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Ruthenium-catalysed asymmetric hydrosilylation of ketoximes using chiral oxazolinylferrocenylphosphines

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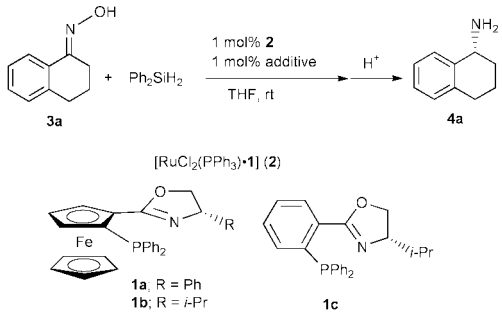
Chiral ruthenium(II) complexes, $RuCl_2(PPh_3)$(oxazolinylferrocenylphosphine), have been found to be effective catalysts for asymmetric hydrosilylation of ketoximes to give the corresponding primary amines in good yields with high enantioselectivities (up to 89% ee) after acid hydrolysis.

Optically active *primary* amines are one of the most useful synthetic intermediates of natural compounds and pharmaceutical drugs.[1] However, the *direct* enantioselective synthesis of optically active *primary* amines with high enantioselectivities is limited only to the hydroboration of ketoxime ethers[2] and the kinetic resolution of *racemic primary* amines.[3] A catalytic hydrogenation of ketoximes producing directly the chiral *primary* amines has been reported by several groups, but no sufficient results have been achieved until now.[4] This is in sharp contrast to the enantioselective hydrogenation and transfer hydrogenation of imines catalysed by transition metal complexes with chiral ligands to afford the corresponding *secondary* amines with high enantioselectivities.[5,6] As an alternative *direct* enantioselective synthesis of chiral *primary* amines, Brunner and co-workers developed the rhodium-catalysed asymmetric hydrosilylation of ketoximes using DIOP (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) as a chiral ligand, but enantioselectivities of the produced *primary* amines were moderate (up to 36% ee).[7] On the other hand, we have recently disclosed that the ruthenium(II)- and iridium(I)-catalysed asymmetric hydrosilylation of imines by using oxazolinylferrocenylphosphines[8] (**1**) as chiral ligands gave the corresponding *secondary* amines with high enantioselectivities after acid hydrolysis (up to 89% ee).[9] As an extension of our studies, we have now investigated the ruthenium(II)-catalysed asymmetric hydrosilylation of ketoximes by using **1** as chiral ligands and have found that the corresponding chiral *primary* amines were produced successfully. Preliminary results are described here.

Treatment of 1-tetralone oxime[10] (**3a**) with 3 equiv. of diphenylsilane in THF in the presence of [$RuCl_2(PPh_3)$·**1a**] (**2a**) (1 mol%) at rt for 24 h afforded 1,2,3,4-tetrahydro-1-naphthylamine (**4a**) in 46% GLC yield with 74% ee (*R*) after acid hydrolysis (Scheme 1; Table 1, run 1).[11] The ee value of **4a** was determined by GLC analysis of the corresponding trifluoroacetamide. The relatively low yield of **4a** to the high conversion of **3a** is considered to be due to the formation of unidentified side products together with 1-tetralone, which was probably formed after the hydrolysis of some intermediates. The addition of AgOTf (1 mol%; OTf = OSO_2CF_3) to the reaction system slightly increased the yield of **4a** (Table 1, run 2). The use of **2b**, bearing *i*-Pr substituted oxazoline, in place of **2a** caused a decrease of the catalytic activity (Table 1, run 3). The ruthenium complex having an oxazolinylphenylphosphine[12] (**1c**) without planar chirality showed a quite low enantioselectivity (Table 1, run 4), compared with that having an oxazolinylferrocenylphosphine (**1a** and **1b**). Reaction in the presence of 2 mol% of **2a** and AgOTf in DME (1,2-dimethoxyethane) gave the best enantioselectivity (up to 83% ee) (Table 1, runs 5 and 6). It is noteworthy that none of the oxazolinylphosphines (**1a**, **1b**, and **1c**) worked effectively as chiral ligands for the rhodium- and iridium-catalysed asymmetric hydrosilylation of ketoximes. For example, the ee values of **4a** obtained by using rhodium and iridium catalysts having **1a** were only 8% (*S*) and 5% (*R*), respectively. Furthermore, no reaction occurred when the ruthenium complex with DIOP was employed under the same reaction conditions, in contrast to Brunner's results[7] described above (Rh-catalysed: up to 36% ee).

Asymmetric hydrosilylation of other ketoximes with diphenylsilane was investigated in the presence of **2** and AgOTf.[13] Typical results are summarised in Table 2. Reactions of 1-indanone oxime (**3b**) and 1-benzosuberon oxime (**3c**) proceeded smoothly, but only moderate enantioselectivities were obtained (Table 2, runs 3–5). In the case of acetophenone



Scheme 1 Asymmetric hydrosilylation of ketoximes.

Table 1 Ruthenium-catalysed asymmetric hydrosilylation of 1-tetralone oxime (**3a**)[a]

Run	Catalyst/ mol%	Additive/ mol%	Reaction time/h	Conv. of **3a** (%)	Yield of **4a** (%)[b]	ee of **4a** (%)[c]
1	**2a** (1)	—	24	>95	46	74 (*R*)
2	**2a** (1)	AgOTf(1)	18	>95	50	78 (*R*)
3	**2b** (1)	AgOTf(1)	80	>95	45	74 (*R*)
4	**2c** (1)	AgOTf(1)	40	77	44	23 (*R*)
5	**2a** (2)	AgOTf(2)	15	>95	71	79 (*R*)
6[d]	**2a** (2)	AgOTf(2)	24	>95	65	83 (*R*)

[a] All reactions were carried out in the presence of a catalyst and an additive using ketoxime **3a** (1.0 mmol) and Ph_2SiH_2 (3.0 mmol) in THF (5 ml) at rt.[b] GLC yield.[c] Determined by GLC analysis of the corresponding trifluoroacetamide.[d] DME was used in place of THF.

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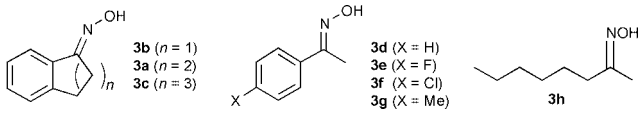
Table 2 Ruthenium-catalysed asymmetric hydrosilylation of ketoximes (**3**)[a]



Run	Ketoxime	Catalyst	Solvent	Reaction time/h	Conv. of **3** (%)	Yield of **4** (%)[b]	ee of **4** (%)[c]
1	**3a**	**2a**	THF	20	>95	50	79 (*R*)
2	**3a**	**2a**	DME	25	>95	62	83 (*R*)
3	**3b**	**2a**	DME	40	>95	26	18 (*R*)
4	**3b**	**2b**	DME	40	>95	10	35 (*R*)
5	**3c**	**2a**	THF	90	>95	45	60 (*R*)
6	**3d**	**2a**	THF	20	>95	5	58 (*R*)
7	**3d**	**2b**	THF	40	>95	21	89 (*R*)
8	**3e**	**2b**	THF	25	>95	22	61 (*R*)
9	**3f**	**2b**	THF	25	70	26	74 (*R*)
10	**3g**	**2b**	DME	40	>95	15	69 (*R*)
11	**3h**	**2a**	THF	90	>95	6	12 (*R*)

[a] All reactions were carried out in the presence of catalyst (0.010 mmol) and AgOTf (0.010 mmol) using ketoxime **3** (0.50 mmol) and Ph_2SiH_2 (2.0 mmol) in solvent (5 ml) at rt.[b] GLC yield.[c] Determined by GLC analysis of the corresponding trifluoroacetamide.

oxime (**3d**),[14] the best enantioselectivity of 89% ee was achieved (Table 2, run 7). Introduction of a *p*-halogeno or *p*-methyl substituent to the aromatic ring of acetophenone oxime slightly decreased the enantioselectivity (Table 2, runs 8–10). When **2b** was used in place of **2a** as catalyst, a slightly better enantioselectivity was obtained in several cases (Table 2, runs 7–10). Dialkyl ketoxime (**3h**) was also converted into the corresponding dialkyl amine, but unfortunately in low yield with low enantioselectivity (Table 2, run 11).

In summary, we have developed the highly enantioselective ruthenium(II)-catalysed hydrosilylation of ketoximes to give the corresponding *primary* amines with high enantioselectivities (up to 89% ee) after hydrolysis. This may provide a versatile method for the straightforward synthesis of chiral *primary* amines because of the ready accessibility of ketoximes by reaction of ketones with hydroxylamine. Further work is currently in progress aiming at the elucidation of the reaction mechanism and broadening the scope of this asymmetric hydrosilylation.

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10 In the present study, the prochiral ketoximes were used as formed from the corresponding ketones and hydroxylamine liberated from hydroxylammonium chloride.[7] A single isomer of each ketoxime was tentatively assigned as (*E*)-form from the following arguments: G. L. Karabatsos and N. Hsi, *Tetrahedron*, 1967, **23**, 1079; K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori and H. Yamamoto, *J. Am. Chem. Soc.*, 1983, **105**, 2831; D. L. Boger and W. L. Corbett, *J. Org. Chem.*, 1992, **57**, 4777; K. D. Sugi, T. Nagata, T. Yamada and T. Mukaiyama, *Chem. Lett.*, 1997, 493.

11 When the reaction of **3a** (2.50 mmol) with diphenylsilane (10.0 mmol) was carried out under the same reaction conditions, **4a** was isolated in 67% yield (70% GLC yield) with 80% ee.

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13 A typical procedure for ruthenium-catalysed asymmetric hydrosilylation of ketoximes is as follows. In a 20 ml flask were placed catalyst **2a** (10.3 mg, 0.010 mmol; 2.0 mol%) and AgOTf (2.6 mg, 0.010 mmol; 2.0 mol%) under N_2. Anhydrous DME (5 ml) was added, and then the mixture was magnetically stirred at rt for 1 h. After the addition of 1-tetralone oxime (**3a**) (80 mg, 0.50 mmol), diphenylsilane (2.0 mmol) was slowly added at rt and the mixture was stirred at rt for an appropriate time. The mixture was then quenched with MeOH (1.0 ml), stirred at rt for 30 min, and subsequently hydrolysed by the addition of 1 N HCl aq. The mixture was extracted with water (50 ml), and 3 N NaOH aq. (20 ml) was added to the aqueous solution to obtain a free amine. This solution was extracted with diethyl ether (50 ml × 3) and the extract was dried over anhydrous $MgSO_4$. For GLC analysis of the yield of **4a**, *n*-tetradecane was added as an internal standard. The optical purity was determined by GLC analysis of the corresponding trifluoroacetamide on a cyclodextrin phase (Chiraldex GT-A, 30 m). The absolute configuration of **4a** was determined by an optical rotation..

14 Acetophenone oxime (**3d**) was assigned as the (*E*)-isomer by ^{1}H NMR; F. G. Bordwell and G.-Z. Ji, *J. Org. Chem.*, 1992, **57**, 3019.