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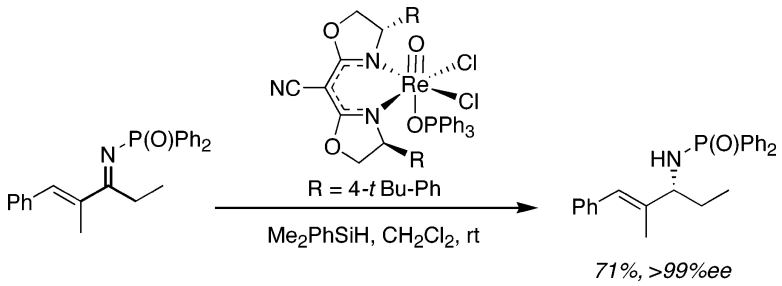

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Enantioselective Reduction of Imines Catalyzed by a Rhenium(V)−Oxo Complex

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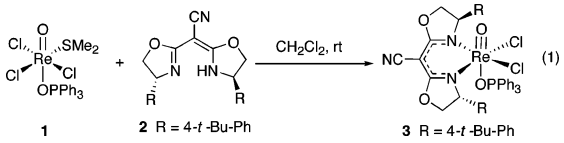
The prevalence of chiral secondary amines in natural products and pharmaceutical targets has fueled considerable research into the asymmetric reduction of imines.[1] These reductions generally employ catalysts derived from transition metals in low-oxidation states. For example, low oxidation state late metal catalysts[2] or titanocene[3] complexes have dominated transition-metal-catalyzed enantioselective hydrosilylation of imines. In contrast, we recently described that the high-oxidation state Re−dioxo complex, $(Ph_3P)_2Re(O)_2I$, serves as a catalyst for the hydrosilylation of ketones and aldehydes.[4] The high-oxidation state of the catalyst allows the reaction to be carried out under "open-flask" conditions, without the need for rigorous exclusion of air and moisture. Herein, we describe the development of a novel Re(V)−oxo complex for the catalytic enantioselective reduction of imines.

Mechanistic studies[5] on the $(Ph_3P)_2Re(O)_2I$-catalyzed hydrosilylation suggested that dissociation of a neutral ligand was essential for the catalytic activity of Re(V)−oxo complexes. This constraint precluded the use of neutral bidentate chiral ligands for the development of a catalyst for enantioselective reductions; therefore, we sought to prepare a Re(V)−oxo complex with monoanionic bidentate ligands. We envisioned that monodeprotonated bis(oxazoline) (box) ligands might serve this purpose. While attempts to prepare (box)Re(V)−oxo complexes were unsuccessful, we were pleased to find that the increased acidity of the cyanobis(oxazoline)[6] ligand (CNbox, **2**) allowed for the facile synthesis of the (CNbox)-Re(V)−oxo complex (**3**) by simply stirring Re(V)−oxo dimethyl sulfide complex **1**[7] in CH_2Cl_2 in the presence of 1.1 equiv of the ligand (eq 1).



1 **2** R = 4-*t*-Bu-Ph **3** R = 4-*t*-Bu-Ph

(CNbox)Re(V)−oxo complex **3** was isolated as a bright green solid. Slow evaporation of a concentrated solution of (*R*,*R*)-**3** in dichloromethane at room temperature yielded X-ray quality, plate-like crystals (Figure 1). The rhenium possesses distorted octahedral geometry, in which the oxo ligand is *trans* to triphenylphosphine oxide and the two chlorides are *trans* to the nitrogens of the CNbox ligand. The short Re−oxo bond length (1.66 Å) indicates substantial triple bond character.[8]

With this complex in hand, we set out to examine its potential as a catalyst for enantioselective phosphinyl imine reduction. Our choice of this imine nitrogen substituent was guided by the requirement that the imine be tolerant to air and moisture that may be present during the course of the reaction; however, once reduction has taken place, the resulting phosphinyl amine can be easily cleaved under acidic conditions.[9] With this in mind, we examined the reduction of imine **4** at room temperature using 2 equiv of silane and 3 mol % of **3** under ambient atmosphere (Table 1). Under these conditions, complex **3** catalyzed the reduction of imine **4** to amine **5** with high selectivity in a range of solvents (entries 1−4), with dichloromethane proving to be the most general.

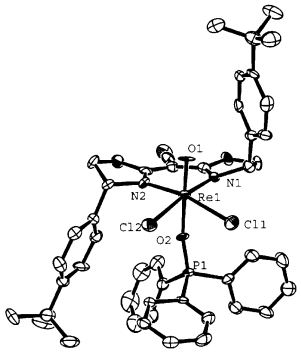
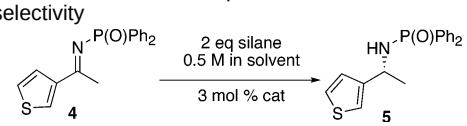


Figure 1. ORTEP drawing of X-ray structure of (*R*,*R*)-**3**. Representative bond angles: C1−C27−C14 (121.0°), N1−Re−N2 (90.1°), O1−Re−O2 (174.7°).

Table 1. Effect of Solvent, Temperature, and Silane on Enantioselectivity



4 **5**

entry	silane	solvent	temp	% yield	% ee
1	DMPS−H	CH_2Cl_2	rt	75	99
2	DMPS−H	THF	rt	96	99
3	DMPS−H	EtOAc	rt	58	99
4	DMPS−H	toluene	rt	51	99
5	DPMS−H	CH_2Cl_2	rt	77	98
6	DMPS−H	CH_2Cl_2	40 °C	81	98

This catalyst system operates well with either dimethylphenylsilane (DMPS−H) or diphenylmethylsilane (DPMS−H) as the hydride source; however, DMPS−H generally provides the best enantioselectivities (entries 1 and 5). Additionally, an increase in reaction temperature to 40 °C had little impact on the enantioselectivity of the reduction (entry 6).

Using these conditions, excellent enantioselectivities were obtained in the Re(V)−oxo-catalyzed reduction of various *N*-phosphinyl imines (Table 2). Reduction of phenyl methyl ketimine **6a** afforded amine (*R*)-**7a**[10] with greater than 99% ee (entry 1). The enantioselectivity remained high in the reduction of ketimines bearing electron-withdrawing and electron-donating groups on the aromatic ring (entries 2 and 3). Heteroaromatic ketimines (entries 5 and 7) were also consistently reduced with excellent enantioselectivity (99% ee). Five-, six-, and seven-membered ring ketimines also reacted to give amines with excellent enantioselectivity (entries 8−10). Notably, contamination by the enamine tautomer does not impact the reactivity or enantioselectivity of the hydrosilylation. For example, reduction of benzosuberone-derived ketimine **6h**, which exists primarily in the enamine form, produced amine **7h** in 71% yield and 96% ee. Furthermore, the reduction is not limited to *N*-phosphinyl imines. Rhenium-catalyzed reduction of *p*-methoxyphenyl (PMP) imine **6k** proceeds with only slightly diminished enantioselectivity compared to that of the phosphinyl imine **6j** (compare entries 10 and 11).[3a] On the other hand, rhenium-catalyzed reduction of aliphatic imine **6l** proceeded with poor enantiocontrol (entry 12).

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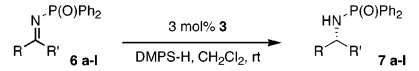
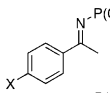
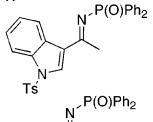
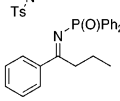
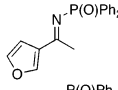
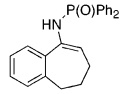
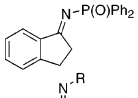
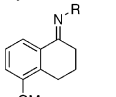
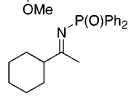
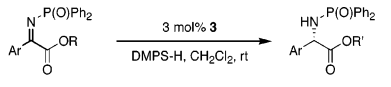
Table 2. Scope of the Enantioselective Imine Reduction[a]



Entry	Imine		% yield	%ee[b]
1		**6a** X = H	51	> 99
2		**6b** = OMe	61	98
3		**6c** = CF_3	78	98
4		**6d** = I	71	99
5		**6e**	81	> 99
6		**6f**	68	> 99
7		**6g**	76	99
8		**6h**	71	96
9		**6i**	89	95
10		**6j** R = $P(O)Ph_2$	69	95
11		**6k** R = PMP	76	92
12		**6l**	69	32

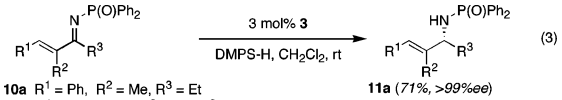
[a] Reaction conditions: 3 mol % of catalyst, 2 equiv of DMPS−H in 0.5 M CH_2Cl_2. [b] The % ee was determined using chiral HPLC.

The rhenium-catalyzed reduction was also applied to the synthesis of phenyl glycine derivatives by the hydrosilylation of α-imino esters (eq 2).[11] These imines were reduced to the corresponding α-amino esters with excellent selectivity without reduction of the ester or epimerization of the α-stereocenter.



8a Ar = Ph R = Et — **9a** (*83%, >99% ee*)
8b Ar = 4-MeOPh R = Me — **9b** (*47%, 95% ee*)
8c Ar = 2-MePh R = Me — **9c** (*69%, 99% ee*)

The chemo- and enantioselective hydrosilylation of α,β-unsaturated imines to allylic amines is extremely rare.[3a] We were, therefore, pleased to find that complex **3** catalyzed the selective reduction of α,β-unsaturated imine **10a** to allylic amine **11a** in 71% yield and 99% ee (eq 3).[12] The reaction tolerates substitution of both electron-donating and electron-withdrawing substituents on the aromatic ring; however, an *ortho*-methyl group resulted in isolation of allylic amine **11d** with diminished enantiomeric excess. Moreover, the rhenium-catalyzed reaction of imine **10f**, which is not conjugated to an aromatic ring, furnished allylic amine **11f** with 83% ee.



10a R^1 = Ph, R^2 = Me, R^3 = Et — **11a** (*71%, >99%ee*)
10b R^1 = 4-MeOPh, R^2 = Me, R^3 = Et — **11b** (*61%, 92%ee*)
10c R^1 = 4-ClPh, R^2 = Me, R^3 = Et — **11c** (*67%, 97%ee*)
10d R^1 = 2-MePh, R^2 = Me, R^3 = Et — **11d** (*63%, 74%ee*)
10e R^1 = Ph, R^2 = H, R^3 = Me — **11e** (*62%, 75%ee*)
10f R^1 = $PhCH_2CH_2$, R^2 = Me, R^3 = Et — **11f** (*48%, 83%ee*)

In conclusion, we have developed an "open-flask" enantioselective reduction of imines and α-imino esters that employs a high oxidation metal−oxo catalyst. Particularly noteworthy is the chemo- and enantioselective reduction of α,β-unsaturated imines to allylic *N*-phosphinyl amines, which can undergo further transformations.[13] This reaction provides a rare example of a catalytic process employing a chiral rhenium complex.[14] While chiral metal−oxo complexes are commonly employed as catalysts in asymmetric oxidation reactions, this method highlights the potential for their use in nonoxidative enantioselective transformations.[15] Studies on the development of this class of catalysts, including application of the complexes described herein, are ongoing in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures, sample spectra, compound characterization data (PDF), and X-ray structure data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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