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Ru(II) Complexes of N-Alkylated TsDPEN Ligands in Asymmetric Transfer Hydrogenation of Ketones and Imines

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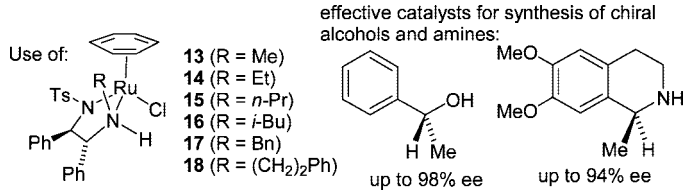
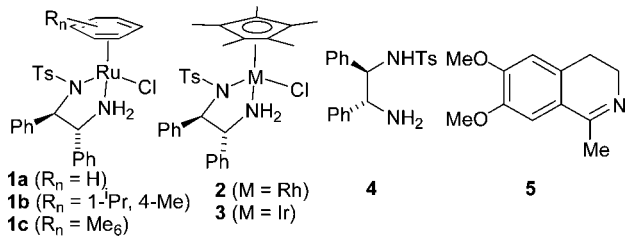
ABSTRACT



N-Alkylated TsDPEN derivatives bearing a small alkyl group act as highly efficient ligands in Ru(II) complexes for the asymmetric transfer hydrogenation of imines and ketones. A larger alkyl group serves to significantly reduce the activity of the catalyst; however, high enantiomeric excesses are still obtained. An X-ray crystal structure of the *N*-benzyl derivative reveals a conformation that permits hydrogen transfer through a six-membered transition state. A transition state structure for the imine reduction process is proposed.

Asymmetric transfer hydrogenation (ATH) of ketones and imines using catalysts based on Ru(II), Rh(III), and Ir(III) complexes (e.g., **1**−**3** respectively) of *N*-tosyl-1,2-diphenylethane-1,2-diamine (TsDPEN) **4** is now a well established and tested synthetic reaction.[1−6]



The mechanism of hydrogen transfer from Ru(II)/η^6-arene based catalysts **1** to ketones is now relatively well established.[6] Mechanistic and computational studies have provided strong support for the "ATH outer sphere" mechanism, as classified by Morris,[1c] in which two hydrogen atoms are transferred to a substrate via a six-membered transition state (TS) (Figure 1a). A π/CH interaction between a hydrogen atom on the η^6-arene and the aromatic ring of a substrate, with a value of ca. 8.6 kJ mol^{-1} is pivotal to the control of

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the absolute product stereochemistry. This effect operates even more strongly through a methyl group on the η^6-arene; value ca. 12.3 kJ mol^{-1}.[6a] However this requires that the substrate contains a suitably located aromatic ring. "Dialkyl" ketones are reduced in much lower enantioselectivity.

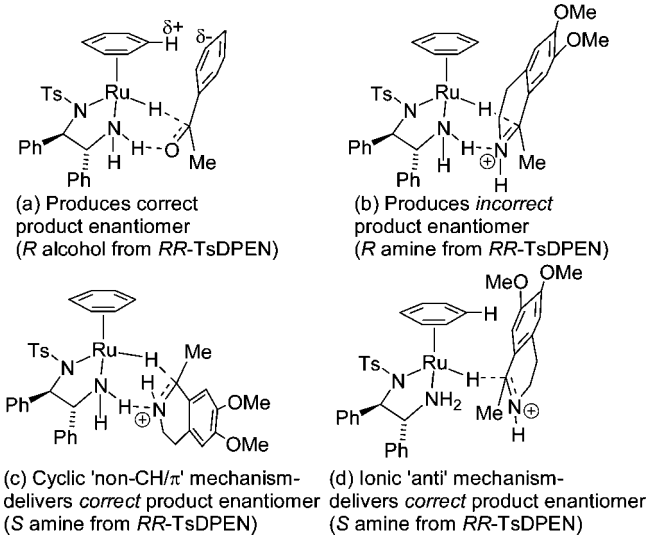


Figure 1. Mode of reduction of acetophenone (a) and potential modes of reduction of imine **5** (b−d) in ATH by catalysts **1**−**3**.

The mechanism of imine reduction is less well understood.[7] Cyclic imine **5** is reduced in high enantioselectivity at a rate higher than that of ketones by ATH catalysts based on TsDPEN.[4a] Bäckvall has demonstrated that only protonated imines are reduced by isolated hydride intermediates through which catalyst **1** operates, an observation that supports an ionic, rather than a concerted, mechanism.[7a] Casey's studies on a related Ru(II)-based catalyst support an outer sphere mechanism of reduction, analogous to the ketone reduction mechanism.[7b] Blackmond's investigation on reduction of imine **5** using Rh(III) **2** catalyst suggests, in contrast, that the unprotonated imine is the true substrate.[7c]

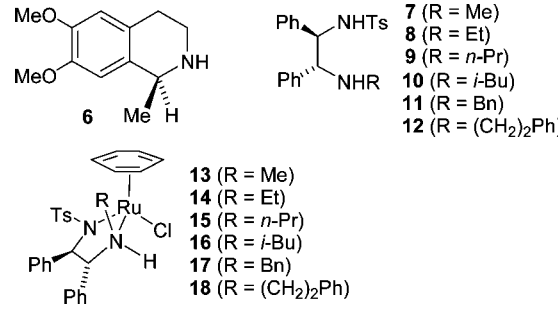
The mechanism of the reduction of imine **5** cannot, however, simply be superimposed upon that accepted for ketone reduction (i.e., Figure 1b). This is because the opposite sense of asymmetric induction is observed compared to that which would be predicted. We suggest that two alternative explanations may be considered:

(i) that the imine(ium) is reduced through a six-membered TS but oriented such that the relative positions of alkyl and aryl groups are reversed (Figure 1c), or

(ii) that the imine is reduced through an ionic mechanism in which the C═N bond of an iminium cation is oriented away from the NH of the amine of the ligand (Figure 1d) and without the involvement of a six-membered transition state. This would allow the analogous CH/π interaction to operate, while delivering the correct (observed) enantiomer of reduction product.

To probe this mechanism, we elected to prepare and investigate the use of N′-alkylated TsDPEN ligands **7**−**12** in the ATH of ketones and imines.[8−10] We speculated that the bridging chain between N and the aromatic ring in **5** would generate an unfavorable steric interaction with an alkyl group at the basic nitrogen atom (see below). In contrast, the ketone, which lacks this group, should be reduced by an N-alkylated ligand without difficulty. If the TS of Figure 1b was operating, it would be predicted that N-alkylated TsDPEN derivatives would reduce acetophenone, but the rate of imine **5** reduction would be significantly reduced. On the other hand, if the TS of Figure 1c or d was operating, then reduction of **5** with modified ligands should not be significantly retarded. Ikariya and Koike have reported illuminating results relating to the reversible decarboxylation of the formate derived from **1b** and its NMe analogue, which is a key step in the mechanism of catalysis by such complexes.[8a] N′-Alkylated derivatives of *N*-tosyl-1,2-diaminocyclohexane[9a,b] and the structurally analogous 2-tosylaminomethyl-pyrrolidine[9c,d] have been used in ketone and imine ATH. However, we are not aware of a systematic study on TsDPEN derivatives in ketone ATH. Ligands **7** and **8** have been employed in an ATH reaction of C═C bonds.[10]

In earlier work in this group, we had attempted to use the N′-BnTsDPEN ligand **11** for an in situ catalyst formation with a Ru(II) source; however, this led to a very poor result when applied to acetophenone ATH.[11] It was therefore considered essential that the preformed complexes be prepared.



To gain a full picture of the effect of an N′-alkyl substituent on the catalysts, we prepared a series of com-

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plexes **13**−**18** from their TsDPEN precursors,[12] in addition to a sample of the known TsDPEN catalyst **1a**.[13] Each was characterized as the monomer in order to ensure comparability. Each of the catalysts were employed in the reduction of acetophenone, and the reductions were followed by ^{1}H NMR spectroscopy (Figure 2). The ee's were collated at the end of the reductions.

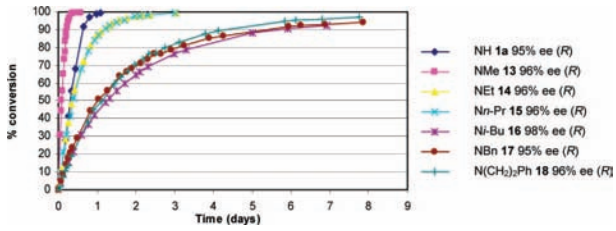

Figure 2. Reduction of acetophenone in ATH by catalysts **1a** and **13**−**18**. Conditions: FA/TEA = 5:2, [ketone] = 0.86 M, 28 °C. S/C = 100. Followed by ^{1}H NMR; ee determined by chiral GC.

Contrary to our previous experience, the *N*-benzyl complex **17**, now isolated, proved to be effective as a reduction catalyst; however, it was not as active as the parent **1a** but was equally enantioselective. Furthermore, N′-methylated complex **13** proved to be even more active than **1** and equally enantioselective. These results suggest that the N-alkylated complexes are still fully capable of reducing ketones through the six-membered transition state established for the non-alkylated parent, although with reduced activity in the case of ligands containing bulky substituents.

In the reduction of imine **5**, the results followed a similar pattern (Figure 3) with the exception that imines were reduced in a matter of hours rather than days.[4a] The enantioselectivities of the reductions were comparable for most complexes, although the NBn complex gave a better result than the others under the particular conditions tested (S/C =100 with MeCN cosolvent). In each case the same configuration of product (*S*) was formed from each *RR*-DPEN derived complex. That the ee's are generally lower than those reported by Noyori for TsDPEN-derived Ru(II) catalysts[4a] may reflect our use of benzene rather than *p*-cymene or hexamethylbenzene as the η^6-arene in the complex (i.e., complexes **1b** and **1c**).

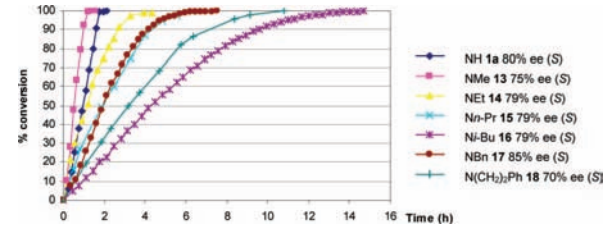

Figure 3. Reduction of imine **5** in ATH by catalysts **1a** and **13**−**18**. Conditions: MeCN, FA/TEA = 5:2, [**5**] = 0.45 M, 28 °C. S/C = 100. Followed by ^{1}H NMR, ee obtained by chiral GC.

An X-ray crystal structure of the *N*-Bn complex **17** was obtained (Figure 4), which revealed that, contrary to our earlier assumptions, the Bn group occupied the position proximal to the η^6-arene ring. Although this group introduces an extra dimension of steric hindrance to the approach of a reagent to the catalyst, it still permits the six-membered TS (Figure 1a) to operate. This would explain the ability of all of the N-alkylated catalysts to reduce acetophenone with the same high ee as **1** but with reduced rates, as the size of the groups on nitrogen increase (if it is assumed that the alkyl group occupies the same position in each complex). The rate acceleration observed for the *N*-Me complex **13** was surprising and reflects Ikariya and Koike's observation that the formate complex of the *p*-cymene derivative of **13** decomposes to the corresponding hydride at approximately twice the rate of **1b**, the TsDPEN derivative.[8a] We have previously demonstrated that Ru hydride formation can be the limiting factor in catalysis by complexes such as **1**,[14] and this may also be the case for the N′-alkylated complexes. It should be noted that **17** is the precursor of the active hydride that performs the reduction. While the relative configuration at the Ru atom relative to the ligand matches that observed in previous X-ray structures, we have assumed and not proven that the corresponding hydride has an identical relative configuration.[2e]

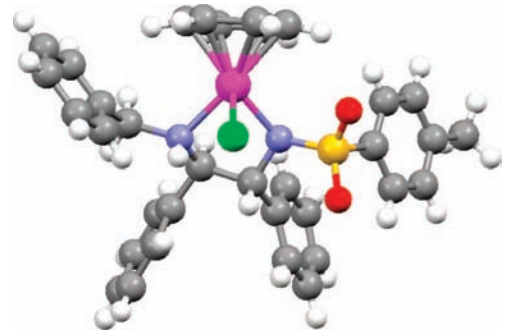

Figure 4. X-ray crystallographic structure of *RR*-**17**. Further views are shown in Supporting Information.

These results provide some information about the probably mode of reduction of imine **5** in this reaction (Figure 5).

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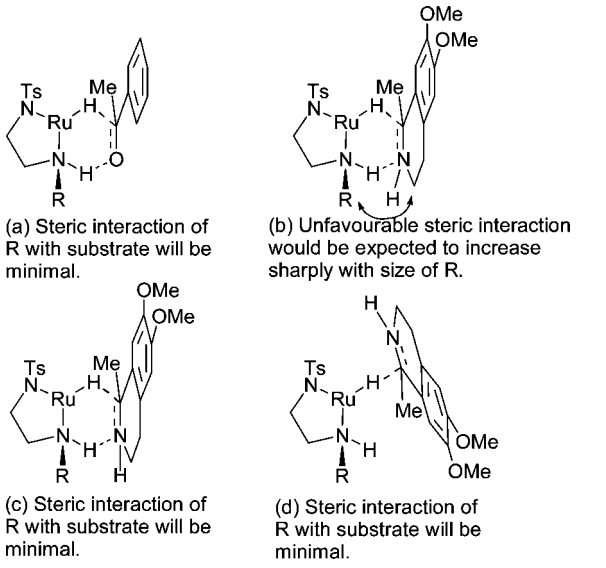

Figure 5. Representations of the relative position of the R group in complexes **13**−**18** to the substrate (view from above arene ring but with arene ring removed for clarity) corresponding to transitions states a−d in Figure 1.

For the established ketone reduction TS (Figures 1a/5a), the R group is relatively distant from the substrate and therefore would be predicted to have a minor steric effect and therefore little influence on the ee's of the products. There would, however, be an electronic influence on the TS that could influence the rate (e.g., **13** vs **1a**). The ketone reduction results thus act as a "baseline" for mostly electronic effects rather than steric ones. In the case of the "superimposed" imine reduction TS (Figures 1b/5b) the R group on the nitrogen atom is very close to the cyclic part of the imine, and therefore large R groups would be predicted to have a major influence on the rate and the ee of the reaction, by severely disrupting the intramolecular hydrogen bonding. However, this is not observed. Given that this TS also delivers the wrong enantiomer of product, the evidence suggests that it does not operate in this reaction.

The remaining two possibilities for the imine reduction TS (Figures 1c/5c and 1d/5d) both require the approach of the substrate through a course that avoids close contacts between the N′-R groups and the substrate. Hence, for each of these, the pattern of rate and ee relative to **1a** would be anticipated to mirror that seen for acetophenone. Since only the TS in Figures 1d/5d permits what is known to be an important CH/π interaction,[6] and given the evidence for the involvement of a protonated imine in the reduction reaction,[7a] we suggest that this could be considered a viable model for further investigations into the precise mechanism by which asymmetric induction is achieved in the ATH of imines.

In a final study of the behavior of N′-alkylated TsDPEN derivatives in imine reduction, we applied the modified conditions reported by Blackmond in which formic acid is added dropwise to a methanol solution of the substrate and triethylamine.[7c] Using these conditions, with catalyst **17**, the amine product was obtained in 94% ee and 97% conversion after 4 h. This indicates that there is significant scope for optimization of the use of N′-alkyated TsDPEN derivatives in ATH applications.

We are continuing our studies on imine reductions in order to establish the further utility of catalysts **13**−**18** and to obtain both experimental and molecular-modeling evidence to support the above proposal.

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Supporting Information Available: Experimental procedures, characterization data, X-ray crystallographic data for **17**, NMR spectra, and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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