A New Chiral Bis(oxazolinylmethyl)amine Ligand for Ru-Catalyzed Asymmetric Transfer Hydrogenation of Ketones

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Asymmetric catalytic transfer hydrogenation using 2-propanol as a hydrogen source offers an attractive route for reducing simple unfunctionalized ketones to chiral alcohols.[1] The reaction uses inexpensive reagents and is usually easy to perform. Notable among the recently developed efficient transition-metal-based chiral reduction catalysts[2] is the Ru(II)−TsDPEN (TsDPEN = *N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine) system reported by Noyori[3] et al., who suggested that an NH moiety in the ligand may promote a cyclic transition state through hydrogen bonding to a ketone substrate.[1c] It therefore appears that the formation of a metal−ligand bifunctional catalyst can greatly increase the substrate affinity to the catalyst active site and induce high enantioselectivity. Earlier results from Noyori and Lemaire with different ligands have also shown a similar "NH effect".[4,5]

Chiral tridentate ligands generally form a deeper chiral concave pocket around the metal center than the corresponding chiral bidentate ligands. An example is the chiral bis(oxazolinyl)-pyridine ligand (pybox), developed by Nishiyama, which has been successfully applied to numerous asymmetric reactions.[6] The two substituents on the oxazoline rings of pybox form a highly enantioselective "chiral fence", which can effectively differentiate the *re* and *si* faces of many substrates. In an ongoing effort to develop effective chiral tridentate ligands for asymmetric catalysis,[2a,b,e] we have designed a bis(oxazolinylmethyl)amine (ambox) ligand system. Thus, by replacing the pyridine backbone of pybox with a secondary amino group, we expected that the new ambox ligand would form a six-membered cyclic transition state similar to that suggested by Noyori and highly enantioselective transfer hydrogenation of simple ketones might be realized (Figure 1). Herein, we present the synthesis of bis[4-(*R*)-phenyloxazolin-2-yl-methyl]amine (**1**, (*R*)-ph-ambox) and initial results for asymmetric transfer hydrogenation of aromatic ketones.

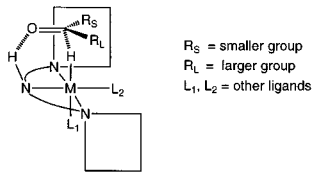
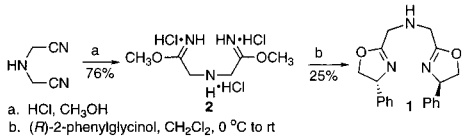


Figure 1. Schematic depiction of transition-metal catalysts of chiral tridentate nitrogen ligands with an NH function. Cyclic transition state for transfer hydrogenation of prochiral ketones.

Scheme 1. Synthesis of (*R*)-ph-ambox (**1**)



We have synthesized this ligand through the route[7] shown in Scheme 1. The imidate ester hydrochloride **2** was obtained in 76% crude yield from the inexpensive starting material, iminodiacetonitrile, and was used in the following step without purification. Treatment of (*R*)-2-phenylglycinol with **2** in CH_2Cl_2 at 0 °C and then warming to room temperature for 12 h afforded **1** in 25% unoptimized yield. The low yield of the second step is due to the formation of a mono-oxazoline as a side product along with reaction products derived from impurities in **2**.

Using catalysts generated in situ from **1** and various transition-metal precursors, our initial results on asymmetric transfer hydrogenation of acetophenone in 2-propanol were disappointing. Poor enantioselectivity was observed with Ru, Ir, and Rh catalysts, and the highest enantiomeric excess (ee) was less than 50% with $RuCl_2(PPh_3)_3$ as the catalyst precursor. In the process of optimizing catalytic conditions with this Ru precursor (Table 1), we found that the catalyst made in situ by refluxing **1** and $RuCl_2(PPh_3)_3$ in 2-propanol was more effective than that made at room temperature (entry 2 vs entry 1). We also discovered *two crucial factors that drastically enhanced both catalytic activity and enantioselectivity*: (a) the free triphenylphosphine ligand released during the complexation of **1** with the Ru(II) precursor must be removed with ether before introducing acetophenone and $NaOPr^i$ (entry 4 vs entry 3); (b) the molar ratio of $NaOPr^i$/catalyst should be 1.0. The reaction became very sluggish when 0.5 equiv of base was used, although good ee was still maintained (entry 5). The reaction was accelerated by 2.0 equiv of base, but was accompanied with a serious erosion of ee (entry 7). Under the optimized conditions, $RuCl_2(PPh_3)_3$ and **1** in 2-propanol were heated at 82 °C for 2 h generating a green solution. After the solvent was removed *in vacuo*, the resulting greenish residue was washed with ether to remove free PPh_3. The solid was redissolved in 2-propanol, followed by addition of substrate and $NaOPr^i$. The transfer hydrogenation reaction was rapid at 82 °C, while much slower reactions (with similar or lower ee) were observed when experiments were conducted at room temperature (entry 8).

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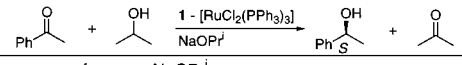
Table 1. Optimization of Catalytic Conditions for Transfer Hydrogenation of Acetophenone Catalyzed by **1**−$RuCl_2(PPh_3)_3$[a]



entry	free PPh_3[b]	$NaOPr^i$ equiv.[c]	T °C	t h	conversion %[d]	ee %[d]
1[e]	+	15	82	0.5	96	45
2[f]	+	15	82	0.25	92	60
3	+	1.0	82	1	67	84
4	-	1.0	82	0.17	91	97
5	-	0.5	82	1	26	95
6	-	0	82	1	0	N/A
7	-	2.0	82	0.17	94	68
8	-	1.0	23	22	91	95

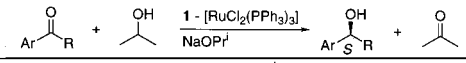
[a] Reactions were carried out with a 0.2 M acetophenone solution in 5 mL of 2-propanol (ketone:Ru(II):1 = 100:1:1.1). [b] + = free PPh_3 existed in the reaction mixture; − = after catalyst was formed, free PPh_3 was washed out with ether before adding acetophenone and $NaOPr^i$. [c] Equivalents of base to Ru(II). [d] See note *b* of Table 2. [e] Catalyst was made by stirring a mixture of **1** and $RuCl_2(PPh_3)_3$ at rt overnight. [f] For entries 2−8, catalysts were prepared by refluxing **1** and $RuCl_2(PPh_3)_3$ at 82 °C for 2 h.

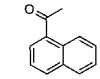
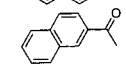
At present, we can only speculate as to the nature of the active Ru catalyst. Our studies on different Ru precursors (e.g., $[Ru(COD)Cl]_2$, $[RhCl_2(C_6H_6)]_2$, 2% ee and 5% ee for reduction of acetophenone, respectively) reveal that 1 equiv of PPh_3 is needed in the enantioselective step. A similar observation was found by Sammakia et al.[2d] in their catalytic transfer hydrogenation system. If the active catalyst species has the structure depicted in Figure 1 (L_1 = PPh_3, L_2 = Cl), it is probably formed after removal of 1 equiv of HCl from the catalytic precursor, **1**−$RuCl_2PPh_3$, by 1 equiv of $NaOPr^i$, followed by extraction of one proton and one hydride from 2-propanol. The Cl in the trans position relative to PPh_3 should be preferentially removed due to a strong trans effect. However, if more than 1 equiv of base is introduced, the chloride in the cis postion relative to PPh_3 can also be substituted by $^-OPr^i$. This could lead to pathways that favor the reverse reaction of ketone reduction, which results in erosion of ee. Free PPh_3 may also interfere with the reaction since it can coordinate to the five-coordinate Ru center. Indeed, the ee dramatically increased from 84% to 97% after removal of free PPh_3 (entry 4 vs entry 3).

Using optimized conditions, a variety of aromatic ketones have been reduced to the corresponding secondary alcohols (Table 2). It is noteworthy that the reaction for most substrates was complete at 82 °C in about 10 min with excellent enantioselectivity. The operational simplicity of this reaction makes this procedure a practical protocol for the synthesis of chiral secondary alcohols. Both ee and conversion are delicately affected by the steric and electronic properties of the substrates. The steric effect of the alkyl substituents of the ketone substrates is apparent from the results for methyl, ethyl, and isopropyl phenyl ketones (entries 1−3). By changing the para substituent from chloride to methoxy, the ee improved, but the conversion was low (entries 11 and 12). Erosion of product ee over time is moderate for most of the ketones tested. Especially for ortho methyl- and chloro-substituted acetophenones, we have seen little erosion throughout the course of reaction (entries 4 and 5). However, when the ortho group is methoxy, a very poor result was obtained (entry 6). This is perhaps due to chelation of the substrate or alcohol product to the ruthenium center, thereby terminating the catalytic cycle.

To understand the role of the NH moiety in the **1**-$RuCl_2PPh_3$ catalyst, we made a new tridentate ligand by substituting the NH in **1** with NCH_3.[8] Under the optimized conditions with **1**−$RuCl_2$-PPh_3 (entry 4, Table 1), poor enantioselectivies and low conversions were obtained with the Ru catalyst prepared from this new ligand at 82 °C (acetophenone, 30 min, 16.5% conversion, 9.9% ee; 2′-chloroacetophenone, 10 min, 10.8% conversion, 10.0% ee). These results are in sharp contrast with ee values obtained with **1**−$RuCl_2PPh_3$ as the catalyst (entries 1 and 5, Table 2). This observation shows that the NH group in **1** indeed plays a crucial role in asymmetric catalysis.

Table 2. Results of Transfer Hydrogenation of Ketones Catalyzed by **1**−$RuCl_2(PPh_3)_3$ under Optimized Conditions[a]



entry	ketone		t min	conversion %[b]	ee %[b]
1		X = CH_3	5 (10)	80 (91)	98 (97)
2		X = Et	10 (20)	77 (92)	95 (92)
3		X = i-Pr	10	15	78
4		X = CH_3	40	96	98
5		X = Cl	5	>99	97
6		X = CH_3O	240	3	19
7		X = CH_3	5 (7)	75 (90)	96 (94)
8		X = Cl	10	5	92
9		X = CH_3O	7 (10)	91 (94)	95 (93)
10		X = CH_3	4	68	95
11		X = Cl	10	97	90
12		X = CH_3O	10	41	98
13			10	42	95
14			2 (5)	72 (98)	96 (94)
15			2 (7)	55 (91)	96 (92)

[a] See text for experimental procedures. Reactions were carried out at 82 °C using a 0.2 M ketone solution in 5 mL of 2-propanol (ketone:Ru:**1**:$NaOPr^i$ = 100:1:1.1:1.0). [b] %ee and %conversion were determined by GC analysis with a Supelco *β*-DEX 120 chiral capillary column. Absolute configurations were determined by comparing optical rotations with literature values. All major secondary alcohol products have the (*S*) configuration.

The Ru−ambox catalyst gives comparable enantioselectivity to the Ru−TsDPEN transfer hydrogenation system,[3] and the reaction proceeds much faster at a higher temperature without loss of enantioselectivity (reaction rate up to ca. 2000 turnovers/cat./h for some substrates at 82 °C vs 10 turnovers/cat./h at room temperature). Moreover, the steric and electronic structure is more tunable with Ru−ambox catalysts since the phosphine ligand, halide and R group on the oxazoline can be varied. Also, the Ru−ambox system is more robust than the Ru−TsDPEN catalyst[9] and can be used at higher temperatures.

In summary, this work presents a new chiral tridentate ligand which forms a highly efficient and practical catalyst with $RuCl_2$-$(PPh_3)_3$ for transfer hydrogenation of aryl alkyl ketones. The presence of an NH moiety in the Ru−ambox is important for obtaining high reactivity and enantioselectivity. The chirality on the oxazoline rings can be readily fine-tuned by incorporating different chiral *β*-amino alcohols. To further elucidate the nature of this catalyst, isolation of the active catalyst species is currently underway. Other asymmetric reactions with this ligand are also being carried out and progress will be reported in due course.

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Supporting Information Available: Experimental details for the preparation of compounds and the transfer hydrogenation reaction (3 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(8) For the synthesis and characterization of the new ligand, see the Supporting Information.

(9) Lower enantioselectivities were obtained above room temperature with the Ru−TsDPEN system, see ref 1c.