Asymmetric Hydrosilylation of Nitrones using Ruthenium(II) Phosphine Complex Catalysts; Syntheses of Optically Active *N,N*-Disubstituted Hydroxylamines and Secondary Amines

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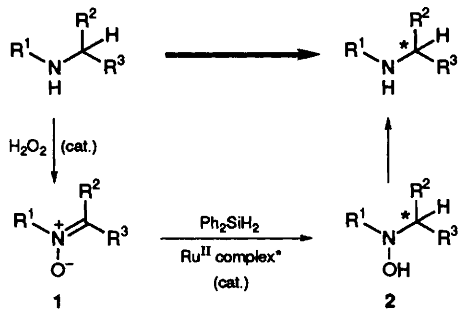
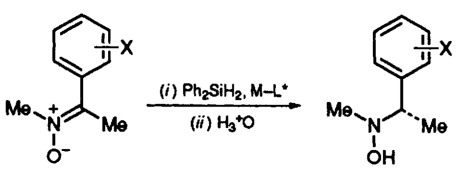
Enantioselective hydrosilylation of carbon–nitrogen double bonds of nitrones with diphenylsilane using Ru_2Cl_4-[(*S*)-(−)-*p*-tolbinap]$_2$(NEt_3) [*p*-tolbinap = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl] catalyst at 0°C gives the corresponding optically active *N,N*-disubstituted hydroxylamines; up to 91% enantiomeric excess (e.e.) is achieved.

Optically active *N*-hydroxylamines bearing an asymmetric centre α to the nitrogen are of importance in view of biologically active nitrogen compounds[1] and the precursors of chiral ligands for asymmetric synthesis. We report the first asymmetric synthesis of *N,N*-disubstituted hydroxylamines **2** by catalytic hydrosilylation of nitrones. Recently, we found that the oxidation of secondary amines with hydrogen peroxide in the presence of catalysts such as sodium tungstate,[2] selenium dioxide[3] and flavinium salts[4] gives nitrones **1** highly efficiently. Therefore, the catalytic oxidation of secondary amines and subsequent asymmetric hydrosilylation of nitrones thus obtained opens a general and powerful strategy for the synthesis of optically active *N*-hydroxylamines from secondary amines as depicted in Scheme 1. Furthermore, reduction of *N*-hydroxylamines thus obtained gives optically active secondary amines.



1 2

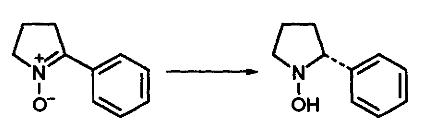
Scheme 1



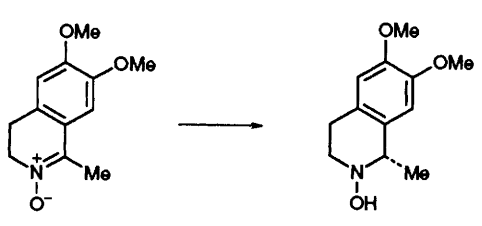
(1)

3 (*S*)-(−)-4

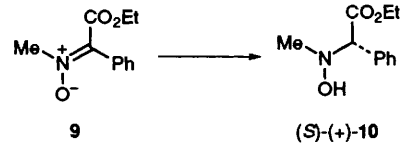
a X = 4-Cl **d** X = H
b X = 4-F **e** X = 4-OMe
c X = 3-Cl



5 (*R*)-(+)-6



7 (*S*)-(−)-8



9 (*S*)-(+)-10

The hydrosilylation of (*E*)-*N*-[1-(4-chlorophenyl)ethylidene]methylamine *N*-oxide **3a** derived from the catalytic oxidation of *N*-methyl-1-(4-chlorophenyl)ethylamine,[2] with a hydrosilane was examined as a typical example in the presence of a catalyst [eqn (1)]. Diphenylsilane is the best hydrosilane among those examined. The observed enantioselectivity increases in the following order; diphenylsilane > diethylsilane > 1-naphthylphenylsilane > methylphenylsilane ≫ phenylsilane. The hydrosilylations of **3a** in the presence of Rh^I complex catalyst such as $[Rh(cod)Cl]_2$–(*R*)-(+)-binap complex and [Rh(cod)((+)-diop)]ClO_4 [diop = 2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane] give poor optical yields. Ruthenium(II) complexes[5] such as Ru_2Cl_4[(*S*)-(−)-*p*-tolbinap]$_2$(NEt_3) and Ru_2Cl_4[(*S*)-(−)-binap]$_2$(NEt_3) are excellent catalysts for the hydrosilylation of **3a**, and high enantioselectivities are obtained. Poor results are obtained, when $Ru(OAc)_2$[(*S*)-*p*-tolbinap] or [RuI(*p*-cymene){(*R*)-binap}]I is used. Ether solvents such as 1,4-dioxane and 1,2-dimethoxyethane are good solvents. The representative

Table 1 Asymmetric hydrosilylation of nitrones[a]

Nitrone	Solvent	*T* /°C	Product[b]	Yield[c] (%)	Optical yield[d] e.e. (%)
3a	Dioxane	35	(*S*)-(−)-**4a**	90	73
3a	Dioxane	0	(*S*)-(−)-**4a**	56	85
3b	Dioxane	0	(*S*)-(−)-**4b**	63	86
3c	Dioxane	0	(*S*)-(−)-**4c**	37	86
3d	Dioxane	0	(*S*)-(−)-**4d**	64	83
3e	Dioxane	0	(*S*)-(−)-**4e**	59	60
5	Dioxane	0	(*R*)-(+)-**6**	29	69
7	CH_2Cl_2	35	(*S*)-(−)-**8**	99	56
9	Dioxane	0	(*S*)-(+)-**10**	24	91

[a] 0.5 mol% of Ru_2Cl_4[(*S*)-(−)-*p*-tolbinap]$_2$(NEt_3) and 2 equiv. of Ph_2SiH_2 are used. The reaction time is 2 h. [b] The absolute configurations of hydroxylamines **4b–e**, **6**, **8** and **10** are determined by comparison with the authentic samples after converting to the corresponding secondary amines: **4b**; determined as (*S*)-(−)-*N*-methyl-1-(4-fluorophenyl)ethylamine.[6] **4c** and **4d**; determined as (*S*)-(−)-*N*-methyl-1-phenylethylamine.[6] **4e**, determined as (*S*)-(−)-*N* methyl-1-(4-methoxyphenyl)ethylamine.[7] **6**; determined as (*R*)-(+)-2-phenylpyrrolidine.[8] **8**; determined as (*S*)-(−)-salsolidine.[9] **10**; determined as (*S*)-(+)-*N*-methylphenylglycine.[10] [c] Isolated by column chromatography (SiO_2). [d] Determined by HPLC analysis using a chiral column. **4b**: Chiralpak AD, 2% propan-2-ol in hexane; **4c**: Chiralpak AD, 1% propan-2-ol in hexane; **4d**: Chiralcel OD, 0.5% propan-2-ol in hexane; **4e**: Chiralcel OD, 1% propan-2-ol in hexane; **6**: Chiralcel OD, 2% propan-2-ol in hexane; **8**: Chiralpak AD, 10% propan-2-ol in hexane; **10**: Chiralcel OJ, 0.5% propan-2-ol in hexane.

results of the asymmetric hydrosilylations using $Ru_2Cl_4[(S)$-$(-)$-p-tolbinap$]_2(NEt_3)$ catalyst are shown in Table 1.

The hydrosilylation of nitrone **3a** is described as a typical experimental procedure. To a solution of nitrone **3a** (1 mmol), which is a pure (*E*)-isomer, and $Ru_2Cl_4[(S)$-p-tolbinap$]_2(NEt_3)$ (0.005 mmol) in dry 1,4-dioxane (1 ml) was added diphenylsilane (2 mmol) at 0°C under argon, and the mixture was stirred at 0°C for 2 h. The product of *O*-silylhydroxylamine and the recovered nitrone was hydrolysed upon treatment with aqueous 2 mol dm^{-3} hydrochloric acid solution (10 ml). The catalyst, silyl derivatives, and the ketone derived from the nitrone were removed by extraction with diethyl ether (3 × 10 ml). The aqueous layer was neutralized by adding $NaHCO_3$ powder carefully and extracted with diethyl ether. Removal of the solvent followed by silica gel column chromatography (ethyl acetate) gave the hydroxylamine (−)-**4a** as a single product (conv. 60, 56% isolated yield). The structure of the product was determined by ^1H NMR, ^{13}C NMR, and IR spectra, and elemental analyses. The optical yield of (−)-**4a** was determined to be 85% e.e. by HPLC analysis using chiral column (CHIRALPAK AD); eluent, 2% propan-2-ol in hexane. The hydroxylamine thus obtained was readily converted into (*S*)-(−)-*N*-methyl-1-(4-chlorophenyl)ethylamine upon treatment with Zn–HCl without losing optical purity. The absolute configuration of (−)-**4a** was determined to be (*S*) by comparison of the secondary amine derived from **4a** with the authentic sample.[6] The opposite enantiomer (*R*)-(+)-**4a** was obtained with a similar e.e. when $Ru_2Cl_4[(R)$-$(+)$-p-tolbinap$]_2(NEt_3)$ was used as a catalyst.

The hydrosilylation of 2-phenyl-1-pyrroline *N*-oxide **5** with Ph_2SiH_2 in the presence of $Ru_2Cl_4[(S)$-$(-)$-p-tolbinap$]_2(NEt_3)$ catalyst in 1,4-dioxane at 0°C gave (*R*)-(+)-1-hydroxy-2-phenylpyrrolidine **6** (conv. 30%; 29% isolated yield; 69% e.e.). The hydrosilylation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline *N*-oxide **7** in CH_2Cl_2 at 35°C with the same catalyst gave (*S*)-(−)-2-hydroxysalsolidine **8** (99% yield, 56% e.e.), which undergoes reduction upon treatment with Zn–HCl to give (*S*)-(−)-salsolidine. These results indicate that, when the (*S*)-binap ruthenium(II) complex is used as a catalyst, (*R*)-hydroxylamines are obtained from (*Z*)-nitrones (**1**, $R^3 > R^2$) such as **5**, while (*S*)-hydroxylamines are obtained from (*E*)-nitrones (**1**, $R^2 > R^3$) such as **3** and **7**. The present catalytic hydrosilylation of nitrones can be rationalized by assuming the mechanism, which involves insertion of the ruthenium phosphine complex into the Si–H bond of diphenylsilane to give silylhydridoruthenium species that undergoes insertion into nitrones enantioselectively, depends on the configuration of nitrones (*Z* or *E*) rather than on the relative bulkiness of the substituents at the prochiral carbon centre of nitrones.

Finally, optically active *N*-hydroxy-α-amino acid ester (*S*)-(+)-**10**, which is an antimetabolite of α-amino acids,[1] is prepared by the asymmetric hydrosilylation of (*E*)-ethyl α-methyliminophenylacetate *N*-oxide **9** (conv. 30%; 24% isolated yield; 91% e.e.) in 1,4-dioxane at 0°C.

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