## An Investigation into the Tether Length and Substitution Pattern of Arene-Substituted Complexes for Asymmetric Transfer Hydrogenation of Ketones

Fung K. Cheung,<sup>†</sup> Changxue Lin,<sup>†</sup> Franco Minissi,<sup>†</sup> Adriana Lorente Crivillé,<sup>†</sup> Mark A. Graham,<sup>‡</sup> David J. Fox,<sup>\*,†</sup> and Martin Wills<sup>\*,†</sup>

Asymmetric Catalysis Group, Department of Chemistry, University of Warwick, Coventry, CV4 7AL, U.K., and Cancer & Infection Chemistry, AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, U.K.

m.wills@warwick.ac.uk

Received September 11, 2007

ORGANIC LETTERS

2007 Vol. 9, No. 22 4659–4662

## ABSTRACT



A series of Ru(II) catalysts were prepared and tested in the asymmetric transfer hydrogenation of ketones. The catalyst containing a "4carbon" tether gave the fastest rates of ketone reduction. This is due to both increased rate of regeneration of hydride "Ru–H" and increased rate of ketone reduction. Several classes of ketone were reduced in enantiomeric excesses of up to 97%. Substituents on the arene ring of the catalyst influence the reaction rate and enantioselectivity.

Enantioselective ketone reduction is a pivotal reaction in asymmetric synthesis and catalysis.<sup>1–3</sup> Asymmetric transfer hydrogenation (ATH) of ketones using monosulfonated diamine complexes of Ru(II) was first reported by Noyori

(2) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. J. Am. Chem. Soc. 1995, 117, 7562. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. J. Am. Chem. Soc. 1996, 118, 2521. (c) Matsumura, K.; Hashiguchi, Ikariya, T.; Noyori, R. J. Am. Chem. Soc. 1997, 119, 8738. (d) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. Org. Lett. 1999, 1, 1119. (e) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. Angew. Chem., Int. Ed. Engl. 1997, 36, 285.

(3) (a) Gladiali, S.; Alberico, E. Chem. Soc. Rev. **2006**, *35*, 226. (b) Ikariya, T.; Murata, K.; Noyori, R. Org. Biomol. Chem. **2006**, *4*, 393.

in  $1995^{2a}$  and has since become one of the most widely studied and applied enantioselective reduction reactions.

In our studies in this field, we recently reported the synthesis and applications of "tethered" catalysts 1 and 2 in which covalent linkages from the diamine to the  $\eta^6$ -arene unit provide extra stability and a significant increase in rate (with 2) relative to "untethered" catalyst 3.<sup>4</sup> Using catalyst 2, acetophenone is fully reduced in 96% ee within 3 h at S/C = 200, presumably through the established TS illustrated in Figure 1.<sup>5,6</sup> The high ee for the reduction of acetophenone derivatives arises from the stabilizing electrostatic interaction

<sup>&</sup>lt;sup>†</sup> University of Warwick.

<sup>&</sup>lt;sup>‡</sup> AstraZeneca.

 <sup>(1) (</sup>a) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.
(b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201. (d) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.

<sup>(4) (</sup>a) Hannedouche, J.; Clarkson, G. J.; Wills, M. J. Am. Chem. Soc. **2004**, *126*, 986. (b) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. J. Am. Chem. Soc. **2005**, *127*, 7318. (c) Morris, D. J.; Hayes, A. M.; Wills, M. J. Org. Chem. **2006**, *71*, 7035.



Figure 1. Relative positions of arene substituents to substrate during ATH by catalysts 1-3.

in the hydrogen transfer transition state illustrated in Figure 1.<sup>5,6</sup> This interaction is not available for dialkyl ketones of a similar size; acetylcyclohexane is reduced by 2 in only 69% ee, arising from weaker steric effects.

In order to increase the activity and versatility of catalyst 2, we wished to examine the effect of tether length and the  $\eta^{6}$ -arene ring substitution pattern. An examination of the crystal structure of 2 reveals that the ipso carbon of the  $\eta^6$ arene lies directly above the nitrogen atom to which it is tethered. As a result, substituents at positions X and Y (Figure 1) are most likely to produce catalysts with improved properties. In contrast, position Z might be usefully substituted with electron-rich or -poor groups.

We identified complexes 4-8 as a series of systematically modified catalysts that were worthy of study. These were prepared in good yield via the route illustrated in Scheme 1.



The precursors, 9a-e, were obtained by Birch reduction of the corresponding arenes. Dimers 10a - e can be employed directly in ketone ATH if the reaction is carried out it formic

acid/triethylamine (FA/TEA) because they are directly converted to the monomers 4-8, respectively, in situ. Hence, for synthetic applications, the dimers and monomers can be used interchangeably.<sup>4</sup> However, for purposes of comparison and analysis, each of the monomers 4-8 were isolated for use in ATH of acetophenone 11. With the exception of 6, which has the longest tether, formation of monomers from dimers took place within a few hours. In the case of 10c, however, only a small amount of 6 was obtained even after extended reaction times.

The results from the ATH studies (Table 1) indicated that the "4C"-tethered complex 5 was the most active, achieving

**Table 1.** ATH of Ketones **11–21** Catalyzed by Ruthenium(II) Catalysts 2 and 4-8<sup>*a,b*</sup> catalyst 4-8, HCO<sub>2</sub>H:Et<sub>2</sub>N 5:2

н ОН

0

	U _	J				
	$R^{1}$ $R^{2}$		rt-40 °C		$R^1 \xrightarrow{7} R^2$	
	1 1.					(61)
	loading	temp		time	conv	ee (%)
catalyst	(mol %)	(°C)	ketone	(h)	(%)	(R/S)
$S,S-2^c$	0.5	40	11	2	100	96S
R,R-4	0.5	40	11	15	19	92 R
R,R-5	0.5	40	11	1.25	100	96 R
R,R-5	0.1	$\mathbf{rt}$	11	8	100	96 R
R,R-5	0.01	$\mathbf{rt}$	11	70	100	96 R
R,R-6	0.5	40	11	6	38	94 R
R,R-7	0.5	40	11	4	100	96 R
R,R- <b>8</b>	0.5	40	11	5	100	93 R
R,R-5	0.5	$\mathbf{rt}$	12	18	100	94 R
R,R-5	0.5	$\mathbf{rt}$	13	3	100	91R
R,R-2	0.5	$\mathbf{rt}$	14	3	100	96S
R,R-5	0.5	$\mathbf{rt}$	14	1	100	96S
R,R-2	0.5	$\mathbf{rt}$	15	3	100	95S
R,R-5	0.5	$\mathbf{rt}$	15	1	100	96S
R,R-2	0.5	$\mathbf{rt}$	16	3	100	$93 \ S$
R,R-5	0.5	$\mathbf{rt}$	16	1	100	94S
R,R-5	0.5	$\mathbf{rt}$	17	2	100	91R
R,R-2	0.5	$\mathbf{rt}$	18	3	100	95 R
R,R-5	0.5	$\mathbf{rt}$	18	1	100	96 R
R,R-2	0.5	$\mathbf{rt}$	19	3	100	94 R
R,R-5	0.5	$\mathbf{rt}$	19	1	100	97 R
R,R-2	0.5	$\mathbf{rt}$	20	3	100	94 R
R,R-5	0.5	$\mathbf{rt}$	20	1	100	94 R
R,R-5	0.5	$\mathbf{rt}$	21	o/n	100	66S
R,R- <b>8</b>	0.5	$\mathbf{rt}$	21	o/n	100	$90 \ S$

<sup>a</sup> Reaction at 28 °C in a 1.62 M solution of ketone in a formic acid/ triethylamine (5:2) azeotrope mixture and S/C = 200 unless otherwise specified. <sup>b</sup> For substrates 12-21, the dimeric precursors were used directly as sources of catalysts 2 and 5. <sup>c</sup> From ref 4b.

full reduction within 75 min at S/C = 200. This is faster than the previously reported "3C"-tethered complex 2 and significantly faster than the "5C" and "2C" complexes 4 and 6. However, the latter catalysts still gave products in high

<sup>(5) (</sup>a) Yamakawa, M.; Yamada, I.; Noyori, R. Angew. Chem., Int. Ed. 2001, 40, 2818. (b) Noyori, R.; Yamakawa, M.; Hashiguchi, S. J. Org. Chem. 2001, 66, 7931. (c) Yamakawa, M.; Ito, H.; Noyori, R. J. Am. Chem. Soc. 2000, 122, 1466.

<sup>(6) (</sup>a) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. J. Am. Chem. Soc. 1999, 121, 9580. (b) Brandt, P.; Roth, P.; Andersson, P. G. J. Org. Chem. 2004, 69, 4885.

ee, suggesting that they are still operating through the TS expected for these compounds, although slowly. As a result of this increased reactivity of 5, the catalyst loading can be decreased to as low as 10 000:1, matching the level at which 2 has been used.

A kinetic study was conducted (see Supporting Information for details) using both <sup>1</sup>H NMR and chiral GC to follow the conversion. These studies were carried out at 40 °C using 1.62 M ketone in FA/TEA, S/C = 200. Catalysts **2**, **4**, **6**, **7**, and **8** demonstrated essentially zero-order kinetics for the majority of the reaction. In contrast, catalyst **5** displayed mixed-order kinetics.

An analysis of these data, assuming second-order kinetics for the ketone reduction<sup>7</sup> by the Ru–H species and firstorder kinetics<sup>8</sup> for the regeneration of Ru–H by formic acid, was carried out (Figure 2). The results indicate that the high



Figure 2. Kinetic data for acetophenone reduction.

rate obtained with catalyst **5** is the result of an increased rate of hydride regeneration *coupled with* rapid ketone reduction. For the other tethered catalysts, the overall reduction rate is limited by the rate of hydride regeneration, until the ketone concentration has fallen to low levels. The Noyori catalyst, **3**, takes 20 h to complete the reduction and exhibits mixed-order kinetics similar to those of **5**.<sup>9</sup> The results obtained with catalysts **7** and **8** are also informative. The reduced reduction rate for the former relative to **2** appears to result from slightly slower hydride regeneration, rather than slower reduction.



The rate of reduction using  $\mathbf{8}$  is particularly slow, yet the ee is not significantly eroded. This indicates that a stabilizing interaction is operating through the methyl group on the arene

ring (Figure 3), which may be electrostatic<sup>5a</sup> in nature or the result of dispersion effects.<sup>6b</sup>



Figure 3. Reduction of acetophenone in 93% ee (*R*) by complex 8.

Catalysts 2 and 5, supplied to the reaction in their dimeric precursor forms, were employed in the reduction of a series of ketones (Table 1); in all cases, the latter catalyst proved to be more active. Ketones 14-16 produce 2-chloro-1-phene-thanols, important synthetic intermediates for enantiomerically pure epoxides and related intermediates.<sup>10</sup> Alcohols derived from cyclic ketopyridines such as 18-20 are useful precursors of chiral ligands for asymmetric hydrogenation reactions<sup>11</sup> and may be converted into the related amines which are currently being evaluated as chemokine receptor binding agents for treatment of HIV<sup>12</sup> and are represented in hydrogenation ligands.<sup>13</sup> Using catalyst **5**, it was possible to reduce 18-20 in ees of 94-97%. Catalyst **2** also worked well in this application but was less active.

Catalyst **5** reduced acetylcyclohexane **21** in only 66% ee; however, catalyst **8** gave a product of 90% ee. Both the sense (opposite to acetophenone) and the increased ee for this substrate suggest that the extra methyl groups on the  $\eta^{6}$ arene ring in **8** force the larger ketone substituent into the less hindered region (Figure 4). This represents the first



Figure 4. Increased steric hindrance increases ee of reduction of acetyl cyclohexanone by complex 8 (left; 90% ee) over 2 (right; 69% ee).

example of a Ru/TsDPEN ATH catalyst designed and demonstrated to have useful levels of enantioselectivity for

<sup>(7)</sup> Wisman, R. V.; de Vries, J. G.; Deelman, B.-J.; Heeres, H. J. Org. Proc. Res. Dev. 2006, 10, 423–429.

<sup>(8)</sup> Koike, T.; Ikariya, T. Adv. Synth. Catal. 2004, 346, 37-41.

<sup>(9)</sup> Noyori has reported a kinetic study of the use of catalyst **3** in the isopropanol/KOH system (ref 2e) and has found that, at high (>0.4 M) concn of ketone (acetone), the turnover limiting step was the regeneration of hydride. However, these studies were carried out under conditions different than ours.

<sup>(10)</sup> Tanis, S. P.; Evans, B. R.; Nieman, J. A.; Parker, T. T.; Taylor, W. D.; Heasley, S. E.; Herrinton, P. M.; Perrault, W. R.; Hohler, R. A.; Dolak, L. A.; Hester, M. R.; Seest, E. P. *Tetrahedron* **2006**, *17*, 2154.

nonaromatic substrates by replacing electronic control elements with steric ones.  $^{\rm 14}$ 

In conclusion, we have demonstrated that the tether length and  $\eta^{6}$ -arene substitution pattern have a significant effect upon the activity of tether Ru(II) ATH complexes. The most active of these complexes (2 and 5) can be applied to the ATH of a range of ketone substrates to give alcohols in high conversion and ee. Increasing the level of substitution at the meta position of the arene ring can deliver an improved ee

(12) Skupinska, K. A.; McEachern, E. J.; Baird, I. R.; Skerlj, R. T.; Bridger, G. J. J. Am. Chem. Soc. 2003, 68, 3546.

(13) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. J. Am. Chem. Soc. 2007, 129, 4536.

(14) (a) Reetz, M. T.; Li, S. J. Am. Chem. Soc. **2006**, 128, 1044. (b) Hamada, T.; Torii, T.; Onishi, T.; Izawa, K.; Ikariya, T. Org. Lett. **2004**, 69, 7391. (c) Schlatter, A.; Kundu, M. K.; Woggon, W.-D. Angew. Chem., Int. Ed. **2004**, 43, 6731.

in the reduction of dialkyl ketones, which are challenging substrates for this application. At present, the reasons for the improved activity relative to untethered complexes are unclear; however, we anticipate that these result from a slight conformational adjustment to the structure which renders the complexes more correctly preorganized toward the reduction reactions. This is the subject of ongoing kinetic studies and molecular modeling, the results of which will be published in due course.

Acknowledgment. We thank the EPSRC (Project studentship to F.M., project grant to C.L., ARF to D.J.F.) and the BBSRC and Astrazeneca (CASE studentship to F.K.C.) for generous financial support of this project, and the EPSRC national Mass Spectrometry service (Swansea) for analyses.

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

OL702226J

<sup>(11) (</sup>a) Kaiser, S.; Smidt, S. P.; Pfaltz, A. Angew. Chem., Int. Ed. 2006, 45, 5194. (b) Bell, S.; Wuestenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. Science 2006, 311, 642. (c) Mazet, C.; Roseblade, S.; Kohler, V.; Pfaltz, A. Org. Lett. 2006, 8, 1879. (d) Kallstrom, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. J. Am. Chem. Soc. 2004, 126, 14308. (e) Kang, J.; Kim, H. Y.; Kim, J. H. Tetrahedron: Asymmetry 1999, 10, 2523. (f) Liu, Q.-B.; Yu, C.-B.; Zhou, Y.-G. Tetrahedron Lett. 2006, 47, 4733. (g) Okano, K.; Murata, K.; Ikariya, T. Tetrahedron Lett. 2000, 41, 9277.