Well-Defined Triflylamide-Tethered Arene−Ru(Tsdpen) Complexes for Catalytic Asymmetric Hydrogenation of Ketones

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Summary: Well-defined triflylamide-tethered arene−Ru(Tsdpen) complexes have been developed as highly efficient catalysts for the asymmetric hydrogenation of ketones, in which the suitable carbon chain length of the tether is responsible for the activation of H_2 as well as the stereochemical outcome of the reaction. The asymmetric hydrogenation of aromatic ketones with the tethered complex with a C_4 side chain gave the corresponding secondary alcohols with 91−98% ee, while the shorter congeners with a C_2 or C_3 side chain provided unsatisfactory results in terms of reactivity and selectivity.

The formal heterolytic cleavage of molecular dihydrogen (H_2) with transition-metal-based catalysts is one of the fundamental steps for the hydrogenation of ketones.[1] Since the discovery of Noyori's bifunctional chiral Ru hydrogenation catalyst,[2] there have been intense efforts to explore new chiral catalyst systems in academia and industry.[3] We have recently developed new asymmetric hydrogenation (AH) catalysts including bifunctional Cp*Ru *amide* complexes bearing chiral NN and PN ligands, which can facilitate the heterolytic cleavage of H_2 with the addition of acidic alcohol as a key step.[4] Analogous heterolytic H_2 cleavage is also possible by using isolable *amine* complexes, Ru(OTf)[(*S*,*S*)-Tsdpen](η^6-arene),[5] which leads to the formation of the corresponding hydride amine complexes along with the concomitant release of strong acids in methanol[6] (Tsdpen = $TsNCH(C_6H_5)CH(C_6H_5)NH_2$; Ts = *p*-$CH_3C_6H_4SO_2$; Tf = CF_3SO_2). These results have prompted us to design novel bifunctional Ru catalysts having a Brønsted acidic unit linked to the η^6-arene ring for the AH of ketones.[7] In this paper, we describe the highly efficient AH of ketones catalyzed by the newly developed triflylamide (NTf)-tethered arene−Ru complex, which has been structurally modified on the basis of the asymmetric transfer hydrogenation (ATH) catalyst, Ru[(*S*,*S*)-Tsdpen](η^6-arene).[7,8]

Reactions of the triflylated 1-(aminoalkyl)-1,4-cyclohexadienes c-$C_6H_7(CH_2)_n$NHTf (n = 2−4) with $RuCl_3 \cdot 3H_2O$ gave the corresponding η^6-arene dimers [(η^6-$C_6H_5(CH_2)_n$NHTf)$RuCl_2$]$_2$ (**1a**−**c**)[9a] in high yields (Scheme 1). The treatment of **1a**−**c** with a base in CH_3CN yielded the novel tethered arene complexes [η^6:η^1-$C_6H_5(CH_2)_n$NTf]RuCl(CH_3CN) (**2a**−**c**).[9b] The mononuclear structures of **2a**,**b** with a three-legged piano-stool configuration were unequivocally determined by X-ray diffraction (Figure 1).

These tethered complexes, **2a**−**c**, have proven to be useful precursors for a series of analogous tethered complexes. For example, the base-induced anionic metathesis of **2a**−**c** with (*S*,*S*)-TsdpenH selectively replaced the chloro ligand in favor of the NTf ligand to produce **3a**−**c**, whose tether moieties remained intact. Notably, the carbon-centered chirality in Tsdpen effectively induced the newly developed Ru-centered chirality in **3a**−**c** in a highly diastereomeric fashion, which was revealed by ^{19}F NMR spectra of the crude products showing one sharp singlet for the Ru-bound NTf group. The absolute configuration of Ru in **3a**,**b**[10] was determined to be S_{Ru} by X-ray diffraction (Figure 2). The solid-state structures of **2** and **3** suggest that the strength of the Ru−NTf bonds is affected by the conformational constraint of the tethered structure. Thus, the angle defined by the centroid of the η^6-arene, Ru, and the NTf nitrogen (θ) is markedly smaller in **2a** and **3a** with a C_2 side chain (θ =

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(9) (a) Detailed synthetic procedures and spectroscopic data for all the novel complexes **1**−**3** are provided as Supporting Information. (b) Spectral changes in ^{19}F NMR and ^{1}H NMR for the C*H*$_2$N*Tf* group are also highly indicative of the formation of the η^1N structure (see the Supporting Information).

(10) Although the structural refinement of **3b** was hampered by a disorder of the Tf group and the solvating THF molecule, the tethered structure as well as the absolute configuration has been determined unambiguously (see the Supporting Information).

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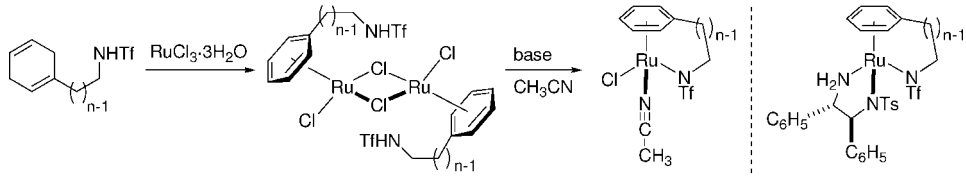
Scheme 1. Preparation of NTf-Tethered Arene−Ru Complexes



1a (n = 2)
1b (n = 3)
1c (n = 4)

2a (n = 2)
2b (n = 3)
2c (n = 4)

3a (n = 2)
3b (n = 3)
3c (n = 4)

ca. 120°) as compared to those in **2b** and **3b** with a C_3 side chain (θ = 124−128°), which may cause the more distorted structure in **2a** and **3a** with less robust Ru−NTf bonds (vide infra).[11]

Next, the isolable tethered arene−Ru complexes **2** and **3** were examined as catalysts for the hydrogenation using acetophenone (**4a**). The reactions were carried out at 30 °C under 30 atm of H_2 for 24 h in methanol containing **4a** and the Ru complex (**4a**:Ru = 100:1, [**4a**] = 0.3 M in methanol). Complexes **2** promoted the hydrogenation of the aromatic ring in **4a** in preference to the carbonyl group, yielding a mixture of cyclohexyl methyl ketone and 1-cyclohexylethanol; however, the diamide complexes **3** caused selective hydrogenation of the carbonyl group to afford 1-phenylethanol (**5a**). Among the complexes examined, the Tsdpen complex **3c** with a C_4 side chain promoted the hydrogenation most efficiently to afford (*S*)-**5a** with 93% ee in quantitative yield. In sharp contrast, complex **3a** with a C_2 side chain afforded (*S*)-**5a** with only 2% ee in 20% yield, while complex **3b** with a C_3 side chain promoted the hydrogenation very sluggishly to afford **5a** in <1% yield under identical conditions. On the other hand, a related untethered complex, Ru(NHTf)[(*S*,*S*)-Tsdpen](η^6-*p*-cymene), which was cleanly generated from Ru[(*S*,*S*)-Tsdpen](η^6-*p*-cymene) by adding an equimolar amount of $TfNH_2$, did not promote the hydrogenation. These results strongly suggest that the suitable carbon chain length of the tether is responsible for the rate enhancement in the present hydrogenation.[7d] Methanol was the best solvent of choice among alcoholic solvents, while the use of solvents other than alcohols (CH_3CN, CH_2Cl_2, and toluene) gave no hydrogenated product under otherwise identical conditions. It should be noted that complex **3c** exhibited no catalytic activity in the absence of H_2, indicating that alcoholic solvents merely participate in the activation of H_2[4a,b] but do not serve as hydrogen sources.[8,12] In fact, complex **3c** was not convertible in 2-propanol or with **5a** to the corresponding Ru hydride or Ru alkoxide complex with the ring-opened side chain bearing an NHTf group. This is probably because the NHTf group is a stronger acid than the OH group in alcohols.

Encouraged by the marked catalytic performance of **3c**, the AH of aromatic ketones was next examined using **3c** as a catalyst. A variety of prochiral aromatic ketones (**4**) undergo hydrogenation enantioselectively in methanol containing **3c** (1

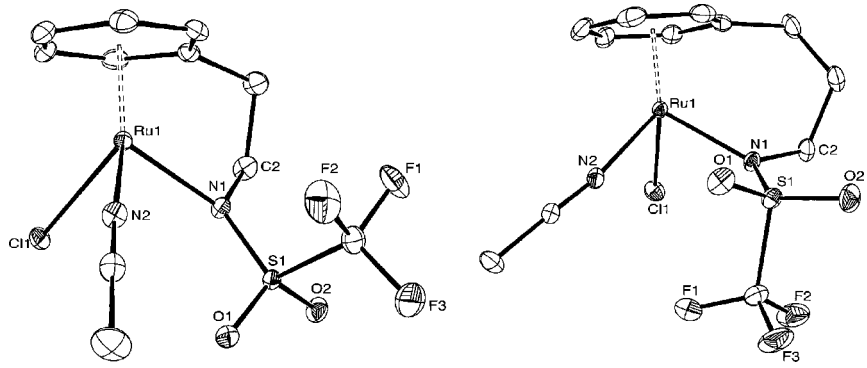


Figure 1. Structures of the Ru complexes **2a** (left) and **2b** (right) with ellipsoids at the 30% probability level. Hydrogen atoms are omitted for clarity.

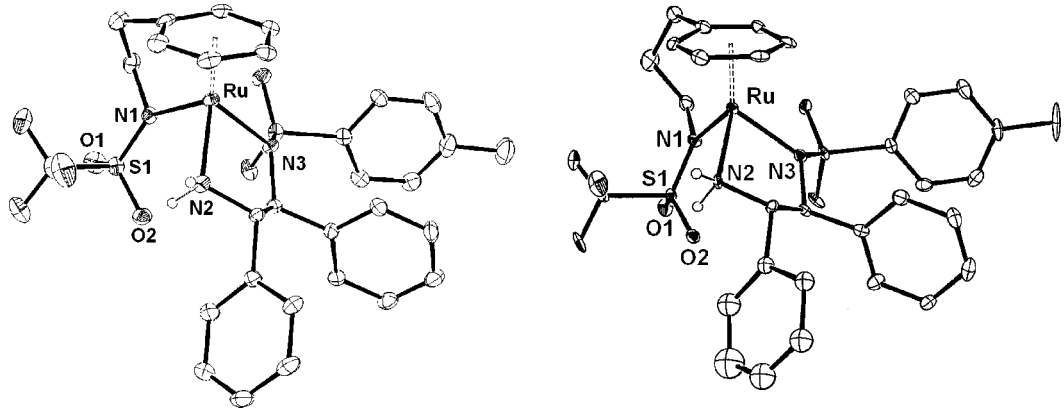
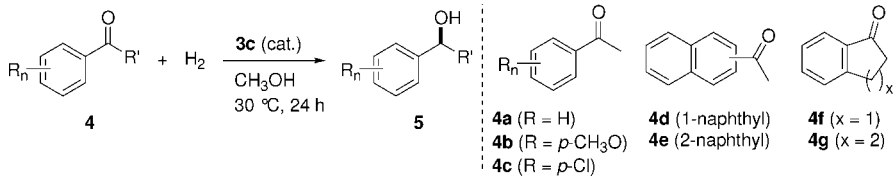


Figure 2. Structures of the Ru complexes **3a** (left) and **3b** (right) with ellipsoids at the 30% probability level. Hydrogen atoms, except those on the protic amine, are omitted for clarity.

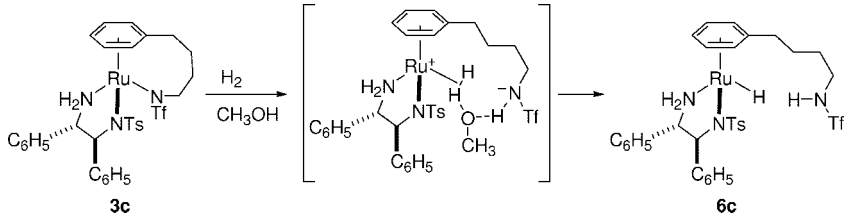
Table 1. Hydrogenation of Various Aromatic Ketones (4) with 3c[a]



run	4	yield, %	ee, %	run	4	yield, %	ee, %
1	**4a**	>99	93	6	**4f**	98	95
2	**4b**	>99	93	7	**4g**	>99	98
3	**4c**	>99	95	8[b]	**4a**	>99	93
4	**4d**	>99	97	9[c]	**4a**	>99	93
5	**4e**	>99	95	10[d]	**4a**	96	92

[a] Unless otherwise noted, hydrogenation was conducted at 30 °C under 30 atm of H_2 with a substrate/catalyst (S/C) ratio of 100 in methanol ([**4**] = 0.3 M in methanol). [b] S/C = 200. [c] S/C = 500, 50 atm of H_2, [**4a**] = 0.5 M in methanol. [d] S/C = 1000, 50 atm of H_2, [**4a**] = 1.0 M in methanol.

Scheme 2. Possible Mechanism for H_2 Activation with 3c



mol%) at 30 °C to afford the corresponding secondary alcohols (**5**) quantitatively within 24 h. Table 1 gives some representative examples.

The substituents on the aromatic ring in aryl methyl ketones did not affect the outcome of the experiment; the corresponding 1-arylethanols were obtained with an enantioselectivity of 93−95% ee (runs 2 and 3). In addition to 1-naphthyl (**4d**) and 2-naphthyl methyl ketones (**4e**), aromatic cyclic ketones such as 1-indanone (**4f**) or 1-tetralone (**4g**) afford the corresponding secondary alcohols very efficiently, and their enantioselectivity is generally greater than 95% ee (runs 4−7). The present hydrogenation proceeds smoothly with increased substrate/catalyst ratios (runs 1 and 8−10) without any serious loss of enantioselectivity.

Although further studies are required to elucidate the exact role of the NTf tether, we believe that the Ru−NTf bond in **3c** readily forms a hydrogen-bonding network[4a,b] with H_2 in methanol, as shown in Scheme 2, to generate **6c**, in which the chain length plays a key role.[7d] Thus, the C_4 tether in **3c** is labile enough to facilitate this process efficiently, while the C_2 tether in **3a** should be more stable and the C_3 tether in **3b** should be the most stable (vide supra).

On the other hand, in **6c**, it is likely that the concerted hydride/proton transfer from the H−Ru−N−H moiety to the ketonic substrates precedes the proton transfer by the ring-opened NHTf side chain, thereby allowing excellent enantioface selection.[8a] The subsequent proton transfer by the tether should effectively prevent the reverse dehydrogenation of (*S*)-**5** to maintain their high enantioselectivities. However, proton transfer due to the shorter side chains could compete with that by the Ru-bound NH_2 group to promote the far less enantioselective hydrogenation pathway[13] to diminish the enantioselectivity dramatically, as in the case of **3a**.

In summary, we have developed novel bifunctional Ru catalysts having an NTf unit linked to a η^6-arene ring for the AH of aromatic ketones. A subtle change in the structure of the tether has a significant effect on the catalytic performance of the bifunctional Ru catalyst. Our results should open up great possibilities for the future design of molecular catalysts for the straightforward hydrogenation of polar organic substrates.[1a]

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Note Added after ASAP Publication. The PDF file in the Supporting Information for this paper, which was published on the Web on October 21, 2008, contained a number of typographical errors. The version that has been posted on the Web on October 28, 2008, is correct.

Supporting Information Available: Text giving experimental procedures and CIF files giving X-ray crystallographic data for **2a**,**b** and **3a**·**CH3CN**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Although less clearly, the more distorted structures of **2a** and **3a** due to the shorter chain were also suggested by their relatively twisted orientation of the trigonal plane around the NTf nitrogen with respect to the η^6-arene plane (see the Supporting Information).

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