Transfer Hydrogenation with Ruthenium Complexes of Chiral (Phosphinoferrocenyl)oxazolines

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Received June 18, 1997

Transfer hydrogenation using 2-propanol as a source of hydrogen is an attractive method for the reduction of ketones to alcohols. The reaction utilizes inexpensive reagents, is simple to perform, and does not require the use of reactive metal hydrides or hydrogen. Because the reaction is governed by mass action, reduction of the ketone can be driven to high conversion by using *iso*-propanol as the solvent. The classical variant of this reaction, the Meerwein−Pondorff−Verley reduction, typically utilizes a stoichiometric amount of an aluminum alkoxide as a promoter. Recently, Backvall and Chowdhury showed that 0.1% $RuCl_2(PPh_3)_3$ (**1**) is an effective catalyst for this transformation, provided that about 2% NaOH is present.[1] This discovery has lead to the development of asymmetric processes which utilize Ru catalysts that are modified with chiral ligands.[2,3] Most notably, Noyori has developed catalysts which will reduce aryl alkyl ketones to the corresponding alcohols in excellent yields and enantioselectivities.[4] We have previously described the preparation of chiral ferrocenyloxazoline complexes which posses complexation induced chirality (i.e., "planar chirality").[5,6] These complexes are prepared in high yield and with excellent diastereoselectivity via the diastereotopic group selective metalation of the parent ferrocenyloxazoline using *sec*-BuLi in ether containing 1 equiv of TMEDA. We have used this method for the preparation of chiral (phosphinoferrocenyl)oxazolines,[7] and describe in this article their use as ligands in conjunction with **1** in the enantioselective transfer hydrogenation of aryl alkyl ketones.

Scheme 1

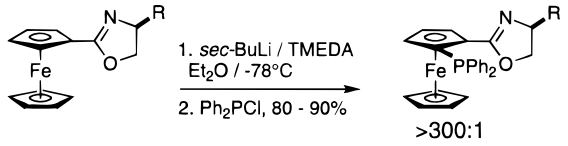
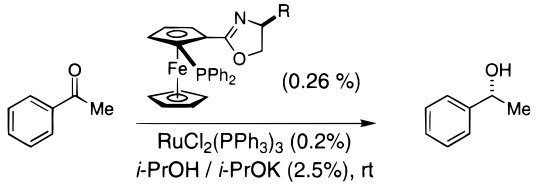


Table 1[a]



entry	R	time (h)	% conversion[b]	%ee[c]
1	Me (**2**)	8	92	92
2	Bn (**3**)	6	93	90
3	*i*-Pr (**4**)	3	93	92
4	Ph (**5**)	6	93	94
5	*t*-Bu (**6**)	6	51	94
6	*d*	20	5	−

[a] See text for conditions. [b] The % conversion was determined by capillary GC using dodecane as an internal standard. [c] Enantioselectivities were measured by capillary GC using a Supelco β-dex 120 column (per-methylated β-cyclodextrin chiral phase) and are reproducible to ±1%. [d] The reaction was performed without the ferrocene ligand.

Our initial efforts focused on screening a variety of ferrocenyloxazolines in which the substituent on the oxazoline is varied in order to ascertain its effect on the reaction (Table 1). We chose acetophenone as our test substrate and performed the reaction at room temperature in 2-propanol at a concentration of 0.125 M using 0.2% **1**, 0.26% of the ferrocene complex, and 6% potassium isopropoxide. The catalysts were prepared *in situ* by the addition of our ligand to **1** in 2-propanol followed by heating the solution to reflux for 1 h. Catalysts prepared in this fashion are significantly more reactive than **1** (ligand accelerated catalysis,[8] Table 1, compare entries 1−5 with entry 6). All of the ligands we examined provide enantioselectivities in excess of 90%, with the phenyl- and *tert*-butyl-substituted oxazolines providing 94% ee (Table 1, entries 4 and 5). Furthermore, all of the reactions containing the ferrocene ligands proceeded to greater than 90% conversion as shown by GC, with the exception of the *tert*-butyl-substituted oxazoline **6** which only proceeded to about 50% conversion (Table 1, entry 5). Thus, the phenyl-substituted oxazoline was deemed to provide the optimal combination of conversion and selectivity.

We have examined the scope of this method for the reduction of aryl alkyl ketones using ligand **5** as shown in Table 2. All reactions were initially attempted at room temperature; however, we found that the reductions of the more hindered or electron rich substrates did not proceed to completion. When these substrates were reduced at elevated temperatures, the reactions pro-

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(3) For other metal-based systems, see: Evans, D. A.; Nelson, S. G.; Gagné, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800; Genet, J.-P.; Ratovelomanana-Vidal, V.; Pinel, C. *Synlett*, **1993**, 478. Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett.* **1993**, *34*, 6897. Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1995**, *6*, 705. Varghese, J.; Iyers, S. *J. Chem. Soc., Chem. Commun.* **1995**, 465;

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(7) For examples of the use of related ligands in asymmetric catalysis, see: Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics* **1995**, *14*, 5486. Richards, C. J.; Hibbs, D. E.; Hursthouse, M. B. *Tetrahedron Lett.* **1995**, *36*, 3745. Zhang, W.; Hirao, T.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 4545; Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419. Zhang, W. B.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 7995.

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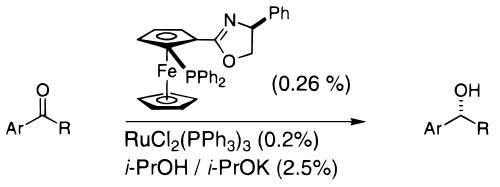
S0022-3263(97)01104-3 CCC: $14.00

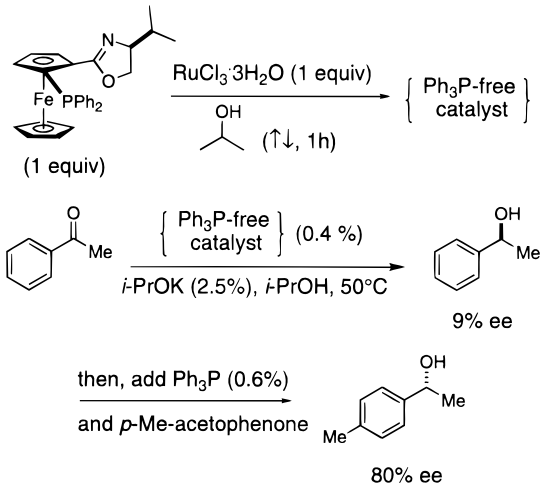
Table 2[a]



entry	Ar	R	temp (°C)	time (h)	%yield	%ee
1	Ph	Me	28	7	80	94
2	Ph	Et	50	1	85	96
3	Ph	*i*-Pr	80	1	87	88
4	1-Np	Me	50	3	92	91
5	2-Np	Me	28	7	82	95
6	*o*-tolyl	Me	50	1	83	93
7	*p*-Cl-Ph	Me	28	6	83	93
8	*p*-OMe-Ph	Me	50	2	75	84
9[b]	mesityl	Me	80	1	81	95

[a] With the exception of the temperature, which is as noted in the table, conditions are the same as for Table 1. [b] This reaction was conducted at a concentration of 0.0725 M.

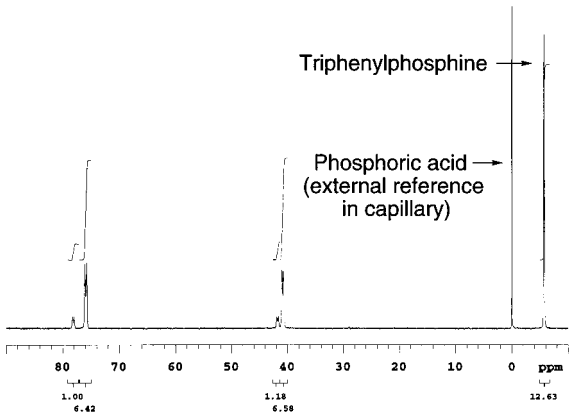
Scheme 2



ceeded to high conversions with only a slight loss of selectivity (Table 2, entries 2, 3, 4, 6, 8, and 9).

We have performed several experiments designed to elucidate the structure of the active catalytic species in this reaction. We have prepared a triphenylphosphine-free catalyst by substituting our ferrocenyl ligand for triphenylphosphine in the literature preparation of $RuCl_2(PPh_3)_3$.[9] This catalyst is much less active than catalyst prepared from **1**, and its use for the reduction of acetophenone provides material of low enantioselectivity (Scheme 2).[10] Interestingly, the selectivity can be largely restored by the addition of triphenylphosphine as illustrated by the following experiment. Reduction of acetophenone using the triphenylphosphine-free catalyst preparation in 2-propanol at reflux provides the *S*-enantiomer of the carbinol (i.e., the opposite of what is observed with the triphenylphosphine-containing preparation) in 60% conversion and in 9% ee after 3 h. If triphenylphosphine and *p*-methylacetophenone are then added to this solution, the *p*-methylacetophenone is reduced to the *R*-enantiomer of the carbinol in 80% ee, suggesting that the triphenylphosphine is bound to the metal in the stereochemistry determining step (Scheme 2).[11,12]

Scheme 3



We have isolated what we suspect is the catalyst formed upon treating **1** with **5**. Heating a 0.05 M *iso*-propanol solution of **1** to reflux in the presence of 1.05 equiv of ligand **5** provides a precipitate (**7**) which is soluble in $CDCl_3$ and which provides ^1H and ^{31}P NMR spectra and elemental analysis consistent with $RuCl_2(PPh_3)$·**5** (see Supporting Information). No free triphenylphosphine is observed in the ^{31}P spectrum. Complex **7** exists as an approximately 5:1 ratio of diastereomers at 24 °C as revealed by NMR and contains two phosphines in each complex. It was also found to have the same reactivity as the catalyst prepared *in situ* from **1** and ligand **5** and will catalyze the reduction of acetophenone to the corresponding alcohol in 85% yield and 94% ee using our standard reaction conditions. Treatment of a $CDCl_3$ solution of **1** with **5** provides the ^{31}P NMR spectrum shown in Scheme 3. In this spectrum, 2 equiv of free triphenylphosphine ($\delta = -5.64$ ppm) are evident as well as complex **7**, indicating that the *in situ* preparation of the catalyst provides complex **7**. The diastereomeric ratio observed by NMR varies with temperature. At 24 °C the ratio is about 6:1 (Scheme 3), but at 57 °C, the ratio is about 2:1, indicating that the diastereomeric complexes are equilibrating on the NMR timescale and on the timescale of the reaction. Unfortunately, we have not been successful in obtaining crystals suitable for X-ray diffraction.

In conclusion, we have described a new and selective catalyst for the enantioselective transfer hydrogenation of aryl alkyl ketones. The system is subject to ligand-accelerated catalysis, and our mechanistic studies indicate that the triphenylphosphine is bound to the Ru during the stereochemistry-determining step. This system is readily amenable to modification, and experiments to further optimize and examine the scope and mechanism of this process are currently in progress.

Acknowledgment. We thank the National Institutes of Health (GM48498), Novartis Pharmaceuticals Corporation, and Pfizer for financial support of this research. T.S. is a recipient of an American Cancer Society Junior Faculty Research Award and is an Alfred P. Sloan Research Fellow (1996−1998).

Supporting Information Available: Characterization of alcohol products, ^{31}P and ^1H NMR spectra of **7** at 24 °C and 57 °C, and experimental details for the preparation and characterization of ligands **2**−**6** and for the typical transfer hydrogenation procedure (6 pages).

JO9711044

(9) $RuCl_2(PPh_3)_3$ is typically prepared by heating to reflux a solution consisting of 1 equiv $RuCl_3·3H_2O$ and 6 equiv triphenylphosphine in methanol for 3 h, during which time the product crystallizes (see: Stephenson, T. A.; Wilkinson, G. *J. Inorg. Nucl. Chem.* **1966**, *28*, 945).

(10) Catalysts prepared using dichloro(1,5-cyclooctadiene)ruthenium(II) polymer or dichloro(*p*-cymene)ruthenium(II) dimer as catalyst precursors are also less reactive and unselective.

(11) Reduction of acetophenone at 50 °C in *i*-PrOH using a catalyst prepared by refluxing $RuCl_3·3H_2O$ (0.4%) with Ph_3P (0.4%) and ligand **5** (0.4%) in *i*-PrOH for 1 h provides the expected (*R*)-carbinol in 90% ee and 76% conversion.

(12) When tributylphosphine is substituted for triphenylphosphine, racemic material is produced at a greatly diminished rate.