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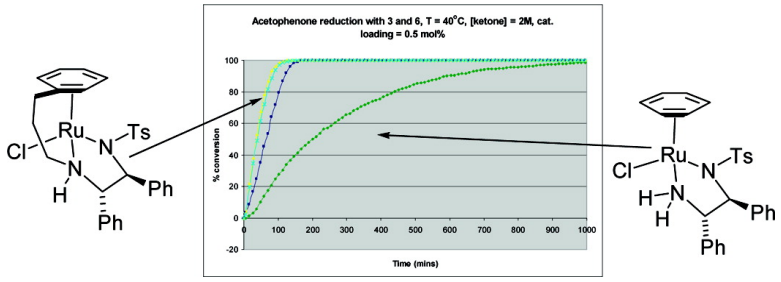
J. Am. Chem. Soc., **2005**, 127 (20), 7318-7319• DOI: 10.1021/ja051486s • Publication Date (Web): 03 May 2005



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A Class of Ruthenium(II) Catalyst for Asymmetric Transfer Hydrogenations of Ketones

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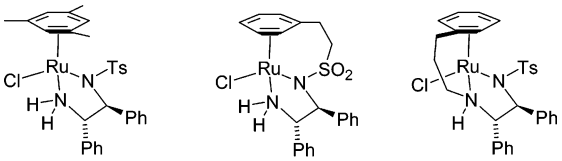
Asymmetric transfer hydrogenation (ATH) has recently been the subject of intense study by a number of groups worldwide.[1] The initial impetus for this was provided by Noyori et al., who reported highly active and robust Ru(II) catalysts based on complexes of monotosylated diamines[2−4] and amino alcohols[5] in the mid-1990s. Although many new catalysts have been reported for this application,[6,7] TsDPEN/Ru(II) complexes, such as **1**, have proved to be the catalysts of choice, as reflected by their applications to date.[8] The best results with TsDPEN/Ru(II) catalysts have been achieved in formic acid/triethylamine,[2] rather than 2-propanol.[3] The former solvent has the advantage that reactions more readily go to completion, whereas in 2-propanol, there is an element of reversibility. A limitation of the methodology is that the reactions are not particularly rapid; overnight reaction times are typically required, although reactions in water are reported to be faster.[9]

As a part of our own program of studies, we recently reported the synthesis and use of catalyst **2** in which the η^6-arene ring and the diamine ligand are connected through a three-atom tether.[7e] As well as increasing the stability of the complex, the tether serves to prevent the rotation of the arene ring, thus offering the potential for the addition of functional groups at various positions in a predictable manner. The opportunity to exploit this for the "fine-tuning" of the catalyst toward specific substrates remains the subject of continuing investigations.

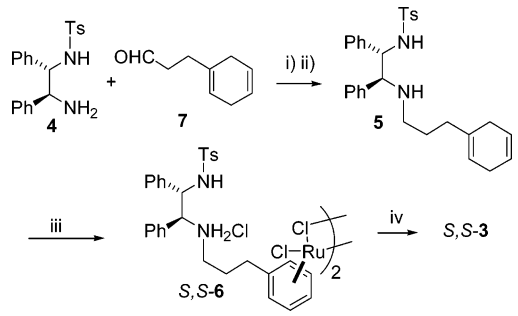


During the course our studies, we found that complex **2**, while highly effective at the reduction of acetophenone and other aryl/alkyl ketones, was no faster or no more enantioselective than the untethered system. For example, cyclohexylmethyl ketone was reduced in only 19% ee. In this paper, we report the synthesis and applications of the "reverse-tethered" complex **3**, which has proven to be significantly more active and versatile.

Complex **3** was prepared by reductive amination of TsDPEN **4** with the known aldehyde **7**[7e] to furnish **5**, which was reacted, as the hydrochloride salt, with ruthenium trichloride to give dimer **6** (Scheme 1). Upon treatment with triethylamine in IPA,[4] **6** was converted to **3**, which was characterized by X-ray crystallography (Figure 1) after purification by chromatography on silica gel. Although both antipodes of **6** were prepared, only (*S*,*S*)-**6** was converted to **3** for isolation and characterization.

Complex **3** proved to be a very active catalyst for ATH. The reduction of acetophenone **8** was completed using 0.5 mol % of **3**

Scheme 1 [a]



[a] Conditions: (i) 4A MS, DCM, o/n; (ii) $LiAlH_4$, THF, 2 h, 47%; (iii) HCl, Et_2O, rt, then $RuCl_3$ hydrate, EtOH, reflux, o/n, 89%; (iv) ^{i}PrOH, Et_3N, 56% or in situ.

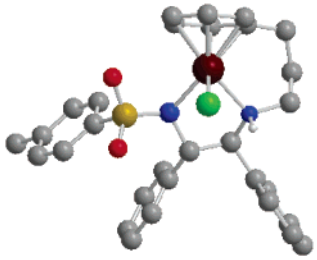


Figure 1. X-ray crystallographic structure of (*S*,*S*)-**3**.

in less than 3 h at 28 °C, and the alcohol was formed in 96% ee. This was a pleasing result since the untethered equivalent complex requires overnight reaction times for this transformation. The rate of the reaction could be increased by raising the temperature to 40 °C without any loss of enantiocontrol, while the time for completion of the reaction was reduced to ca. 100 min. A kinetic plot, obtained by following a reduction by ^{1}H NMR, revealed that the tethered compound was significantly more active than the untethered complex formed in situ through the combination of TsDPEN and $[Ru(cymene)Cl_2]_2$ (see Supporting Information).

It was found that it was not necessary to isolate monomer **3**; the direct use of **6** at 40 °C resulted in full acetophenone reduction within 3 h in 96% ee. In this experiment, **6** was heated in the formic acid/triethylamine for 30 min prior to addition of ketone. However, if **6** was treated for 3.5 h at 40 °C before the addition of ketone, then the reduction took place as rapidly as with **3** alone, reflecting the complete prior conversion of dimer to monomer. In view of these results, dimer **6** was used as catalyst in most subsequent investigations (Table 1).

Decreasing the catalyst loading to 0.1 mol % increased the time for complete reaction using **3** (40 °C) to 5 h but with no loss of enantioselectivity. At 80 °C, the reaction time was reduced to 20 min with a loss of enantiomeric excess of only 2%. Catalyst **3** was active and equally enantioselective at a loading as low as 0.01 mol %, which is unprecedented for this class of ATH catalyst. The

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10.1021/ja051486s CCC: $30.25

Table 1. Asymmetric Transfer Hydrogenation of Aromatic Ketones **8**−**13** Catalyzed by Ruthenium(II) Dimer **6** or Monomer **3**[a]

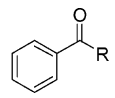
catalyst	loading (mol %)	*T* (°C)	ketone	*t* (h)	% conv.	%ee (*R*/*S*)
(*S*,*S*)-**3**	0.5	28	**8**	3	100	96 (*S*)
(*S*,*S*)-**3**	0.5	40	**8**	2	100	96 (*S*)
(*R*,*R*)-**6**	0.5	40	**8**	3	100	96 (*R*)
(*R*,*R*)-**6**	0.5	40	**8**	2	100	96 (*R*)
(*S*,*S*)-**3**	0.1	40	**8**	5	100	96 (*S*)
(*S*,*S*)-**3**	0.01	40	**8**	79	98	96 (*S*)
(*S*,*S*)-**3**	0.1	80	**8**	0.33	99	94 (*S*)
(*R*,*R*)-**6**	0.1	40	**8**	12	100	96 (*R*)
(*R*,*R*)-**6**	0.5	40	**9**	3	100	94 (*R*)
(*R*,*R*)-**6**	0.5	40	**10**	24	92	95 (*R*)
(*R*,*R*)-**6**	0.5	40	**11**	32	95	77 (*R*)
(*R*,*R*)-**6**	0.5	40	**12**	24	90	94 (*R*)
(*R*,*R*)-**6**	0.5	28	**13**	24	100	69 (*S*)

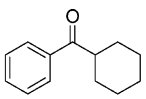
[a] Reaction at 28 °C in a 2 M solution of ketone in a formic acid/triethylamine (5:2) azeotrope mixture, and *S*/*C* = 200 unless otherwise specified.

longevity of catalyst **3** was also demonstrated by an experiment in which further portions of acetophenone were repeatedly added to the reaction mixture (together with additional formic acid) after the reduction had gone to completion. After each addition, the catalyst continued to be effective in achieving full reduction without loss of enantioselectivity, over seven cycles (see Supporting Information).

A further series of ketones were reduced using **3** and **6** (Table 1). Studies focused on the variation of the alkyl group in the series **8**−**12**, while the alkyl/alkyl ketone **13** represents a substrate which does not usually work very well with this class of catalyst. In the event, all ketones proved to be compatible substrates, although the best results were at 40 °C. At this temperature, ketones **9**, **10**, and **12** were reduced in excellent enantioselectivity, while the enantiomeric excess for **11** was lower. These results compare favorably with other ATH catalysts employed for these substrates.[1b,6b,c] Using the untethered **1**, **10** is reported to be reduced in just 41% yield (83% ee), and **11** is not reduced to any measurable extent.[2b]

8 (R=Me)
9 (R=Et)
10 (R=iPr)
11(R=tBu)





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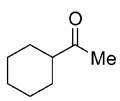

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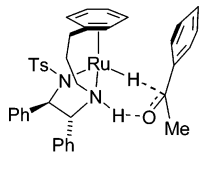
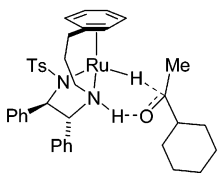
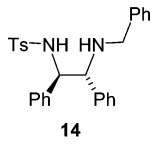
Ketone **13** was reduced in 69% ee, which is the best result for any TsDPEN-related transfer hydrogenation catalyst.[5,10] Ketones **8**−**12** were all reduced to the *R* enantiomer using *R*,*R*-catalyst, which represents the same configuration with respect to the position of the aromatic ring, while **13** gave the *S* product using the *R*,*R*-catalyst, indicating hydride delivery from the opposite face. These results suggest that **3** reduces aryl/alkyl ketones through a transition state in which a stabilizing π-aryl−arene interaction ensures a high enantiomeric excess.[2,3] The reversed selectivity for **13** suggests that when this interaction is not available, the transition state has the larger ketone substituent facing away from the arene ring. We have obtained direct evidence (^{1}H NMR) for the formation of both the 16-electron Ru(II) and the Ru−H intermediates involved in this reaction mechanism (see Supporting Information).

Other than through stabilization of the catalyst, the role of the tether is not fully clear. However, it is not merely the effect of a secondary amine over a primary; a nontethered complex formed from *N*-benzyl-*N*′-tosyl-DPEN **14** was totally ineffective as a catalyst.[11] This confirms that the fixed positioning of the tether is important to its activity.

The catalyst is exceptionally practical and easy to prepare and use as it is a single-component catalyst which merely has to be







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added to a triethylamine/formic acid mixture prior to addition of ketone. The ligand/metal stoichiometry is effectively "built-in" to the catalyst design. The reduction rates exceed those reported for the untethered complexes, and the catalyst is effective at loadings of as low as 0.01 mol %. The reduction enantioselectivity is, in most cases, superior to that in other ATH catalysts.

Acknowledgment. We thank the EPSRC and Warwick University (research fellowship to A.M.H.) for financial support of this project.

Supporting Information Available: Experimental procedures, characterization data, NMR spectra, chiral chromatography analysis of reduction products, and data of single-crystal X-ray analysis of **3**. This material is free of charge via the Internet at http://pubs.acs.org.

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