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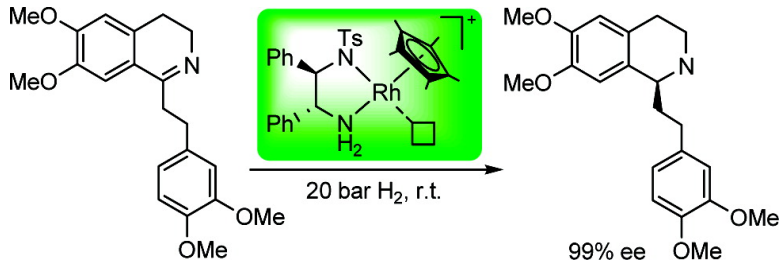

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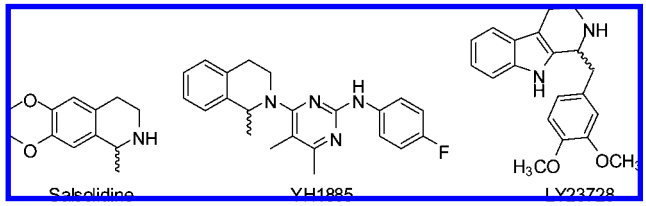
Asymmetric Hydrogenation of Cyclic Imines with an Ionic Cp*Rh(III) Catalyst

Chaoqun Li and Jianliang Xiao*

Department of Chemistry, Liverpool Centre for Materials and Catalysis, University of Liverpool, Liverpool L69 7ZD, U.K.

Received July 15, 2008; E-mail: j.xiao@liv.ac.uk

Tetrahydroisoquinoline and tetrahydro-β-carboline rings exist widely in alkaloids, and their derivatives display high bioactivities.[1,2] Representative examples include salsolidine,[1a] YH 1885,[1b] and the tetrahydro-β-carboline LY23728.[1c] While methods for the asymmetric synthesis of these molecules have been developed,[1d,2] including chiral auxiliaries[2a,e] and organocatalysis,[2b,c] a straightforward, "greener" method is asymmetric hydrogenation of the corresponding imines.

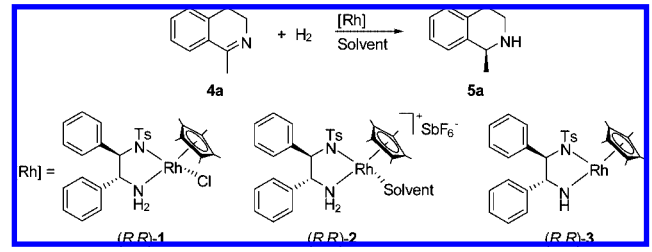


Although many excellent catalysts are now available for the asymmetric hydrogenation of olefins and ketones, developing catalysts for the closely related imines remains a considerable challenge.[3] In the particular case of isoquinoline-type imines, there are only a few papers thus far reporting reduction under either hydrogenation[4] or transfer hydrogenation[5] conditions. Apart from Buchwald's titanocene catalyst that allows a tetrahydroisoquinoline to be obtained in 95% ee, all the reported hydrogenation catalysts employ phosphorus-containing ligands, affording ee's lower than 90% for tetrahydroisoquinolines and tetrahydro-β-carbolines in almost all the cases. We now disclose a cationic Rh(III)-diamine catalyst that enables cyclic imines to be hydrogenated to give these amines with excellent ee's.

The Rh-TsDPEN complex **1** is a well-known catalyst for asymmetric transfer hydrogenation of ketones and imines (Scheme 1).[6] Recently, Noyori, Ohkuma and co-workers discovered that the closely related Ru(II) catalyst can be activated to hydrogenate ketones when replacing the chloride with triflate.[7] We set out by examining **1** for the hydrogenation of a model imine **4a**. The hydrogenation was initiated by introducing 20 bar of H_2 into an autoclave charged with **4a** and **1** (0.5 mol%) in dichloromethane (DCM) at room temperature. No reduction was observed after either 0.5 h or a prolonged time of 4 h under such conditions. Making the reaction conditions more basic or acidic did not bring about any significant changes. The screening results are seen in Table S1 (Supporting Information).

From the recent work of Noyori[7b] and Rauchfuss,[8] one would expect that the corresponding cationic Rh(III) species might be more reactive toward H_2 to form the necessary Rh−H hydride. With this in mind, we then tested the effect of a range of silver salts on the reduction, aiming to remove the chloride from the coordination sphere. Upon introduction of a silver salt, some reduction did take place. Much to our delight, a remarkably accelerated reduction was observed in the case of $AgSbF_6$, in the presence of a small quantity of water; a 36%

Scheme 1



conversion was recorded, with **5a** being produced in an excellent ee of 99% (Table S1).[9] Under such conditions, **1** is presumably converted into **2**, which bears a bulky counteranion SbF_6^-. In surprising contrast, AgOTf, $AgPF_6$ and related salts afforded conversions <5%. Additionally, somewhat lower conversions were observed when the solvent was MeOH, toluene, or neat water (Table S1).

This dramatic anion effect is further demonstrated by the kinetic profiles shown in Figure 1. While **1** showed no reduction, the conversions effected by the corresponding OTf^- and PF_6^- salt were less than 20% after a 4 h reaction time. By way of contrast, the in situ generated **2** afforded a conversion of 93% (99% ee). This is surprising, as the related, weakly coordinating OTf^- salt of Ru(II) is active for ketone hydrogenation.[7] However, a similar effect of anions has previously been revealed by Pfaltz and co-workers in olefin hydrogenation with iridium catalysts containing P^N ligands.[10]

Consistent with the ionic **2** being the key for hydrogen activation, the catalyst derived from AgOAc, which contains a coordinating OAc^-, led to a conversion of only 10% after 10 h (Table S1). Furthermore, addition of 2 equiv of Bu_4NBr (relative to rhodium) completely stopped the hydrogenation with **2**. Still further, when the 16e species **3** (Scheme 1) was used to replace **2**, no hydrogenation took place. However, hydrogenation occurred when $HSbF_6$ was introduced, indicating that **3** is protonated, *in situ* affording the

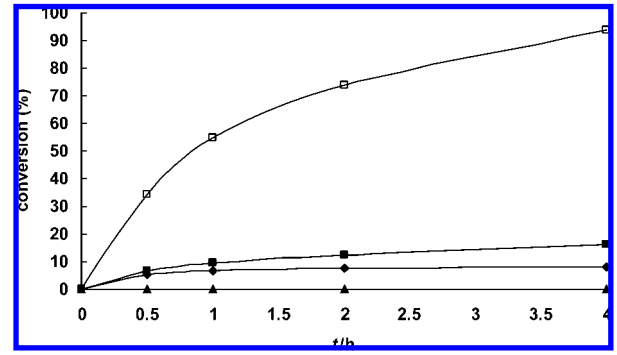


Figure 1. Effect of anion (▲ Cl^-, ◆ PF_6^-, ■ OTf^-, □ SbF_6^-) on the rate of hydrogenation of **4a** in DCM at room temperature. The catalyst was either **1** or *in situ* derived from **1** (0.5 mol%) in the presence of a silver salt; see Table S1 (entries 12−15) for conditions.

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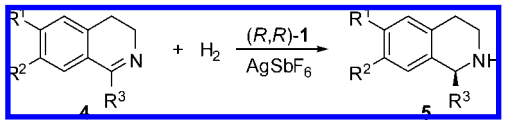
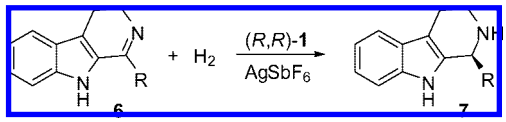
Table 1. Asymmetric Hydrogenation of Imines **4** To Give Amines **5**[a]



entry	$R_1/R_2/R_3$	time (h)	yield (%)[b]	ee (%)[c]
1	H/H/Me **4a**	1	94	99[d]
2	H/H/Et **4b**	8	95	97
3	H/H/^{i}Pr **4c**	4	90	40
4	H/H/Cy **4d**	4	90	65
5[e]	H/H/^{i}Pr **4c**	24	85	83
6[e]	H/H/Cy **4d**	24	90	91
7	MeO/MeO/Me **4e**	4	95	96
8	MeO/MeO/Et **4f**	4	90	93
9	MeO/MeO/^{i}Pr **4g**	4	95	93
10	MeO/MeO/Cy **4h**	4	94	95
11	MeO/MeO/R **4i**[f]	5	95	99

[a] Reaction conditions: 0.5 mmol **4**, 1 mol% **1**, 4 mol% $AgSbF_6$, 2 mL of DCM, 30 μL of water, 20 bar of H_2 at room temperature. [b] Isolated yields. [c] *S* product, determined by HPLC with a Chiralcel OD-H column. [d] Determined by GC (Table S1). [e] ^{i}PrOH as solvent; 50 bar of H_2. [f] R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$.

Table 2. Asymmetric Hydrogenation of Imines **6** To Give Amines **7**[a]



entry	R	time (h)	yield (%)	ee (%)[b]
1	Me **6a**	3	95	99
2	Et **6b**	3	96	99
3	^{i}Pr **6c**	3	94	98
4	Cy **6d**	3	95	98
5[c]	Cy **6d**	24	91	98
6	^{t}Bu **6e**	12	97	>99
7	C_6H_5 **6f**	4	94	99
8	4-$MeOC_6H_4$ **6g**	3	96	20
9[d]	4-$MeOC_6H_4$ **6g**	4	97	97
10	4-$CF_3C_6H_5$ **6h**	5	95	96[e]
11	R′ **6i**[f]	5	95	99

[a] The conditions were the same as those in Table 1 except with MeOH as solvent. [b] *S* product. [c] 0.1 mol% **1** and 0.4 mol% $AgSbF_6$ at 50 bar of H_2. [d] A similar Ir(III) catalyst was used. [e] Determined using a Chiralpak AD column. [f] R′ = 3,4-$(MeO)_2C_6H_3CH_2CH_2$.

active catalyst **2**.[8] Unlike asymmetric transfer hydrogenation,[5a,b] the Ru(II) analogue of **2** was less effective in the asymmetric hydrogenation (Table S1).

Using the optimized conditions, *viz*. with **2** being generated *in situ* from **1** (1 mol%), a range of imines were hydrogenated. The results on 3,4-dihydroisoquinolines and 3,4-dihydro-6,7-dimethoxyisoquinolines are given in Table 1. As can be seen, **4a** was completely reduced, affording **5a** in 99% ee and 94% isolated yield after 1 h (entry 1). However, replacing the methyl with the bulkier Et, ^{i}Pr, and Cy substituents necessitated longer reaction times, and the enantioselectivity decreased significantly in the case of **4c** and **4d** (entries 3 and 4). On the other hand, when the solvent was changed to isopropanol, the ee's were improved to 83% and 91% for **5c** and **5d**, respectively (entries 5 and 6). Delightfully, excellent yields and ee's were observed for 3,4-dihydro-6,7-dimethoxyisoquinolines. Thus, the compounds **4e**−**4i** were all fully reduced in 4−5 h, with ee's up to 99% being obtained. These results suggest that the poor behavior of **4c** and **4d** cannot simply be ascribed to steric effects. Since the enantioselectivity of the hydrogenation may be determined by weak C−H π interactions between the Cp* methyl group and the imine aromatic ring,[11] the more electron-rich **4g** and **4h** might be expected to give rise to stronger interactions and so higher ee's.

The applicability of **2** was also demonstrated in the hydrogenation of imine precursors to tetrahydro-β-carbolines (Table 2). Unlike the reduction of **4**, the reactions were performed in methanol, in which **6** is more soluble. In contrast to **4a**−**4d**, all the alkyl substituted imines **6** gave rise to excellent ee's, including those having cyclohexyl and ^{t}Bu groups, although **6e** necessitated a longer time. The catalyst loading could be lowered to 0.1% without compromising the ee (entry 5). Remarkably, the electronic properties of the aryl substituents appear to impact significantly on the enantioselectivity (entries 8 vs 10). In line with this, when the electronic effect is mitigated with a spacer, a high ee of 99% was obtained (entry 11). However, when switching to a similar Ir(III) catalyst, a high ee of 97% was obtained in hydrogenating **6g** (entry 9).

In conclusion, an efficient Rh(III)-diamine catalyst has been identified, which affords excellent enantioselectivities in asymmetric hydrogenation of imines to give bioactive tetrahydroisoquinolines and tetrahydro-β-carbolines. The cationic nature and the bulky noncoordinating counteranion appear to be the key to the success of **2**.

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Supporting Information Available: Experimental details and spectroscopy data (^{1}H, ^{13}C NMR, and HPLC). This material is available free of charge via the Internet at http://pubs.acs.org.

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