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SYNPHOS®, a new chiral diphosphine ligand: synthesis, molecular modeling and application in asymmetric hydrogenation

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Abstract—A new optically active diphosphine ligand, [(5,6),(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine) (SYNPHOS®) has been synthesized and used in ruthenium-catalyzed asymmetric hydrogenation. This new ligand has been compared to other diphosphines (BINAP and MeO-BIPHEP), regarding their dihedral angles and the enantioselectivity in the ruthenium mediated hydrogenation reaction. © 2003 Elsevier Science Ltd. All rights reserved.

The search for new chiral ligands capable of high enantioselectivity in homogeneous catalysis is a current challenge in applied chemical research.[1] Development of optically active phosphine ligands, especially C_2-chiral atropoisomeric diphosphines, like BINAP[2] or MeO-BIPHEP[3] (Fig. 1) were used in late transition-metal complexes as (pre)catalysts and provided a great advancement in asymmetric hydrogenation.[4] However, no universal system, i.e. a chiral ligand chelated to a metal, has yet been found, since asymmetric transformations are often substrate-dependent. In our continuous interest for the transition-metal-catalyzed enantioselective hydrogenation reactions,[4c–e,5] we have designed new chiral diphosphine ligands in the last few years.[6] Since atropoisomeric ligands bearing heteroatoms like MeO-BIPHEP, CnTunaPhos[7] or SEGPHOS[8] have shown to provide excellent enantioselectivity in the ruthenium-catalyzed hydrogenations, we have turned our attention to oxygen-based diphosphines. We report here the synthesis of a new atropoisomeric ligand bearing a benzodioxane core, hereafter named SYNPHOS®,[9] the study of its structural properties via molecular modeling and its use in ruthenium-mediated hydrogenation. During the preparation of this manuscript, this ligand was independently synthesized by Chan et al.[10]

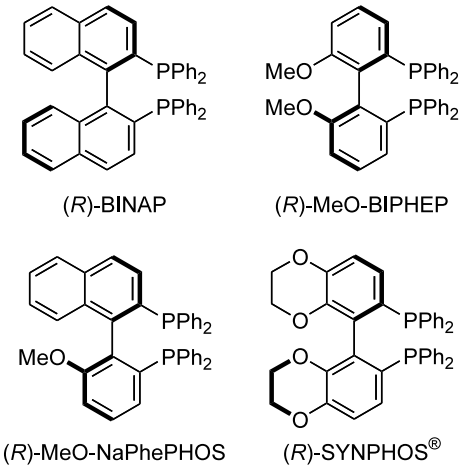

Figure 1.

As illustrated in Scheme 1, 1,2-ethylenedioxybenzene **1** was selectively brominated with *N*-bromosuccinimide in DMF to afford 4-bromo-1,2-ethylenedioxybenzene **2** in quantitative yield. Phosphorylation of compound **2** was achieved by a sequence of lithiation, addition of chlorodiphenylphosphine and oxidation with hydrogen peroxide to provide (3,4-ethylenedioxyphenyl)diphenylphosphine oxide **3** in 90% yield. Ortholithiation of compound **3** and further oxidative coupling with anhydrous ferric chloride furnished [(5,6),(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine oxide) **4** in 50% yield. The optical resolution of *rac*-**4** afforded,

Keywords: diphosphine ligand; molecular modeling; asymmetric hydrogenation; ruthenium.

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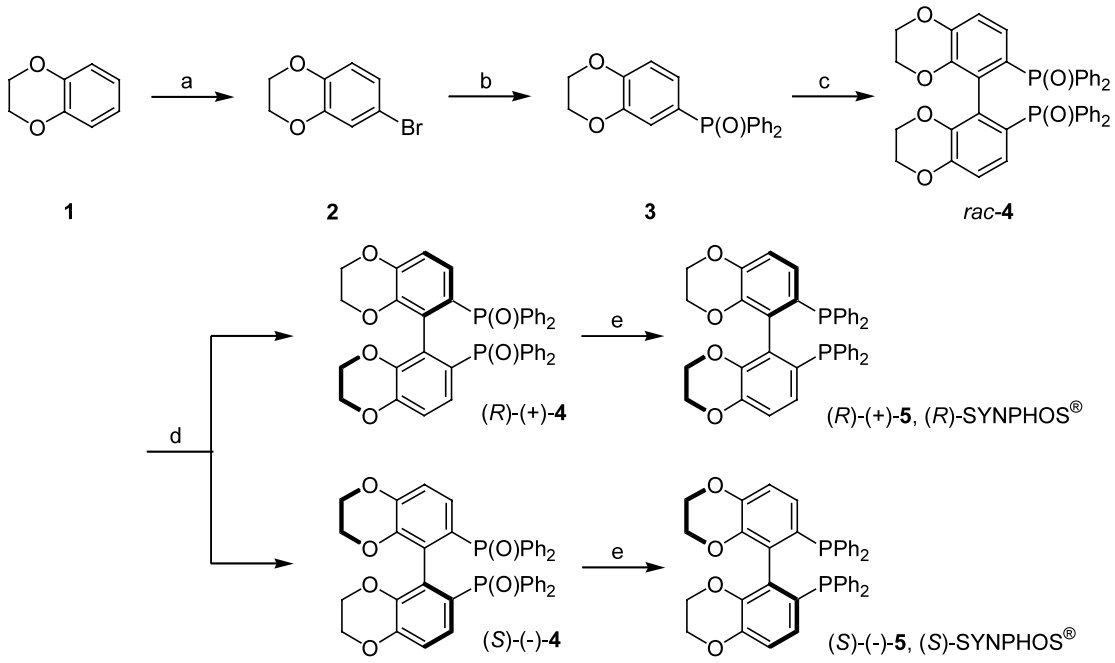


Scheme 1. (a) NBS, DMF, rt, 100%; (b) (1) *n*-BuLi, THF, −70°C (2) $ClPPh_2$, −70°C to rt (3) H_2O_2, MeOH, 0°C, 90%; (c) (1) *t*-BuLi, THF, −100 to −70°C (2) $FeCl_3$, −70°C to rt, 50%; (d) (1) (−)-DBTA, $CHCl_3$:AcOEt = 1:3, fractionnal crystallization; then (+)-DBTA, $CHCl_3$:AcOEt = 1:3, fractionnal crystallization (2) KOH, 70%; (e) $HSiCl_3$, Bu_3N, xylene, 140°C, 91%.

either (−)-**4** with (2*R*,3*R*)-(−)-*O*,*O*′-dibenzoyltartaric acid [(−)-DBTA], or (+)-**4** with (2*S*,3*S*)-(+)-*O*,*O*′-dibenzoyltartaric acid [(+)-DBTA] in 70% yield based on *rac*-**4**. The absolute configuration of (−)-**4** was determined by X-ray analysis of the complex of (−)-**4** with (−)-DBTA. From the internal comparison with (−)-DBTA, the absolute configuration of (−)-SYNPHOS® oxide ((−)-$SYNPHOSO_2$) is defined to be *S* (Fig. 2). Like in the MeO-BIPHEP series,[3a] a 'through process' **3**→(*RS*)-**4**→(*R*)-**4** and (*S*)-**4** was also developed, enabling us to recover the unreacted starting material **3** by simple concentration of the filtrate at the end of step (d). Reduction of the resolved **4** was performed by heating with an excess of $HSiCl_3$ in xylene in the presence of Bu_3N in yields of 91–98% for (*S*)-(−)-**5** and (*R*)-(+)-**5**.

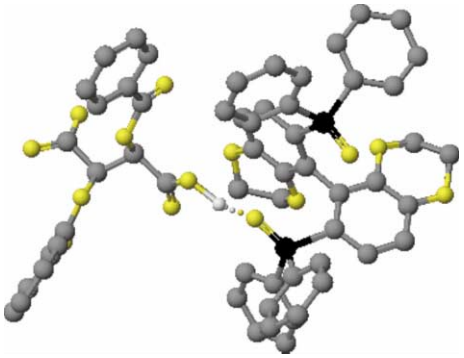


Figure 2. X-Ray drawing of (−)-DBTA/(−)-(*S*)-**4** (Chem3D representation, H omitted for clarity). The crystal consists of polymeric chains of alternating $SYNPHOSO_2$ and DBTA molecules connected by hydrogen bonds.

(*S*)-(−)-**4** and (*R*)-(+)-**4** were enantiomerically pure (>99% e.e.) according to HPLC (Chiralcel OD column). Furthermore, subsequent oxidation of diphosphines (*S*)-(−)-**5** and (*R*)-(+)-**5** with hydrogen peroxide showed no racemization during the reduction process, according to the enantiomeric purity determined by HPLC. The enantiomeric purity of diphosphines (−)-**5** and (+)-**5** was also confirmed by the assignment of the ^1H NMR shifts of the in situ formed Pd complex with (+)-di-μ-chlorobis[2-[(dimethylamino)methyl]phenyl-*C*,*N*]-dipalladium.[11,12] It has to be noted that the absolute configuration of (−)-**4** obtained in the resolution step with (−)-DBTA is also in agreement with the results of Saito[13] (SEGPHOS series) and Schmid[3a] (MeO-BIPHEP series). When (−)-DBTA is used as the resolving agent, the absolute configuration of the diphosphine oxide thus obtained is *S*, in the case of SEGPHOS and diMeO-BIPHEP. In the case of MeO-BIPHEP and triMeO-BIPHEP, the absolute configuration of the diphosphine oxide thus obtained is opposite, i.e. *R*. The absolute configuration of the diphosphine oxide derived from bisbenzodioxanPhos obtained by Chan et al. with (−)-DBTA was *R*.[10]

Like Heiser, Broger and Crameri,[14] we had noticed through several examples in the past few years that MeO-BIPHEP ligand exhibited higher enantioselectivities, comparing to BINAP ligand, in the ruthenium-mediated hydrogenation reactions of a series of functionalized ketones, e.g. thioketones, β-ketosulfones, fluorous β-ketoesters and phosphonic acid.[15] It is now well established that steric[7,13] and electronic[3b] effects

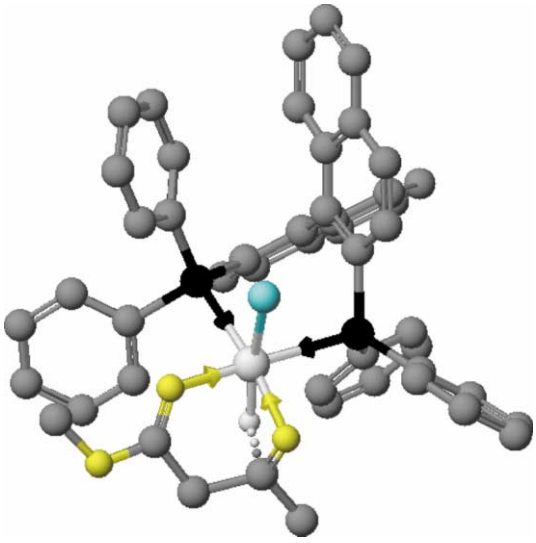


Figure 3. Ruthenium-mediated hydrogenation intermediate model (CAChe MM2 representation, H omitted for clarity).

Table 1. Dihedral angles of diphosphines in Ru-complexes

Diphosphine ligand	Dihedral angle, θ (°)
BINAP	80
MeO-BIPHEP	76
SYNPHOS®	75

play a crucial role. Thus, we decided to look at the dihedral angle of the binaphthyl or biphenyl systems of the atropoisomeric ligands. The steric considerations based on the effect of varying the dihedral angle (θ) in biaryl backbone are expected to explain the differences in the enantioselectivities. We decided to minimize the energy of a ruthenium-mediated hydrogenation intermediate model,[16] as shown in Figure 3. This model represents an intermediate model-complex formed of RuHCl[(*S*)-Binap] and methylacetoacetate. Dihedral angles have been measured in the models, bearing three diphosphine ligands (BINAP, MeO-BIPHEP and SYNPHOS®), by a CAChe MM2 calculation method. This method is only based on the steric effects but not on the electronic properties of the model. The results are shown in Table 1.

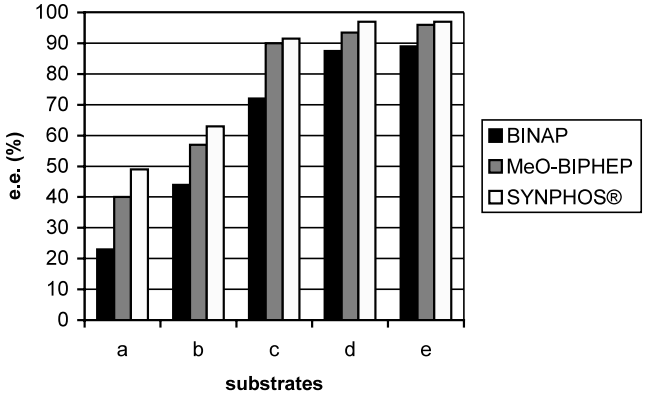
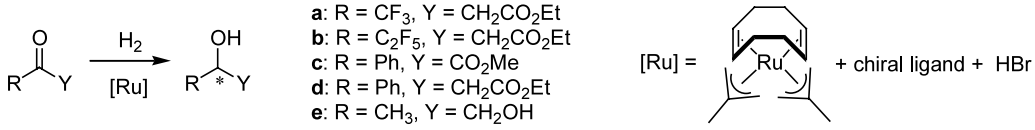


Figure 4. Ketone substrates and correlation θ/e.e.

The calculated dihedral angles decrease in the following order: BINAP, MeO-BIPHEP and SYNPHOS®.

We have then compared these ligands in the hydrogenation of several substrates (Scheme 2), in order to determine the influence of the dihedral angle on the enantioselectivities. All hydrogenation reactions were conducted twice, and in the same conditions of pressure, temperature and time (24 h) for each ligand, with 1 mol% of catalyst.[17] The results are summarized in Table 2.

As shown in Figure 4, the enantioselectivities in the hydrogenation of the selected substrates are remarkably influenced by the dihedral angle of the ligand. The narrower dihedral angle, the higher the enantioselectivities. When the catalysts bears a ligand with a narrow dihedral angle, the interactions between the steric bulk of the diphenylphosphino group and the substrate are enhanced, and thereby, the enantioselectivities are much higher.



Scheme 2. Asymmetric hydrogenation of functionalized ketones.

Table 2. Asymmetric hydrogenation results

Substrate[a]	Ligand	Solvent	H_2 (bar)	T (°C)	e.e. (BINAP)[b] (%)	e.e. (MeO-BIPHEP)[b] (%)	e.e. (SYNPHOS®)[b] (%)
a	(*S*)	EtOH	20	99	23	40	49
b	(*S*)	EtOH	20	99	44	57	63
c	(*R*)	MeOH	20	50	72	90	92
d	(*R*)	EtOH	10	80	87	93	97
e	(*S*)	MeOH	30	65	89	96	97

[a] Conversion rates were determined by ^{1}H NMR (100%).
[b] The enantiomeric excess was determined by GC analysis (Lipodex A for substrates **a**–**d** and Hydrodex-β-G-TBDM for substrate **e**).

In summary, we have described the synthesis, characterization and use of a new and very efficient atropoisomeric diphosphine ligand, SYNPHOS®. We also confirmed that the dihedral angles, in diphosphine ligands from the same family, influence clearly the enantioselectivities in the ruthenium-mediated hydrogenation reactions.

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