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# Phosphite–oxazoline ligands for Rh-catalyzed asymmetric hydrosilylation of ketones

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**Abstract**

A series of phosphite–oxazoline ligands was tested in the Rh-catalyzed hydrosilylation of ketones. Systematic variation of the electronic and steric properties at the biphenyl phosphite moiety and at the oxazoline moiety provide useful information about the ligand parameters that control the enantiodiscrimination. The results show that the enantiomeric excesses are dependent on the properties on both the phosphite and oxazoline moieties of the ligand and on steric and electronic properties of the substrate. Low-to-moderate enantiomeric excesses (up to 62%) were obtained in the hydrosilylation of several aryl ketones.


*Keywords:* Hydrosilylation; P–N ligands; Asymmetric catalysis; Phosphite; Ketones

## 1. Introduction

In the last few decades, the asymmetric rhodium-catalyzed hydrosilylation of ketones has been recognized as versatile method for providing optically active secondary alcohols [1]. Most of the chiral ligands developed for the asymmetric hydrosilylation of ketones are N- and P-containing compounds possessing either $C_1$ or $C_2$-symmetry [1,2]. Mixed N–N′ [2a,b,e,g] and P–N[2h,j–l,q,r] ligands have played a dominant role among the heterodonor ligands [1]. Regarding P–N heterodonor ligands, the phosphite–oxazoline combination have been less studied despite the early success of the TADDOL-based phosphite–oxazoline ligands developed by Heldmann and Seebach for this process [3]. More research is therefore needed to study the possibility offered by the phosphite–oxazoline as a new type of ligands for this process.

In this context, we have recently developed a new class of modular phosphite–oxazoline ligands (Fig. 1) that proved to be highly effective in the Pd-catalyzed allylic substitution reactions [4]. In this paper we present the application of this family of ligands in the Rh-catalyzed hydrosilylation of several ketones. The highly modular construction of these ligands enables us to easily study the effects of both the phosphite and the oxazoline moieties on catalytic performance (activity and enantioselectivity).

## 2. Results and discussion

### 2.1. Ligand design

Ligands **1**–**8** consist of a 2-hydroxyphenyl cyanide scaffold to which several chiral aminoalchols and several atropoisomerically chiral biphenyl phosphorocholoridite moieties are attached (Scheme 1).

The influence of the oxazoline substituents on enantioselectivity was investigated by comparing the results obtained with ligands **1**–**4**, which have a tetra(*tert*-butyl)biphenyl phosphite moiety.

The influence of the different groups attached to the *ortho*- and *para*-positions of the biphenyl phosphite moiety was studied using ligands **4**–**6**, which have an ethyl substituent at the oxazoline moiety. This influence was also corroborated by comparing ligands **1** and **7**, with an isopropyl oxazoline substituent.

Finally, the effect of the configuration of the stereocenter at the oxazoline was studied with ligands **3** and **8**, which have a tetra(*tert*-butyl)biphenyl phosphite moiety and a phenyl substituent at the oxazoline.

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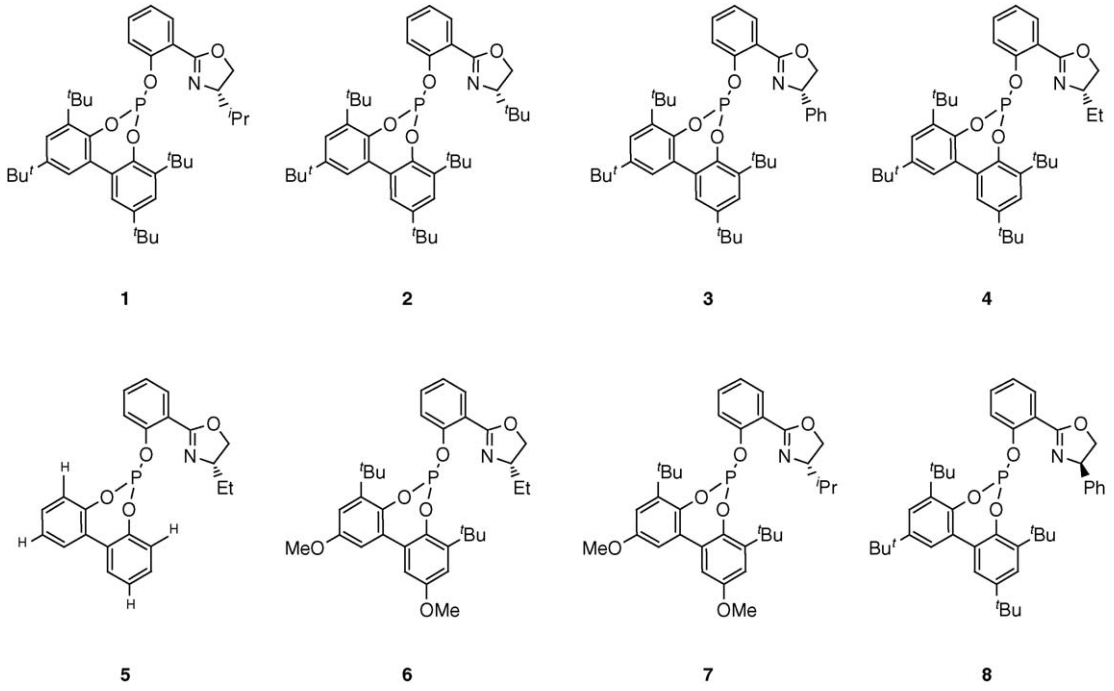



Fig. 1. Phosphite–oxazoline ligands **1**–**8**.

### 2.2. Asymmetric hydrosilylation of ketones

We first investigated the Rh-catalyzed hydrosilylation of acetophenone **3a**, which is widely used as a model substrate [1]. The catalysts were generated in situ by adding the corresponding ligand to the catalyst precursor.

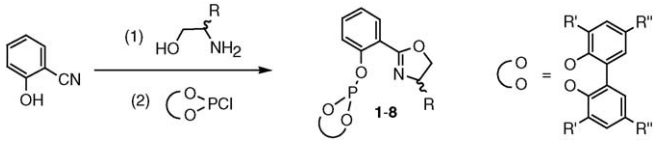
The effect of the solvent, catalyst precursor and the ligand-to-rhodium ratio were investigated using the catalyst precursor containing ligand **1**. The results are summarized in Table 1.

Our results indicate that both solvent and catalyst precursor affected catalytic performance. Toluene as solvent and $[Rh(\mu\text{-}Cl)(cod)]_2$ (cod = 1,5-cyclooctadiene) as catalyst precursor provided the best combination of activity and enantioselectivity (entry 6 versus 1–5). Adding a one-fold excess of ligand has a positive effect on activity and enantioselectivity (entry 7 versus 6).

The results of using the rest of the phosphite–oxazoline ligands (**1**–**8**) under the optimized conditions are showed in Table 2. Our results indicate that the enantiomeric excesses are dependent on the substituents at both the oxazoline and the biphenyl phosphite moieties.

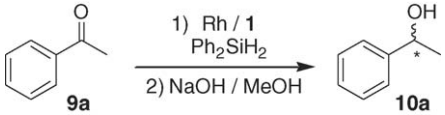
The effect of the oxazoline substituents in the catalytic performance was studied using ligands **1**–**4** (entries 1–4). The results indicated that both activity and enantioselectivity were best when either an isopropyl (ligand **1**) or a phenyl (ligand **3**) substituent were present.

The effect of the phosphite moiety was studied with ligands **4**–**6**, with an ethyl oxazoline substituent. We observed that this moiety affect the catalytic performance. The presence of bulky substituents in the *ortho* positions of the biphenyl phosphite moiety has a positive effect on enantioselectivity and activity (entries 4 and 6 versus 5). Moreover, the substituents in the *para* positions of the biphenyl-phosphite moiety have an important effect on enantioselectivity, while they do not affect activity (entries 4 versus 6). Enantioselectivities are therefore highest when *tert*-




Scheme 1. Synthesis of ligands **1**–**8**.

Table 1
Effect of the solvent, catalyst precursor and ligand-to-rhodium ratio in the hydrosilylation of acetophenone **9a** using ligand **1**[a]




| Entry | Precursor | Solvent | Conv.[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | $[Rh(cod)_2]BF_4$ | THF | 67 | 35 (*R*) |
| 2 | $[Rh(cod)_2]BF_4$ | $CH_2Cl_2$ | 64 | 35 (*R*) |
| 3 | $[Rh(cod)_2]BF_4$ | Toluene | 74 | 36 (*R*) |
| 4 | $[Rh(\mu\text{-}Cl)(cod)]_2$ | THF | 75 | 38 (*R*) |
| 5 | $[Rh(\mu\text{-}Cl)(cod)]_2$ | $CH_2Cl_2$ | 82 | 38 (*R*) |
| 6 | $[Rh(\mu\text{-}Cl)(cod)]_2$ | Toluene | 83 | 39 (*R*) |
| 7[d] | $[Rh(\mu\text{-}Cl)(cod)]_2$ | Toluene | 87 | 43 (*R*) |

[a] Reaction conditions: **9a** (1 mmol), $Ph_2SiH_2$ (1.1 mmol), **1** (0.011 mmol), **1**/Rh = 1.1, solvent (2 mL), room temperature.
[b] Conversion after 15 h. Determined by GC using undecane as internal standard.
[c] Enantiomeric excess determined by GC.
[d] **1**/Rh = 2.

Table 2
Rh-catalyzed asymmetric hydrosilylation of acetophenone **9a** using ligands **1–8**[a]

| Entry | Ligand | Conv.[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | **1** | 74 | 43 (*R*) |
| 2 | **2** | 48 | 11 (*R*) |
| 3 | **3** | 77 | 45 (*R*) |
| 4 | **4** | 56 | 8 (*R*) |
| 5 | **5** | 5 | 0 |
| 6 | **6** | 58 | 4 (*R*) |
| 7 | **7** | 73 | 23 (*R*) |
| 8 | **8** | 85 | 45 (*S*) |

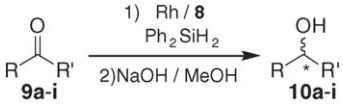
[a] Reaction conditions: **9a** (1 mmol), $Ph_2SiH_2$ (1.1 mmol), ligand (0.02 mmol), $[Rh(\mu\text{-Cl})(cod)]_2$ (0.005 mmol), toluene (2 mL), room temperature.
[b] Conversion after 15 h determined by GC using undecane as internal standard.
[c] Enantiomeric excess determined by GC.

butyl groups are present at both the *ortho* and *para* positions of the biphenyl-phosphite moiety. This trend was also corroborated using ligands **1** and **7**, with an isopropyl oxazoline substituent (entries 1 and 7).

The use of ligand **8**, whose configuration of the oxazoline moiety is opposite to that of ligand **3**, produced the same enantioselectivity though in the *S*-product (entry 8).

We then studied how the steric and electronic properties of the ketone affected the outcome of the reaction. For this purpose, a series of substituted benchmark aryl ketones **9a–i** were tested using the catalyst containing ligand **8**. The results are summarized in Table 3. The results when using acetophenones **9a–d** (entries 1–4), which contain different *para*-phenyl substituents, clearly show that the catalytic performance is affected by the electronic properties of the substrate. Therefore, both activities and enantioselectivitiers were better for ketones without electron-withdrawing groups at the *para*-phenyl positions. If we compare the results from using *para*-, *meta*- and *ortho*-substituted methoxy acetophenones **9d–f** (entries 4–6), we can clearly see that the steric bulk caused by the *ortho*-methoxy substituent led to increased enantioselectivity. As expected when 2-napthtylmethyl ketone **9g** was used the enantioselectivity was similar to that seen when acetophenone **9a** was used (entry 1 versus 7). Finally, replacing the methyl substituent in the ketone by an ethyl (**9h**) or a chloromethyl (**9i**) group hardly affected the catalytic performance (entries 1, 8 and 9).

Table 3
Rh-catalyzed asymmetric hydrosilylation of ketones **9a–i** using phosphite–oxazoline ligand **8**[a]




| Entry | Ketone | R | R′ | Conv.[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **9a** | $C_6H_5$ | Me | 85 | 45 (*S*) |
| 2 | **9b** | 4-F-$C_6H_4$ | Me | 52 | 40 (*S*) |
| 3 | **9c** | 4-$CF_3$-$C_6H_4$ | Me | 50 | 39 (*S*) |
| 4 | **9d** | 4-OMe-$C_6H_4$ | Me | 94 | 51 (*S*) |
| 5 | **9e** | 3-OMe-$C_6H_4$ | Me | 87 | 49 (*S*) |
| 6 | **9f** | 2-OMe-$C_6H_4$ | Me | 83 | 62 (*S*) |
| 7 | **9g** | 2-Naphthyl | Me | 80 | 46 (*S*) |
| 8 | **9h** | $C_6H_5$ | Et | 82 | 45 (*S*) |
| 9 | **9i** | $C_6H_5$ | $CH_2Cl$ | 79 | 44 (*R*) |

[a] Reaction conditions: **9** (1 mmol), $Ph_2SiH_2$ (1.1 mmol), ligand (0.02 mmol), $[Rh(\mu\text{-Cl})(cod)]_2$ (0.005 mmol), toluene (2 mL).
[b] Conversion after 15 h determined by GC using undecane as internal standard.
[c] Enantiomeric excess determined by GC.

## 3. Conclusions

Phosphite–oxazoline ligands **1–8** bearing substituents with different steric and electronic demands onto the oxazoline and phosphite moieties have been tested in the Rh-catalyzed asymmetric hydrosilylation of aryl ketones. Our results show that enantiomeric excesses depend strongly on the substituent on both the oxazoline and phosphite moieties of the ligand and on the electronic and steric properties of the substrate. Regarding the oxazoline effect, the presence of an isopropyl or phenyl substituent has a positive effect on enantioselectivity. Concerning the effect of the phosphite moiety, the presence of bulky *tert*-butyl groups at both *ortho* and *para* positions of the biphenyl phosphite moiety has a positive effect on the catalytic performance (activity and enantioselectivity). Regarding the effect of the substrate on enantioselectivity, enantiomeric excesses were higher when an electron-rich substituent in the aryl moiety of the ketone was present.

## 4. Experimental

### 4.1. General comments

All syntheses were performed using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. $^1H$, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. Chemical shifts are relative to $SiMe_4$ ($^1H$ and $^{13}C$) as internal standard or $H_3PO_4$ ($^{31}P$) as external standard. Ketones were used as commercially available. Phosphite–oxazoline ligands **1–8** [4] and complexes $[Rh(\mu\text{-Cl})(cod)]_2$ [5] and $[Rh(cod)_2]BF_4$ [6] were prepared according literature procedures.

#### 4.1.1. General procedure for asymmetric hydrosilylation reactions

To a solution of the desired catalyst precursor (0.01 mmol Rh) in the corresponding solvent (2 mL), the ligand (0.02 mmol) was added. The mixture was stirred for 30 min. Ketone (1 mmol), $Ph_2SiH_2$ (1.1 mmol) and undecane as GC internal standard (0.1 mL) were then added. After the desired reaction time, the reaction was quenched with methanol (7 mL) and 2.5 M aqueous NaOH (5 mL). The mixture was extracted with diethyl ether ($3 \times 5$ mL), the combined ether phases were dried over $Na_2SO_4$ and filtered. The conversion were determined by GC using a CP Chirasil DEX CB column. The determination of enantiomeric excess for alcohols **10a** [7], **10d** [7] **10e** [7], **10f** [7] **10h** [7] and **10i** [8] were performed as described in the literature by GC. For compounds **10b**, **10c** and **10g**, enantiomeric excesses were measured by GC using CP Chirasil DEX CB column (hold 110 °C for 15 min, rate 10 °C $min^{-1}$ to 180 °C and hold for 20 min).

- For compound **10b**: $t_R$ ($R$ isomer) = 9.3 min; $t_R$ ($S$ isomer) = 10.9 min.
- For compound **10c**: $t_R$ ($R$ isomer) = 9.3 min; $t_R$ ($S$ isomer) = 10.9 min.
- For compound **10g**: $t_R$ ($R$ isomer) = 24.6 min; $t_R$ ($S$ isomer) = 24.9 min.

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