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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 747–750

Rhodium-catalysed asymmetric hydrosilylation of ketones using HETPHOX ligands

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Received 20 September 2006; revised 18 November 2006; accepted 30 November 2006
Available online 19 December 2006

Abstract—The HETPHOX ligand class was applied to the rhodium-catalysed asymmetric hydrosilylation of a range of substituted acetophenones. Enantioselective hydrosilylation of acetophenone with the *tert*-butyl substituted HETPHOX ligand gave (*R*)-phenylethanol in excellent enantioselectivity (84% ee) and in good conversion (80%). When applied to the hydrosilylation of other ketones conversions up to 93% and enantioselectivities up to 88% were observed.

Rhodium-catalysed hydrosilylation is a highly versatile procedure for the synthesis of enantioenriched alcohols and amines.[1–4] The first chiral catalysts for asymmetric hydrosilylation were based on neutral cationic rhodium(I) precursors in combination with chiral bidentate ligands, and was demonstrated with nitrogen-based ligands, such as Pythia **1**, giving excellent results employing alkyl aryl ketones as substrates.[5] The bis(oxazoline)pyridine, Pybox **2** and the phosphine oxazoline ligand (PHOX) **3** were subsequently shown to be successful in the catalytic asymmetric hydrosilylation of ketones (Fig. 1).[6–8]

Korostylev and co-workers have applied rhodium complexes of the phosphite ligand **4** to hydrosilylation with acetophenone giving the enantioenriched alcohol with an ee of 58%.[9] Similarly, Tao and Fu applied rhodium complexes of the planar P,N ligand **5** and obtained enantiomeric excesses of over 90% in 88–90% yield with acetophenone and also provided high enantiomeric excess (up to 96%) with dialkyl ketones, which are more challenging substrates.[10]

Recently we applied the HETPHOX ligands to the asymmetric intermolecular Heck reaction and the asymmetric hydrogenation of olefins and imines.[11,12] In our preliminary explorative work with this ligand class, we chose to investigate the thiophene phosphino-oxazolines **6a–c**. We recently expanded this series to include analogue **6d** and applied ligands **6a–d** in the asymmetric intramolecular Heck reaction.[13] Herein, we describe the results of the asymmetric hydrosilylation of acetophenone and substituted acetophenones using rhodium complexes of the HETPHOX ligands **6** (Fig. 2).

In order to compare the HETPHOX ligands with previously used ligands **1–5**, acetophenone **7** was used as the substrate for the initial screening reactions.

The hydrosilylations were carried out by treating acetophenone **7** with a silane in the presence of a rhodium ligand complex that was generated in situ. This was stirred for 3 days at 20 °C and quenched on the addition of methanol and 1 M HCl (Scheme 1).[14]

Of the four HETPHOX ligands **6a–d** examined, it was found that the HETPHOX *iso*-propyl substituted ligand **6a** gave the highest conversion of 78% with an ee of 37% (Table 1, entry 1). The Ph-substituted ligand **6c** afforded the product in 70% conversion and with an ee of 44% (Table 1, entry 3). The sterically demanding indanol-derived HETPHOX ligand **6d** showed a lower conversion (62%) and enantioselectivity (38%) (Table 1, entry 4).

During our optimisation studies we had applied the monosubstituted silane, phenylsilane but only produced racemic product when ligand **6a** was used. Previous studies by Fu have shown that the size of the aromatic

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doi:10.1016/j.tetlet.2006.11.172

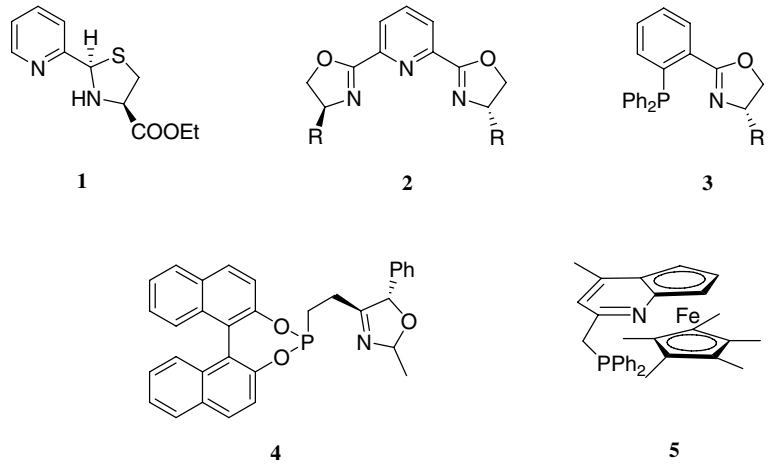


Figure 1. Useful chiral ligands for rhodium-catalysed enantioselective hydrosilylation.

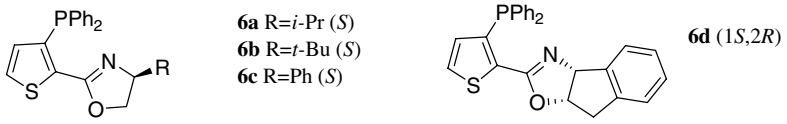
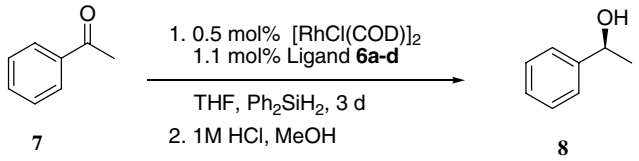


Figure 2. HETPHOX ligands used in the rhodium-catalysed hydrosilylation of substituted acetophenones.



Scheme 1. Hydrosilylation of acetophenone **7**.

group on the silane has a significant effect on enantioselectivity.[10] Therefore we prepared more sterically demanding silanes than diphenylsilane and applied naphthylphenyl silane and mesitylphenyl silane[15–17] with ligand **6a**. The naphthylphenyl silane was found to give lower conversion (32%) than diphenylsilane, although a slight increase in enantioselectivity to 42% was observed (Table 1, entry 5). The more sterically demanding mesitylphenyl silane gave no reaction over the 3 days.

The influence of solvent was examined for the hydrosilylation of acetophenone using HETPHOX ligand **6a**. In all, a total of four solvents were examined and the reaction was also carried out under solvent-free conditions (Table 1, entries 6–9). When the reaction was performed under solvent-free conditions (Table 1, entry 9), the conversion was highest at 85% but there was a decrease in enantioselectivity to 15%. Water was included as a solvent after a recent report on the aqueous asymmetric rhodium(I) catalysed Pauson–Khand reaction, which showed that high yields and enantiomeric excesses were possible using water as a solvent.[18] Interestingly, when the reaction was carried out in water (Table 1, entry 8), the conversion was low at 28% but the enantioselectivity was 30%, higher than all the other organic solvents examined apart from THF. The optimum solvent for the reaction was determined to be THF (Table 1, entry 1).

It has been reported that changing the ratio of Rh:ligand has an effect on the enantiomeric excess.[17,19] The effect of varying the ratio of the Rh:HETPHOX ligand was therefore investigated (Table 2).

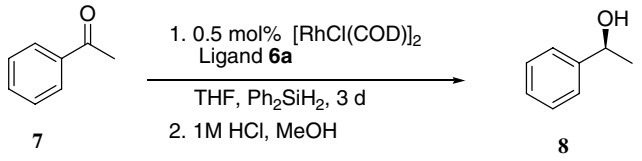
The change in Rh:ligand ratio had a significant effect on the enantioselectivity of the hydrosilylation using

Table 1. Hydrosilylation of acetophenone **7** using HETPHOX ligands **6a–d** under various conditions at 20 °C

Entry	Ligand	Silane	Solvent	Conversion[a] (%)	ee (%) (*R*)[b]
1	**6a**	Ph_2SiH_2	THF	78	37
2	**6b**	Ph_2SiH_2	THF	64	24
3	**6c**	Ph_2SiH_2	THF	70	44
4	**6d**	Ph_2SiH_2	THF	62	38
5	**6a**	$NaphthPhSiH_2$	THF	32	42
6	**6a**	Ph_2SiH_2	Et_2O	35	17
7	**6a**	Ph_2SiH_2	CH_2Cl_2	13	29
8	**6a**	Ph_2SiH_2	H_2O	28	30
9	**6a**	Ph_2SiH_2	None	85	15

[a] Conversion was determined by ^1H NMR after 3 days. Reaction was carried out at 20 °C, whhich was found to be the optimum temperature.
[b] ee Determined by chiral GC, β Dex 120 column, 30 m × 0.25 mm, column 120 °C, injector 200 °C, detector 220 °C.

Table 2. Hydrosilylation of acetophenone **7** catalysed by Rh(I)/HETPHOX ligand varying the Rh(I):ligand ratio



Entry	Ligand	Ratio Rh:ligand (mol %)	Conversion[a] (%)	ee (%) (*R*)[b]
1	**6a**	1:1.1	78	37
2	**6a**	1:5.5	79	62
3	**6a**	1:11	83	68
4	**6b**	1:1.1	64	24
5	**6b**	1:5.5	65	70
6	**6b**	1:11	66	84
7	**6c**	1:1.1	70	44
8	**6c**	1:5.5	79	65
9	**6c**	1:11	78	57
10	**6d**	1:1.1	62	38
11	**6d**	1:11	59	72

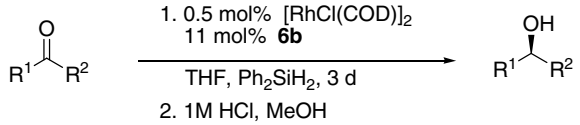
[a] Conversion was determined by ^{1}H NMR after 3 days.
[b] ee Determined by chiral GC, β Dex 120 column, 30 m × 0.25 mm, column 120 °C, injector 200 °C, detector 220 °C.

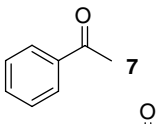
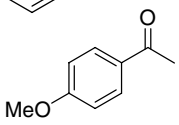
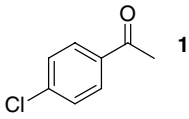
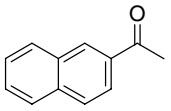
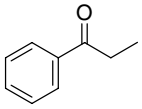
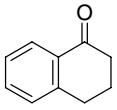
HETPHOX ligands **6a–d**. On increasing the ratio of the ligand **6a** to 1:5.5 mol % (fivefold increase in ligand, Table 2, entry 2), the ee was increased to 62%. On further increasing the ligand **6a** ratio to 1:11 mol % (Table 2, entry 3), the ee increased to 68%, with a corresponding small increase in the conversion to 83%. The increases observed with ligand **6a** were also noted with ligands **6c** and **6d** (Table 2, entries 7–11). With the bulky indanol-derived ligand **6d**, the enantioselectivity was found to increase to 72% (Table 2, entry 11) on increasing the Rh:ligand ratio to 1:11. In the case of ligand **6b**, the increase in the Rh:ligand ratio had a significant effect on the enantioselectivity. Increasing the ratio of Rh:ligand **6b** to 1:11 mol % (Table 2, entry 6) gave a significant increase of enantioselectivity to an optimal ee of 84%.

It was decided to expand the scope of the Rh/HETPHOX ligand **6b** catalyst system to substituted acetophenones and other aryl/alkyl and alkyl/alkyl ketones (Table 3).

The introduction of electron-donating and electron-withdrawing groups onto acetophenones **9** and **10** was found to have an effect on both conversions and enantioselectivities. In the case of the *p*-methoxy-substituted 2-acetophenone **9**, there was an increase in conversion (93%) with a decrease in ee to 71% (Table 3, entry 2). The electron poor *p*-chloro-substituted acetophenone **10** showed a lower conversion of 52% but with a higher ee of 88% (Table 3, entry 3). Employing acetonaphthone **11** as substrate gave a higher conversion of 91% and an ee of 83% (Table 3, entry 4). When propiophenone **12** was used instead of acetophenone **7**, there was a dramatic drop in the conversion to 35%, but with a similar level of enantioselectivity (86%) (Table 3, entry 5). Small changes to the structure about the ketone were also found to have a large effect when α-tetralone **13** was

Table 3. Catalytic asymmetric hydrosilylation of ketones using Rh/HETPHOX **6b**



Entry	Ketone	Conversion[a] (%)	ee (%) (*R*)
1	 **7**	66	84[b]
2	 **9**	93	71[c]
3	 **10**	52	88[c]
4	 **11**	91	83[c]
5	 **12**	35	86[c]
6	 **13**	49	62[b]
7	 **14**	90	56[b]

[a] Determined by ^{1}H NMR after 3 days.
[b] ee Determined by chiral GC, β Dex 120 column, 30 m × 0.25 mm, column 120 °C, injector 200 °C, detector 220 °C.
[c] ee Determined by HPLC Chiralcel-OD column (250 × 4.6 mm), hexane/IPA 99:1, 1 ml/min, 245 nm.

tested and a 49% conversion and 62% ee were observed (Table 3, entry 6). When the reaction was carried out with pinacalone **14**, a high conversion was seen (90%) although a moderate ee of 56% was observed (Table 3, entry 7). In general, dialkyl ketones are difficult substrates to reduce in the enantioselective hydrosilylation but both the conversion and enantioselectivity found here are comparable to other P,N ligands.[17,20]

In conclusion the HETPHOX ligands were screened in the rhodium-catalysed hydrosilylation of ketones. The initial screening showed poor enantioselectivity, however, with a variation in the ligand loading, higher enantioselectivites were observed. The *tert*-butyl substituted HETPHOX ligand **6b** afforded the optimal enantioselectivity at 84% for the range of ligands tested with acetophenone. The *tert*-butyl substituted ligand **6b** was applied to a range of ketones and the highest ee was observed with *p*-chloroacetophenone **10** at 88%. These enantioselectivities are comparable to previous work reported in the literature. Further studies on these ligands

and other substrates are currently in progress and the results of this study will be reported at a later date.

Acknowledgements

A.G.C. thanks the Science Foundation of Ireland (SFI) for financial support (Grant No. 04/BR/C0702). The donation of rhodium(III) chloride is gratefully acknowledged from Johnson Matthey.

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14. *Typical experimental procedure for rhodium-catalysed asymmetric hydrosilylations*: Di-μ-chlorobi(1,5-cyclooctadiene)rhodium (2.1 mg, 0.5 mol %) and HETPHOX ligand (1.1 mol %) were placed under a nitrogen atmosphere in a Schlenk tube. The ketone (0.86 mmol) was added, followed by dry THF (1 ml) and the resulting solution stirred at ambient temperature for 1 h. The solution was then cooled to 0 °C and the silane (1.5 equiv) was added dropwise via syringe. The reaction was stirred at ambient temperature for 72 h. The reaction was cooled to 0 °C and worked up by the addition of methanol (3 ml) and 1 M HCl (3 ml). After stirring for 1 h the solution was transferred to a separating funnel, neutralised with saturated sodium bicarbonate and extracted with diethyl ether (2×10 ml). The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo to give the crude product. The products were purified by column chromatography on flash silica gel (230–400 mesh ASTM) and eluted with pentane/diethyl ether (1:1), ^1H NMR analysis provided the percentage conversion. The ee was determined by chiral GC or HPLC depending on the ketone used. Mesitylphenyl silane,[15] naphthylphenyl silane[16] and di-μ-chlorobi(1,5-cyclooctadiene)rhodium[21] were synthesised according to literature procedures.
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