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# Chiral biphosphine ligands for the Ru-catalyzed enantioselective hydrogenation of β-ketoesters

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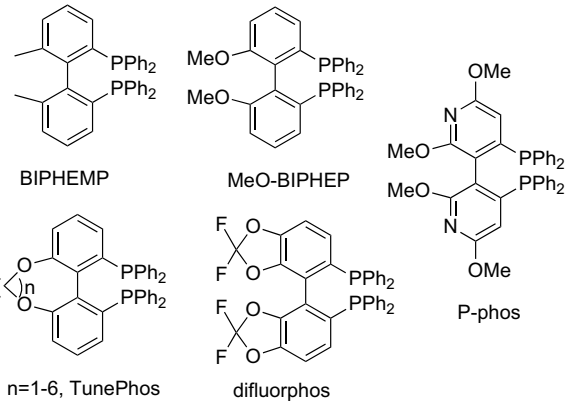
**Abstract**—Three new biaryl phosphine ligands **4a–c** have been prepared and their application in the Ru-catalyzed asymmetric hydrogenation of β-ketoesters investigated. Ruthenium catalysts containing these ligands are highly effective in the hydrogenation of β-ketoesters with up to 99.9% ee being obtained.


Transition metal-catalyzed reactions are widely employed in the preparation of enantiomerically pure compounds, in which the chiral ligands play an important role.[1] Much effort has been devoted to the design and synthesis of numerous chiral ligands. Since Knowles and Sabacky[2] and Horner et al.[3] first utilized chiral phosphines in asymmetric hydrogenation in 1968, Kagan and Dang have reported the asymmetric hydrogenation of α-dehydroamino acid esters (up to 85% ee) with DIOP,[4] derived from tartaric acid. These results gave us the idea for the development of new biphosphine ligands. Atropoisomeric $C_2$-symmetric biphosphines are amongst the most important ligands, BINAP,[5] BIPHEMP,[6] MeO-BIPHEP,[6] TunePhos,[7] P-Phos,[8] SEGPhos,[9] difluorphos[10] (Scheme 1) and other important biaryl phosphine ligands[11] have been developed over the past 20 years. It is not rare to obtain very decent ee with the reported ligands; however, developing easily-preparable, fine-tunable, easy-handable, inexpensive yet efficient ligands is still a challenging issue.




**Scheme 1.** Some atropoisomeric phosphine ligands.

Geometric, steric and electronic properties of the chiral ligand are important to the enantioselectivity and reactivity. The dihedral angles of the biaryl phosphine ligands have also been proven to be predominant in controlling the regioselectivity and/or enantioselectivity in transition metal-catalyzed refractions.[7,9,10,12] It is understandable that when biphosphine ligands with different dihedral angles coordinate a transition metal with multiple coordination numbers, the two phosphorus atoms may locate either at the equatorial–equatorial or at equatorial–axial positions (Fig. 1);[12c] this results in the difference in regio- and/or enantioselectivity. Zhang et al. have studied the asymmetric hydrogenation of β-ketoesters with C*n*-TunePhos as a model;[7] Saito et al. designed the SEGPhos series ligands with small dihedral angles and applied them to the asymmetric hydrogenation of ketones.[9] Genêt et al. prepared difluorphos and

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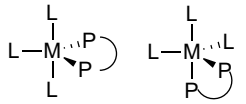


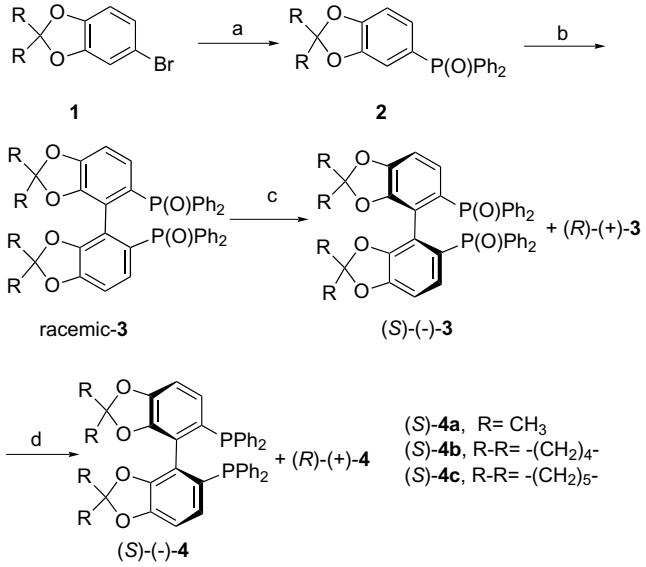

**Figure 1.** Possible coordination model of biphosphine ligands with different dihedral angles.

studied the dihedral angle effect in asymmetric hydrogenation reactions.[10] The results revealed that the dihedral angle is crucial in achieving high enantioselectivity.

Although SEGPhos (Fig. 2) has been proved excellent ligand in asymmetric hydrogenation reactions, it is not an ideal model to investigate the dihedral angle effect in asymmetric hydrogenation reactions, since the coordination environment for the phosphorus atoms has been changed when modifying the substituents at the phosphorus atoms (Fig. 2). We designed a working model bearing a SEGPhos backbone by introducing substituents at the 1,3-dioxole ring to investigate the dihedral angle effect. MM2 calculation showed that when the substituents at the 1,3-dioxole ring change, the dihedral angles for the free ligands also change remarkably (Fig. 2).

Herein, we report the synthesis, resolution (Scheme 2) and determination of the absolute configurations of three new biaryl ligands **4a**–**c** and their applications in asymmetric hydrogenation reaction.

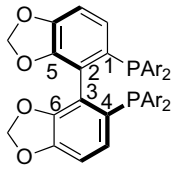
The racemic ligands can be prepared according to a procedure similar to that reported in the synthesis of SEGPhos (Scheme 2). Treatment of 5-(diphenylphosphinoyl)-2,2-dimethyl-benzo[1,3]dioxole **2a** with 1.2 equiv of LDA at low temperature (−15 °C) for 4 h and then oxidative coupling with anhydrous ferric chloride affords **3a** in moderate yield (67.5%). Compounds **3b** and **3c** were obtained in similar way except for the lithiation step. Up to 2.4 equiv of LDA and a higher reaction temperature were needed to achieve



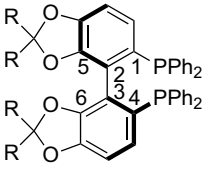

**Scheme 2.** Synthesis of ligands **4a**–**c**. Reagents and conditions: (a) (i) Mg, THF, (ii) $Ph_2PCl$, (iii) $H_2O_2$; (b) (i) LDA, −15 to 2 °C, 4 h; (ii) $FeCl_3$, 0 °C; (c) (i) −DBTA, EtOAc or $CH_2Cl_2$, (ii) NaOH; (d) $HSiCl_3$, $PhNMe_2$, reflux, 10 h.

good yields for the lithiation of **2b** (−5 °C) and **2c** (−2 °C), with **3b** and **3c** being obtained in 81.5% and 79.3% yields, respectively.

Resolutions of **3a** and **3b** were both performed by employing (−)-2,3-dibenzoyl tartaric acid [(−)-DBTA] as the resolving agent in ethyl acetate, while the resolution of **3c** was performed in $CH_2Cl_2$. The phosphine oxides (−)-**3a**, (−)-**3b** and (−)-**3c** were reduced to (−)-**4a**, (−)-**4b** and (+)-**4c** with $HSiCl_3$, respectively. The absolute configurations of (−)-**3a** and (−)-**3b** were defined to be *S* by means of single crystal X-ray diffraction of their salts of (−)-DBTA. The enantiomeric purity of the ligands was determined either by HPLC on a chiral column (for **4b**, the precursor **3b** can be separated on a Chiralpak AD-H column) or by measuring the $^{31}P$ NMR of



**SEGPhos:**
Coordination environment changes
when Ar changes (dihedral angle also changes)



**Our working model:**
Coordination environment does not change when R changes (only dihedral angle changes)

| | Dihedral angle (°) | |
|---|---|---|
| | C1-C2-C3-C4 | C5-C2-C3-C6 |
| SEGPHOS | 79.9 | 73.6 |
| R=$CH_3$ | 82.2 | 74.7 |
| R,R=-$(CH_2)_4$- | 91.4 | 81.7 |
| R,R=-$(CH_2)_5$- | 83.5 | 75.5 |

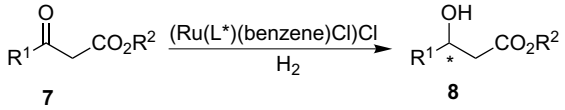
**Figure 2.** A working model to investigate dihedral angle effect (dihedral angles were obtained by MM2 calculation, Cache 6.1.1).

the complexes of biphosphines (**4a** or **4c**) and (+)-bis-(μ-chloro)bis[(*R*)-dimethyl(α-methyl-benzyl)aminato-$C^2$N]dipalladium(II).[6b,13]

We chose the asymmetric reduction of β-ketoesters as the model reaction for studying the dihedral angle effect of the ligands. The reaction was performed in an alcohol solvent with [Ru(L*)(benzene)Cl]Cl complex as catalyst.[14]

Ligands **4a**–**c** are excellent ligands for the asymmetric reduction of alkyl acetoacetates, with up to 99.9% ee being obtained, regardless of the bulkiness of the alkyl group (Table 1, entries 1–8). When 4,4-dimethyl-3-oxo-pentanoic acid ethyl ester **7d** was employed as the substrate for the asymmetric reduction, **4a** proved best (ee was up to 97.9%), while **4c** was inferior to **4a** and **4b** (Table 1, entries 9–11). 4-Chloro-3-oxo-butyric acid ethyl ester is different from other substrates. Its ee value is highly dependent on the reaction temperature: if the reaction was carried out at a lower temperature, the ee was lower (Table 1, entries 12, 13); however, if the temperature was increased, the ee values also increased (Table 1, entries 14–17).[15] The reduction was very effective with no ee decrease when the reaction was carried out with 0.1 mol% catalyst (Table 1, entries 18–20).

**Table 1.** Asymmetric hydrogenation of $R^1COCH_2CO_2R^2$ with (Ru(L*)(benzene)Cl)Cl[a]



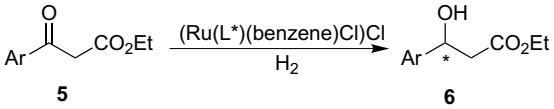

**7** **8**

| Entry | $R^1/R^2$ **7** | Temp. (°C) | Time (h) | **4** | **8** %ee[b] |
|---|---|---|---|---|---|
| 1 | Me/Et **7a** | 65 | 20 | **4a** | 99.9 |
| 2 | Me/Et **7a** | 65 | 20 | **4b** | 99.9 |
| 3 | Me/Et **7a** | 65 | 20 | **4c** | 99.9 |
| 4 | Me/$^i$Pr **7b** | 65 | 20 | **4a** | 99.4 |
| 5 | Me/$^i$Pr **7b** | 65 | 20 | **4b** | 99.9 |
| 6 | Me/$^i$Pr **7b** | 65 | 20 | **4c** | 99.6 |
| 7 | Me/$^t$Bu **7c** | 65 | 20 | **4a** | 99.5 |
| 8 | Me/$^t$Bu **7c** | 65 | 20 | **4b** | 99.4 |
| 9 | $^t$Bu/Et **7d** | 65 | 20 | **4a** | 97.9 |
| 10 | $^t$Bu/Et **7d** | 65 | 20 | **4b** | 96.7 |
| 11 | $^t$Bu/Et **7d** | 65 | 20 | **4c** | 92.3 |
| 12 | $ClCH_2$/Et **7e** | 60 | 20 | **4a** | 88.2[c] |
| 13 | $ClCH_2$/Et **7e** | 60 | 20 | **4b** | 89.3[c] |
| 14 | $ClCH_2$/Et **7e** | 85 | 3 | **4a** | 95.9[c] |
| 15 | $ClCH_2$/Et **7e** | 85 | 3 | **4b** | 95.8[c] |
| 16 | $ClCH_2$/Et **7e** | 95 | 3 | **4a** | 96.2[c] |
| 17 | $ClCH_2$/Et **7e** | 95 | 3 | **4b** | 96.4[c] |
| 18[d] | $ClCH_2$/Et **7e** | 95 | 3 | **4a** | 96.5[c] |
| 19[d] | $ClCH_2$/Et **7e** | 95 | 3 | **4b** | 95.3[c] |
| 20[d] | $ClCH_2$/Et **7e** | 95 | 3 | **4c** | 96.8[c] |

[a] All of the reactions were carried out in EtOH with a substrate concentration of 0.5 M, under 30 atm of $H_2$. Substrate/[Ru(benzene)$Cl_2$]$_2$/ligands = 200/0.5/1.1, conversion: 100%.
[b] Ee values were determined by GC on a β-DEX 325 capillary column.
[c] The product was acylated to 3-acetoxy-4-chloro-butyric acid ethyl ester **9e** in pyridine and acetic anhydride. Ee (%) of **9e** was determined by GC on a β-DEX 325 capillary column.
[d] Substrate/[Ru(benzene)$Cl_2$]$_2$/ligands = 1000/0.5/1.1.

These ligands were also successful in the asymmetric hydrogenation of 3-oxo-3-arylpropionic acid ethyl esters **5**; good enantioselectivity was obtained. The enantiomeric excess of **6** was comparable to when SEGPhos[9] was employed as ligand, and better than when BINAP (89.3% ee)[11c] or MeO-BIPHEP (74.8% ee)[9] was used as the ligand. Hydrogenation of **5** was not sensitive to the substituents (*m*, *o*, *p* and electron donating or electron withdrawing) on the aromatic ring (Table 2).

**Table 2.** Asymmetric hydrogenation of $ArCOCH_2CO_2Et$[a]

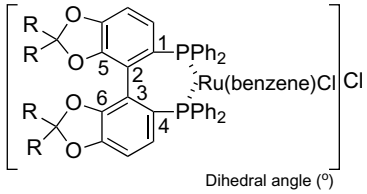



**5** **6**

| Entry | Ar | Ee | | |
|---|---|---|---|---|
| | | **4a** | **4b** | **4c** |
| 1 | Ph **5a**[b] | 97.9 | 96.2 | 96.3 |
| 2 | 4-Me–$C_6H_4$ **5b**[c] | 97.4 | 96.7 | 95.2 |
| 3 | 4-MeO–$C_6H_4$ **5c**[c] | 95.7 | 93.0 | 95.8 |
| 4 | 4-F–$C_6H_4$ **5d**[b] | 96.8 | 95.7 | — |
| 5 | 4–Cl–$C_6H_4$ **5e**[d] | 96.2 | 95.1 | 97.0 |
| 6 | 4-Br–$C_6H_4$ **5f**[d] | 96.3 | 95.3 | — |
| 7 | 3-Me–$C_6H_4$ **5g**[b] | 96.6 | 96.0 | — |
| 8 | 3–Cl–$C_6H_4$ **5h**[d] | 96.5 | 95.2 | 96.6 |
| 9 | 2-Me–$C_6H_4$ **5g**[d] | 94.4 | 93.3 | 91.9 |
| 10 | 2–Cl–$C_6H_4$ **5h**[c] | 96.4 | 96.7 | 96.7 |

[a] All of the reactions were carried out at 65 °C with a substrate concentration of 0.5 M, under 30 atm of $H_2$ in EtOH for 20 h. Substrate/[Ru(benzene)$Cl_2$]$_2$/ligands = 200/0.5/1.1, conversion 100%.
[b] Ee values were determined by HPLC on a Chiralcel OD-H column.
[c] Ee values were determined by HPLC on Chiralpak AS-H column.
[d] Ee values were determined by HPLC on Chiralpak AD-H column.

The dihedral angles of the [Ru(L*)(benzene)Cl]Cl complex were also calculated by MM2, Cache 6.1.1 software and PM3 (semi-empirical), Spartan software. MM2 calculations revealed that the dihedral angles (C1–C2–C3–C4) of the three ligands were smaller than SEGPhos, with **4a** having the smallest dihedral angle. PM3 (semi-empirical) calculations indicated that **4a** and **4c** had smaller dihedral angles than SEGPhos did, though the difference was not significant (Fig. 3). The difference did not make a remarkable change in enantioselectivity in




Dihedral angle (°)

| | C1-C2-C3-C4 | C5-C2-C3-C6 |
|---|---|---|
| R=H | 73.5 (74.7) | 66.2 (67.6) |
| R=$CH_3$ | 72.8 (72.6) | 61.4 (67.5) |
| R,R=-$(CH_2)_4$- | 73.9 (73.8) | 64.0 (68.5) |
| R,R=-$(CH_2)_5$- | 72.5 (73.9) | 61.5 (68.4) |

**Figure 3.** Spartan PM3 (semi-empirical) calculation of [RuCl(benzene)L]Cl (data in the parenthesis refer to the dihedral angles calculated by MM2, Cache 6.1.1).

the asymmetric hydrogenation of β-ketoesters, however, these finely tunable ligands could provide the opportunity for better enantioselectivity in asymmetric hydrogenation where narrow dihedral angles are needed.

In conclusion, we have developed three novel biphosphine ligands and set up a model to investigate the dihedral angle effect in Ru-catalyzed enantioselective hydrogenation of aryl, alkyl substituted β-ketoesters with high enantioselectivity was achieved. Applications of these ligands to extend the scope of asymmetric reductions and asymmetric C–C bond forming reactions are currently in progress.

## Acknowledgements

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