seen in excess, may remain in excess throughout the catalytic cycle. Even though during the catalytic cycle the complex goes through a two-legged 16-electron intermediate which provides an opportunity for racemisation at the ruthenium ion to occur, the benzylic substituent may exert sufficient influence to allow for the continual reformation of the active species which leads to the alcohol enantiomer formed in excess. The second consideration is that the catalytically active species derived from the two disatereoisomers observed in solution may each exhibit different levels of activity. And as each catalyst diastereoisomer would lead to opposite product configurations, any differences in activity could result in preferential formation of one of the product alcohol enantiomers. Previous studies have detected the presence of the two diastereoisomers of a tethered ruthenium-hydride complexes during acetophenone reduction, where one diastereoisomer was determined to be significantly less active than the other [16, 21]. An insight into potentially different levels of activity for each diastereoisomer of the current complexes can be gleaned from structural data collected for **1b**. A comparison of the Cl-Ru-N-H torsion angle within each structure can serve as a proxy for the H-Ru-N-H torsion angle in the corresponding hydride analogues for which we do not have structural data for. For the diastereoisomer represented by **A** (Fig. 2) the Cl-Ru-N-H torsion angle was measured as -17.1°, whilst for diastereoisomer **B** the torsion angle was measured to be 24.3°. Earlier work has shown that higher catalyst activity results when the H-Ru-N-H torsion angle is closer to zero [22, 23], suggesting that **A** would be expected to result in greater catalytic activity. In addition, the distance between the chloride ligand and the amine proton is less in **A** (2.731 Å) than in **B** (2.867 Å). The combination of the expected differences in torsion angle and hydride-proton distance in these complexes provides grounds for expecting the activity of the catalytically active hydride species derived from **A** to be greater than that derived from **B**. Finally, the position of the benzylic substituent (parallel or perpendicular to the η^6-arene) within the active catalysts may also play a role in the stereocontrol of the reduction, potentially through stabilising electrostatic interactions with the substrate, or via steric repulsion.

3. Conclusions

In conclusion, tethered ruthenium(II) η^6-arene complexes have been prepared where a benzylic substituent is incorporated into the ligand structure. In each case, the complexes were isolated as a mixture of diastereoisomers due to two possible stereochemical configurations being accessible at the metal centre. The complexes showed activity in the ATH of ketones in formic acid/triethylamine, with modest enantioselectivities being observed. These results demonstrate that the ligand frameworks reported here are a potential alternative route towards the enforcement of chirality at the metal centre in half-sandwich complexes. An area for immediate improvement in ligand design would be to reduce the flexibility of the diamine component of the tether so that only one of the two possible stereochemical configurations at the metal ion is accessible. This would allow access to complexes where only one diastereoisomer is formed, and would allow access to novel chiral-at-metal complexes for investigations in catalysis and biological systems.

‡ Structural data for **1a** showed the presence of the four possible stereoisomers of the complex arising from the stereocentres at the benzylic carbon and the ruthenium ion. HPLC analysis of the starting (*R*)-2-phenyl-propionic acid (purchased at 98% ee), and the corresponding product following

Birch reduction, confirmed the enantiopurity of the ligand used in the synthesis of **1a**. It is postulated that the mixture of stereoisomers present in the crystals of **1a** analysed by single-crystal X-ray diffraction is not representative of the bulk sample, and is most likely a result of the co-crystallisation of the stereoisomers relating to **1a** and **1b**, with the presence of structures relating to **1b** originating from the presence of the minor enantiomer in the starting ligand.

Declaration of competing interests

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article, including experimental procedures for all novel compounds and X-ray diffraction parameters, can be found in the online version.

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