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The Hydrogenation/Transfer Hydrogenation Network: Asymmetric Hydrogenation of Ketones with Chiral η^6-Arene/*N*-Tosylethylenediamine−Ruthenium(II) Catalysts

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Asymmetric transfer hydrogenation (ATH) with organic reducing agents catalyzed by transition metal complexes is mechanistically linked with asymmetric hydrogenation (AH) using molecular hydrogen because both reactions commonly involve metal hydride species.[1,2] However, most of the existing chiral catalysts are effective for only one of these reactions.[3−5] We have long conjectured that certain chiral metal complexes can be made to catalyze both ATH and AH by switching reaction parameters so that the conditions can tolerate acid/base-sensitive substrates. In this context, the extensive mechanistic investigation on the Ru-catalyzed ATH[6,7] has led us to rationally explore an effective AH of unfunctionalized ketones. We disclose here that chiral η^6-arene/*N*-tosylethylenediamine−Ru(II) complexes, known as excellent catalysts for ATH,[8] can be used for AH as well. This discovery provides a long-sought method for enantioselectively hydrogenating simple ketones under nonbasic or acidic conditions.[9]

The blue arrows in Figure 1 illustrate the pathway of ATH of aromatic ketones with 2-propanol catalyzed by the chiral Ru chloride **1** (X = Cl) and an alkaline base.[6,7] The strong base is required for the irreversible elimination of HCl from **1** forming the 16e Ru amide complex **2**. Dehydrogenation of 2-propanol by **2** gives the RuH species **3**, which in turn hydrogenates Ar(R)C═O forming chiral Ar(R)CHOH with recovery of **2**. These ketone/alcohol redox processes occur via a Ru−H−C−O−H−N six-membered pericyclic transition structure. When the reaction starts with preformed **2** as catalyst,[8] no additional base is necessary, but the presence of an acid totally diminishes its catalytic activity. Under such conditions, no ketone reduction takes place under a H_2 gas atmosphere. However, the pink arrows in Figure 1 suggest the possibility of AH using the same Ru catalysts simply *by switching the conditions from basic to acidic*. The key is the generation of the cationic Ru species **4** by ionization of **1**. An alternative method is the protonation of the amido ligand of **2** to prevent dehydrogenation of secondary alcohols. The resulting cationic 16e amino Ru complex **4** (solvate) can accept reversibly a H_2 molecule to form the η^2-H_2 complex **5**, whose deprotonation leads to RuH **3** as a common reductive species.

We selected 4-chromanone (**6a**) as substrate, for which no practical AH methods exist (Figure 2).[10] The difficulty arises from the cyclic planar structure and the relatively high acidity of C(3)-H_2 caused by the oxygen atom.[11−13] The mechanism-based catalytic scenario in Figure 1 was first investigated by using the 18e RuCl complex, (*S*,*S*)-**8a**, with a substrate-to-catalyst molar ratio (*S*/*C*) of 3000 ([**6a**] = 0.3 M, [**8a**] = 0.10 mM in a silanized glass vessel,

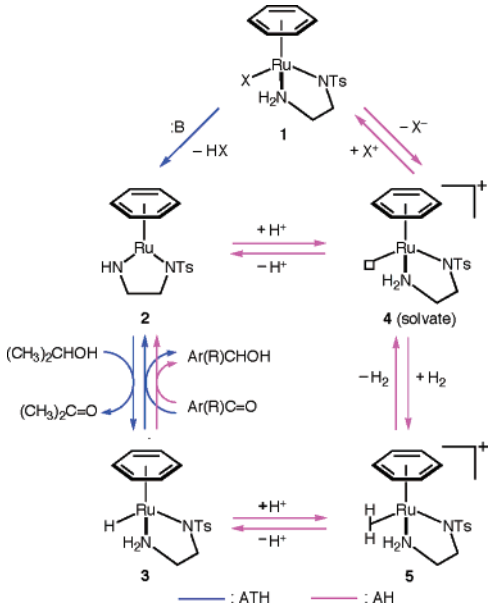

Figure 1. Mechanism of asymmetric transfer hydrogenation (ATH) and asymmetric hydrogenation (AH) of aromatic ketones catalyzed by chiral η^6-arene/*N*-tosylethylenediamine−Ru complexes. Substituents in the arene and ethylenediamine ligands are omitted for clarity.

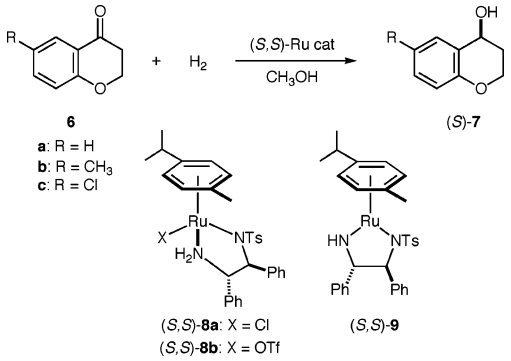

Figure 2. Asymmetric hydrogenation of 4-chromanones.

10 atm, 30 °C, 15 h). We anticipated that ionization of **8a** in a polar solvent would directly generate a catalytic Ru cation (**1** → **4**). In fact, although no reaction took place in 2-propanol (ϵ = 20; the best solvent for ATH[5−8]), hydrogenation in more polar ethanol (ϵ = 25) or methanol (ϵ = 33) gave (*S*)-**7a** in 7% yield (93% ee) and 34% yield (97% ee), respectively. Reaction in methanol at 60 °C and 50 atm increased the yield to 99% (97% ee). As expected, addition of 1 equiv of $(n\text{-}C_4H_9)_4NCl$ to **8a** (*S*/*C* = 3000, methanol,

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Table 1. Asymmetric Hydrogenation of 4-Chromanones Catalyzed by Chiral Ru Complexes[a]

				conditions		(*S*)-**7**[d]	
ketone	cat	S/C[b]	additive[c]	H_2, atm	*T*, °C	% yield	% ee
6a	(*S*,*S*)-**8a**	3000		10	30	34	97
6a	(*S*,*S*)-**8a**	3000		10	60	64	95
6a	(*S*,*S*)-**8a**	3000		50	60	99	97
6a	(*S*,*S*)-**8b**	3000		10	60	100	97
6a	(*S*,*S*)-**8b**	7000		100	60	100	96
6a	(*S*,*S*)-**9**	7000	1.0 TfOH	10	60	60	96
6a[e]	(*S*,*S*)-**9**	1000	1.0 TfOH	17	36−57	99	98
6a	(*S*,*S*)-**9**	3000	1.0 HBF_4	10	60	99	97
6a	(*S*,*S*)-**9**	3000	0.7 $Yb(OTf)_3$	15	50	98	95
6b	(*S*,*S*)-**8b**	1500		10	60	95	98
6c	(*S*,*S*)-**8b**	1000		10	60	100	98

[a] Unless otherwise stated, reactions were conducted using a 0.3−1.0 M solution of **6** and a 0.1−3.5 mM solution of **8** or **9** in methanol in a silanized glass vessel. The reaction time was 15 h. [b] Substrate/catalyst molar ratio. [c] Molar equiv to Ru. [d] Determined by NMR, the sign of rotation, and chiral HPLC analysis. [e] A 2.4 kg scale reaction using a 2.0 M solution of **6a** in a 20 L SUS autoclave for 8 h.

30 °C, 10 atm, 15 h) retarded the reaction to afford (*S*)-**7a** with 92% ee in only 6% yield.

This AH procedure, though viable, remains unoptimized because the Ru−Cl bond in the precatalyst is not fully dissociated in alcohols. The concentration of the cationic amino Ru complex **4** can be maximized by using a more ionizable precatalyst **1** (X = weakly nucleophilic anion) or by combining the 16e amido Ru complex **2** and an appropriate acid. Notably, the operation of a specific acid/base catalysis requires careful adjustment of the acidity and basicity of the reaction medium to retain a smooth metal−ligand bifunctional catalytic cycle (Figure 1). Pure alcoholic solvents are unable to protonate **2**.[8] Strong acid additives facilitate this step, but hamper the deprotonation of **5** and also decoordinate the ethylenediamine ligand from Ru.

The best solution to this problem was provided by invention of the chiral Ru triflate (*S*,*S*)-**8b**, which could be obtained simply by adding CF_3SO_3H (TfOH) to (*S*,*S*)-**9**[8] in CH_2Cl_2 at 0 °C. In methanol, the Ru triflate precatalyst is cleanly converted to an ion pair acting as an ideal AH catalyst. An equimolar mixture of (*S*,*S*)-**9** and TfOH in methanol was also usable. TfOH could be used in slight excess but not large excess. Thus, when the simple ketone **6a** was hydrogenated in methanol under 10 atm of H_2 with *S*/*C* = 3000 in a silanized glass vessel ([**6a**] = 1.0 M, [**8b**] = 0.33 mM, 60 °C, 15 h), (*S*)-**7a** was obtained in 100% yield and 97% ee (Table 1). The reaction with *S*/*C* of 7000 took place smoothly at 100 atm. The hydrogenation was accomplished even on a 2.4 kg scale in 8 L of methanol, giving (*S*)-**7a** with 98% ee in 99% yield. Now less polar alcohols may be used in place of methanol, though the reaction is somewhat slower. TfOH was the best acid to activate (*S*,*S*)-**9**, but other non-nucleophilic acids can be employed as well. For example, an equimolar mixture of (*S*,*S*)-**9** and $HBF_4{\cdot}O(CH_3)_2$ or $Yb(OTf)_3$ in methanol catalyzed the hydrogenation of **6a** at 10 atm giving (*S*)-**7a** in 97% ee in high yield. The results of AH of some 4-chromanone derivatives **6** are listed in Table 1.

The reaction mixture retains a yellow color throughout the hydrogenation. This implies that the amide complex (*S*,*S*)-**9** (purple) is mostly protonated to the amino compounds under the steady-state catalytic conditions. Reduction does not proceed without H_2, indicating that this is a net hydrogenation using H_2 gas. Alcohols are involved in the catalytic cycle, but only as proton sources and bases, not as reducing agents. The sense and degree of enantioselection are the same as those observed in ATH[13] because both AH and ATH involve a common chiral RuH intermediate possessing an *R* configuration at Ru.[8]

In summary, chiral η^6-arene/*N*-tosylethylenediamine−Ru(II) complexes are excellent catalysts not only for ATH but also for AH of aromatic ketones. Various base-sensitive ketonic substrates can be enantioselectively hydrogenated by this method.[14]

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Supporting Information Available: Preparative methods and properties of chiral Ru complex **8b**, procedures for asymmetric hydrogenation of chromanones, NMR, GC, and HPLC behavior, and $[\alpha]_D$ values of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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