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# SYNPHOS: a New Atropisomeric Diphosphine Ligand. From Laboratory-scale Synthesis to Scale-up Development

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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. Laboratory-scale synthesis and scale-up development of this ligand are described herein. This new atropisomeric diphosphine was also used in ruthenium-catalyzed asymmetric hydrogenation.**

## Introduction

In the last two decades, considerable efforts have been undertaken for the design of new ligands to develop highly efficient metal-catalyzed asymmetric transformations, and this topic remains a current challenge in applied chemical research.[1] Development of optically active phosphine ligands, especially $C_2$-chiral atropisomeric diphosphines, such as BINAP[2] or MeO−BIPHEP,[3] provided a great advancement in asymmetric hydrogenation. Since atropisomeric ligands bearing heteroatoms such as MeO−BIPHEP or SEGPHOS[4] have demonstrated excellent enantioselectivity in the ruthenium-catalyzed hydrogenations, we have turned our attention to oxygen-based diphosphines. We report here the laboratory-scale synthesis of a new atropisomeric ligand bearing a benzodioxane core, hereafter named SYNPHOS,[5] its scale-up development, and its use in ruthenium-mediated hydrogenation. In the meantime, Chan and co-workers[6] have synthesized this ligand as well.

**Laboratory-Scale Synthesis.** The synthesis of SYNPHOS ligand was accomplished in a five-step procedure starting from commercial benzo-1,4-dioxane (Scheme 1).[7] In the first step, benzo-1,4-dioxane **1** was readily brominated with *N*-bromosuccinimide in DMF in quantitative yield. Bromobenzo-1,4-dioxane **2** was then lithiated by lithium−halogen exchange with 1.1 equiv of *n*-butyllithium at −70 °C in THF, further reacted with 1.1 equiv of $ClPPh_2$ and finally oxidized with hydrogen peroxide to afford phosphine oxide **3** as a pale yellow solid in high yields. Dimerization of compound **3** was a key step for the synthesis of SYNPHOS ligand. The first aim was to achieve ortholithiation of compound **3**. The lithiated intermediate was oxidized by $FeCl_3$ to provide bis(phosphine oxide) **4**. Best results were obtained with *t*-BuLi at low temperature (−100 °C then −70 °C), under thermodynamically controlled conditions,[8] and compound **4**, hereafter named $SYNPHOSO_2$ was obtained in 50% yield. Racemic $SYNPHOSO_2$ was resolved with *O*,*O*-dibenzoyltartaric acid[9] [(+)- or (−)-DBTA] by fractional crystallization. A solution of racemic $SYNPHOSO_2$ in chloroform and a solution of (−)-DBTA in ethyl acetate were mixed at room temperature ($CHCl_3$/AcOEt, 1:3). After a few minutes, precipitation of a 1:1 complex of (−)-DBTA and (*S*)-$SYNPHOSO_2$ was observed. Treatment of the tartrate complex with aqueous base (1 N KOH) provided enantiomerically enriched (*S*)-$SYNPHOSO_2$ (ee = 70%, according to HPLC, Chiralcel OD column). Enantiomerically pure (*S*)-$SYNPHOSO_2$ was obtained by repeating this operation four times, in 70% yield based on *rac*-**4**. Enantiomerically enriched (*R*)-$SYNPHOSO_2$ was recovered from the mother liquor after treatment with aqueous base. Similary, enantiomerically pure (*R*)-$SYNPHOSO_2$ was then obtained from enantiomerically enriched (*R*)-**4** by using (+)-DBTA in 70% yield based on *rac*-**4**. The final step in the synthetic route was the reduction of bis(phosphine oxide) **4**. This was accomplished by treatment of $SYNPHOSO_2$ with trichlorosilane-tributylamine in refluxing xylene producing (−)-(*S*) and (+)-(*R*)-SYNPHOS with a global yield of 28% from **1**.

**Scale-Up Synthesis.** The laboratory synthesis was suitable for producing several grams of ligand but would be problematic for producing kilograms for several reasons. The main drawback was the low yielding *t*-BuLi/$FeCl_3$ coupling step. At best, only 50% of compound **4** was obtained along

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‡ SYNKEM S.A.S.

(1) (a) Kagan, H. B. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. I, Chapter 2, p 9. (b) Ojima, I. *Catalytic Asymmetric Synthesis*; John Wiley and Sons: New York, 2000.

(2) (a) Miyashita, A.; Yasuda A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(3) (a) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370. (b) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter U. *Pure Appl. Chem.* **1996**, *68*, 131.

(4) (a) Saito, Sayo, T. N.; Xiaoyaong, Z.; Yokozawa, T. (Takasago International Corporation). EP 0850945, 1998. (b) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; T. Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(5) Duprat de Paule, S.; Champion, N.; Vidal, V.; Genêt, J.-P.; Dellis, P. French Patent 0112499; PCT FR02/03146.

(6) Pai, C. C.; Li, Y. M.; Zhou, Z. Y.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 2789.

(7) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Tetrahedron Lett.* **2003**, *44*, 823.

(8) Brown, J. M.; Woodward, S. C. *J. Org. Chem.* **1991**, *56*, 6803.

(9) Brunner, H.; Pieronczyk, W.; Schönhammer, B.; Streng, K.; Bernal, I.; Korp J. *Chem. Ber.* **1981**, *114*, 1137.

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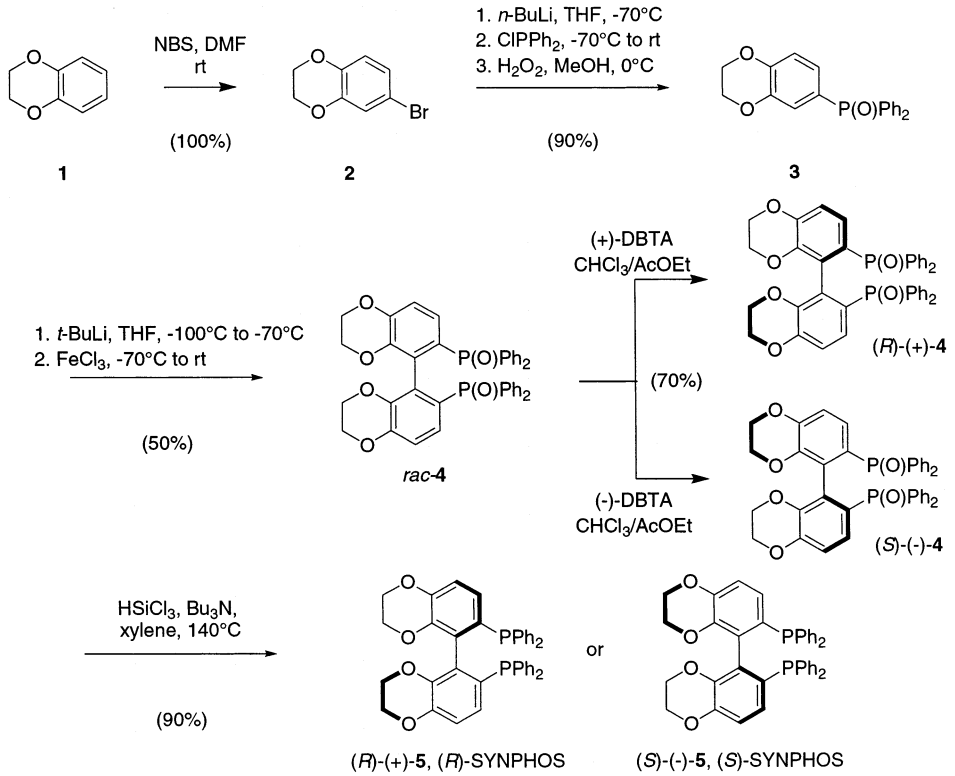
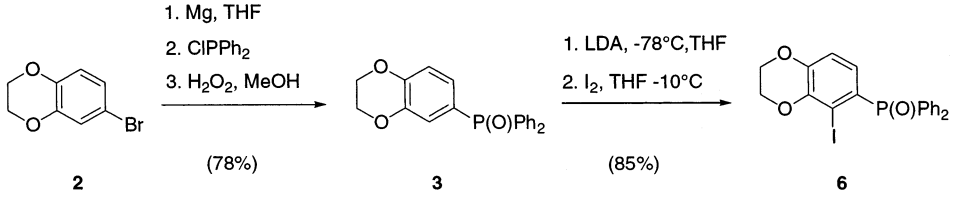
***Scheme 1.*** **SYNPHOS laboratory synthesis**



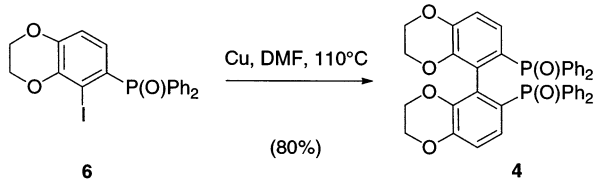

***Scheme 2***




with starting material. Though the uncoupled compound **3** could be recovered from the mother liquors during the resolution step and recycled, a higher conversion would have been required. We were also interested in performing the reaction at a higher temperature, −100 °C being not compatible with our facilities. Replacement of the very flammable *t*-BuLi by a cheaper and safer reagent was also a requirement. Furthermore substantial degradation of the dioxane moiety was observed with *t*-BuLi in THF above −70 °C.[10]

At this point, we decided to investigate another approach using a two-step sequence of ortholithiation-iodination[3a,6] of compound **3** and then Ullmann reaction of the corresponding iodide **6** to get racemic compound **4** (Schemes 2 and 3). Starting from compound **2**, we alternatively obtained phosphine oxide **3** with 78% yield via the Grignard reagent which was reacted with chlorodiphenylphosphine (technical grade) and subsequently oxidized by aqueous hydrogen peroxide. This sequence, which had previously been described,[11] advantageously allowed us to suppress the low temperature

***Scheme 3***




*n*-BuLi metalation step and to use magnesium as cheaper reagent.

LDA at low temperature in THF gave the best results for the ortholithiation/iodination sequence. The ortholithiation temperature and the sense of addition, i.e., normal or inverted addition of the iodine solution, were two critical parameters to obtain the expected compound **6** with good conversion. For instance, ortholithiation of compound **3** for 3 h at −70 °C and quenching this solution at −70 °C with iodine solution in THF (direct addition) gave the expected compound **6** with only 35−40% conversion along with starting material and a complexe mixture of benzodioxane-ring-opening byproducts. Increasing the ortholithiation temperature to −40 °C lowered the formation of compound **6** and favored the formation of degradation byproducts. On the other hand, ortholithiation of compound **3** for 3 h at −70 °C, followed by the addition of the resulting

(10) (a) Ranade, A. C. Jayalakshmi S. *Chem. Ind.* **1978**, 234. (b) Mattson, R. J.; Sloan, C. P.; Lockart, C. C.; Catt, J. D.; Gao, Q.; Huang, S. *J. Org. Chem.* **1999**, *64*, 8004.

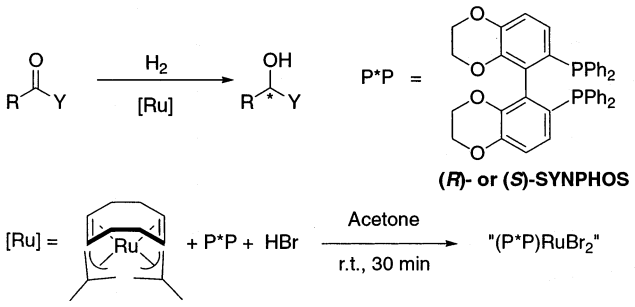
(11) (a) Laue, C.; Schröder, G.; Arlt, D. U.S. Patent 5,710,339, 1998. (b) Foricher, J.; Schmid, R. EP 0926152 A1, 1998.

solution to a iodine solution (inverted addition) at −60 °C gave satisfactory conversion (typically 80−85% by HPLC). The reaction was successfully achieved even when the lithiated derivative of compound **3** was added to the iodine solution up to a temperature of −10 °C. The crude reaction mixture was directly used in the Ullmann coupling step using copper powder in DMF (Scheme 3). After 2.5 h at 110 °C no more starting material was detected and racemic compound **4** was obtained along with compound **3** in a 80/20 ratio (**4**/**3**), according to the HPLC. Reduction of compound **6**, which is a common side reaction in Ullmann conditions, did not exceed 5 to 10%, depending on the experiment and taking into account that compound **3** was already present in crude compound **6** (typically 10 to 15% by HPLC).

The resolution step was optimized to shorten and improve the initial enrichment process (five successive resolutions, 70% yield based on *rac*-**4**). The conditions described earlier (formation of the (−)-DBTA/(*S*)-SYNPHOSO$_2$ complex in AcOEt/$CHCl_3$ mixture) were indeed difficult to control on a larger scale and if the reaction mixture was not filtered within a few minutes of the precipitate forming, the enrichment was not efficient. Alternatively, if the reaction mixture was maintained for a longer period (at least 1 h at 20 °C), the 50/50 mixture of both (−)-(*S*)-**4**/(−)-DBTA and (+)-(*R*)-**4**/(−)-DBTA complexes was obtained with a 95% yield as a white solid after filtration. This procedure was actually advantageous both to purify the crude reaction mixture from the Ullmann coupling step and to recover unreacted compound **3** from the mother liquor. Optically pure (+)-(*R*)-**4**/(−)-DBTA complex was finally obtained after two slurries of the 50/50 complexes mixture in $CH_2Cl_2$. Destruction of the complex with potassium hydroxide afforded enantiopure (+)-(*R*)-**4** in 79% yield based on *rac*-**4**. The combined filtrates containing the soluble (−)-(*S*)-**4**/(−)-DBTA was treated with 1 N KOH. After usual workup (see Experimental Section), the resulting white solid was then similarly treated with (D)-(+)-dibenzoyltartaric acid, providing enantiopure (−)-(*S*)-**5** in 78% yield based on *rac*-**4**.

**Asymmetric Hydrogenation.** Ruthenium-catalyzed asymmetric hydrogenation is known to be a very convenient method for producing optically active alcohols and chiral building blocks, especially with atropoisomeric diphosphine ligands.[12] Based on an in situ procedure,[13] catalysts were prepared from commercially available [Ru(COD)-(2-methylallyl)$_2$] and SYNPHOS ligand by addition of a methanolic solution of HBr in acetone as detailed in Scheme 4. After removal of the solvent in vacuo, these complexes were used without further purification.

***Scheme 4.*** **Asymmetric hydrogenation of functionalized ketones**




Using SYNPHOS, we investigated the hydrogenation reactions of various carbonyl substrates: $\beta$-keto esters, α-keto esters, and functionalized ketones. Hydrogenations were carried out on a 1-mmol scale using 1 mol % catalyst, in a stainless steel autoclave. The conversions were determined by $^1$H NMR spectroscopy, and enantiomeric excesses of the products were determined by chiral GC or HPLC. The results are given in Table 1.

In all cases, complete conversion was obtained. The catalytic system based on SYNPHOS ligand gave high enantiomeric excesses with $\beta$-keto esters under 4 bar of hydrogen and at 50 °C, providing the corresponding substituted $\beta$-hydroxy esters with enantiomeric excesses ranging from 97 to >99% for the aromatic compound (entry 5) and the aliphatic compounds (entries 1−4), respectively. Ruthenium-mediated hydrogenations of fluorinated substrates are known to give poor ee even at high temperature (99 °C),[14] but SYNPHOS ligand displayed a higher enantioselectivity of 49% (entry 6, 23% with BINAP ligand).[14] Enantioselectivities, regarding other ketone substrates, turned out to be very high, too. α-Hydroxy esters, resulting from the asymmetric hydrogenation of the corresponding carbonyl compounds, were obtained with enantiomeric purities of 92−94% under 20 bar of hydrogen and at 50 °C (entries 7−8). Various functionalized ketones, such as hydroxyacetone (entry 9), a $\beta$-thioketone (entry 10), a $\beta$-keto phosphonate (entry 11), and a 1,3-diketone (entry 12), were also hydrogenated with ee above 97%.

These complexes were also efficient using a substrate: catalyst ratio up to 10 000 under 20 bar of hydrogen at 50 °C, providing pure (3*R*)-methyl hydroxybutanoate as shown in Scheme 5.

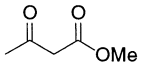
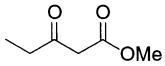
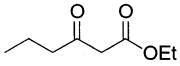
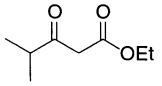
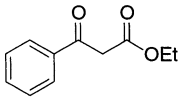
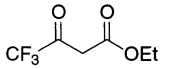
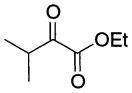
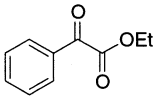
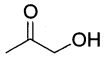
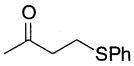
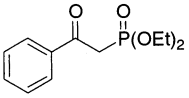
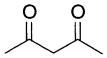
Furthermore, SYNPHOS compared favorably with two well-known atropisomeric diphosphine ligands BINAP and MeO−BIPHEP, in ruthenium-catalyzed asymmetric hydrogenation of several model substrates (Table 2) and using the same in situ method for each catalyst preparation.[13] Comparative hydrogenation reactions with these three ligands were conducted using 1 mol % catalyst in the same conditions of temperature, pressure, time, and concentration (0.5 mmol/mL) for each substrate, and we observed that SYNPHOS gave the highest enantioselectivities.[7]

(12) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994. (b) Noyori, R. *Tetrahedron* **1994**, *50*, 4259. (c) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; 2000; pp 1−110. (d) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (e) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (f) Ratovelomanana-Vidal, V.; Genêt, J.-P. *J. Organomet. Chem.* **1998**, *567*, 163. (g) Genêt, J.-P. *Pure Appl. Chem.* **2002**, *74*, 77.

(13) (a) Genêt, J.-P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Cano de Andrade, M. C.; Laffitte, J.-A. *Tetrahedron: Asymmetry* **1994**, *5*, 665. (b) Genêt, J.-P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Cano de Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte J.-A. *Tetrahedron: Asymmetry* **1994**, *5*, 675. (c) Genêt, J.-P. *Reductions in Organic Synthesis*; ACS Symposium Series 641; American Chemical Society: Washington, DC, 1996; pp 31−51.

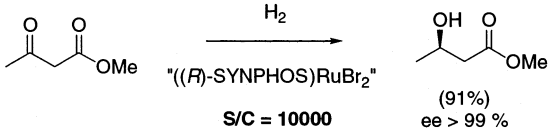
(14) Blanc, D.; Ratovelomanana-Vidal, V.; Gillet, J.-P.; Genêt J.-P. *J. Organomet. Chem* **2000**, *603*, 128.

***Table 1.*** **Hydrogenation results**

| Entry | Substrate[a] | Ligand (config.) | solvent | $pH_2$ [bar] | $T$ [°C] | $t$ [h] | $ee$[b] (config.) |
|---|---|---|---|---|---|---|---|
| 1 |  | (*R*) | MeOH | 4 | 50 | 24 | > 99% (*R*) |
| 2 |  | (*R*) | MeOH | 4 | 50 | 24 | > 99% (*R*) |
| 3 |  | (*R*) | EtOH | 4 | 50 | 24 | > 99% (*R*) |
| 4 |  | (*R*) | EtOH | 4 | 50 | 24 | > 99% (*S*) |
| 5 |  | (*R*) | EtOH | 10 | 80 | 24 | 97% (*S*) |
| 6 |  | (*S*) | EtOH | 10 | 99 | 1 | 49% (*R*) |
| 7 |  | (*S*) | EtOH | 20 | 50 | 24 | 94% (*S*) |
| 8 |  | (*R*) | MeOH | 20 | 50 | 24 | 92% (*R*) |
| 9 |  | (*S*) | MeOH | 30 | 65 | 7 | 97% (*S*) |
| 10 |  | (*R*) | MeOH | 30 | 30 | 24 | 98% (*R*) |
| 11 |  | (*R*) | EtOH | 20 | 50 | 24 | > 99% (*S*) |
| 12 |  | (*R*) | MeOH | 20 | 30 | 72 | >99% (*R*, *R*) d.e. >99% |

[a] All conversions were 100%, according to $^1$H NMR. [b] Enantiomeric excess measured by chiral GC.

***Scheme 5.*** **Multigram-scale asymmetric hydrogenation of methyl acetoacetate**



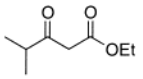
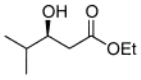
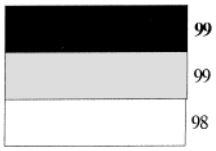
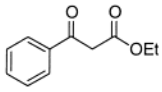
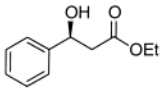
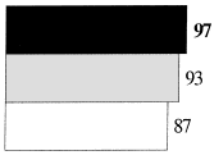
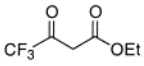
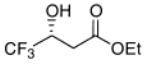
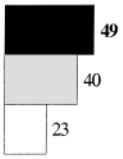
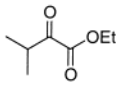
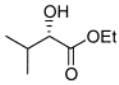
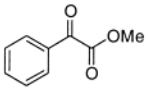
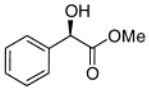
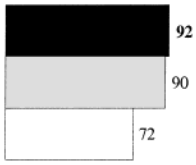
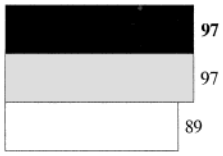

## Conclusions

In summary, we have reported here the synthesis of a new atropisomeric chiral diphosphine ligand SYNPHOS that proved to be very efficient when used in ruthenium-catalyzed asymmetric hydrogenation with numerous substrates. A scale-up route has been studied that relies on an ortholithiation/iodination sequence and a subsequent Ullmann reaction as the key steps. Following this sequence a "through process" **3** → **6** → *rac*-**4** → (+)-**4** or (−)-**4** has been performed without any purification by chromatography, providing an access to enantiopure diphosphine **5** with a global yield of 34−40% from **2**.

## Experimental Section

**General Remarks.** $^1$H NMR spectra were recorded on a Bruker AC 200 at 200 MHz or on a Avance 400 at 400 MHz, $^{13}$C NMR spectra were recorded on a Bruker AC 200 at 50 MHz and $^{31}$P NMR spectra were recorded on a Avance 400 at 162 MHz; chemical shifts ($\delta$) are reported in ppm downfield relative to internal $Me_4Si$ or external $H_3PO_4$; coupling constants ($J$) are reported in Hz and refer to apparent peak multiplicities. Mass spectra were determined on a Ribermag instrument; ionization was obtained either by electronic impact (EI), chemical ionization with ammonia (DCI/$NH_3$), or electrospray (ESI) for compounds (−)-(*S*)-**5** and (+)-(*R*)-**5**. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm (sodium lamp). Melting points (mp) were determined on a Kofler melting point apparatus. GC analyses were performed on a Hewlett-Packard 5890 series II instrument connected to a Merck D-2500 or D-2000 integrator, using flame ionization detector; enantiomeric excesses were determined on chiral capillary columns: Lipodex A, Hydrodex-$\beta$-6-TBDM, Chirasil-Val, Megadex 5, or Chirasil-DEX CB. HPLC analyses of

***Table 2.*** **Comparative study between SYNPHOS, MeO−BIPHEP and BINAP**

| Substrate[a] | Ligand (config.) | Solvent | Conditions | Product | *ee* (%)[b] |
|---|---|---|---|---|---|
|  | (*R*) | EtOH | 4 bar, 50°C, 24h |  |  |
|  | (*R*) | EtOH | 10 bar, 80°C, 24h |  |  |
|  | (*S*) | EtOH | 10 bar, 99°C, 1h |  |  |
|  | (*S*) | EtOH | 20 bar, 50°C, 24h |  |  |
|  | (*R*) | MeOH | 20 bar, 50°C, 24h |  |  |
|  | (*S*) | MeOH | 30 bar, 65°C, 7h |  |  |

[a] All conversions were 100%, according to $^1$H NMR.
[b] Enantiomeric excess measured by chiral GC.



compound **4** were conducted with Waters 600 system, using Daicel chiral stationary phase column: Chiralcel OD, hexane/2-propanol, 90:10.

**4-Bromo-1,2-ethylenedioxybenzene 2.** 1,2-Ethylenedioxybenzene (150 g, 1.10 mol) and anhydrous DMF (800 mL) were mixed at 0 °C in a 2-L double-jacket reactor provided with a thermometer and a mechanical stirrer. *N*-Bromosuccinimide (235.3 g, 1.32 mol) was added by portions at 0 °C. After stirring for 24 h at room temperature, the solution was concentrated in vacuo. The residue was filtered, and the precipitate was washed with 200 mL of $CH_2Cl_2$. The resulting filtrate was treated with 200 mL of a 30% aqueous solution of $Na_2S_2O_3$ and washed with brine. After evaporation and distillation under reduced pressure (bp = 116 °C, 2 mbar), compound **2** was obtained as a colourless oil (236.9 g, quantitative). $^1$H NMR ($CDCl_3$): $\delta$ = 4.25 (s, 4H), 6.74 (d, $J$ = 8.5 Hz, 1H), 6.93 (dd, $J$ = 8.5, 2.3 Hz,-1H), 7.02 (d, $J$ = 2.3 Hz, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ = 64.1, 112.7, 118.5, 120.1, 124.1, 142.8, 144.2. EI-MS *m*/*z* $^{81}$Br 216 $(M)^+$.

**(3,4-Ethylenedioxyphenyl)diphenylphosphine Oxide 3.** Magnesium turnings (14.9 g, 0.614 mol) were suspended in 45 mL of THF under nitrogen in a 1-L double-jacket reactor provided with a condenser, thermometer, mechanical stirrer, and dropping funnel with pressure compensation. The reaction mixture was heated to 55 °C, and a few drops of 1,2-dibromoethane were added. A solution of 4-bromo-1,2-ethylenedioxy-benzene **2** (120 g, 0.558 mol) in THF (240 mL) was then added to the suspension within 30 min while stirring vigorously with the temperature being held at 60−

65 °C. After completion of the dropwise addition, the resulting gray solution was stirred at reflux for 2 h. The reaction mixture was cooled to −8 °C and treated dropwise within 2 h with a solution of 135.4 g (0.614 mol) of chlorodiphenylphosphine in 270 mL of THF. After completion of the dropwise addition, the reaction mixture was heated to 25 °C and held at this temperature for 2.5 h. Subsequently, 100 mL of methanol were added thereto from a dropping funnel while stirring with the temperature rising to a maximum of 37 °C. The reaction mixture was then cooled to 0 °C, and 100 g of 35% hydrogen peroxide solution was added dropwise at such a rate that the reaction temperature did not exceed 30 °C. Shortly after completion of the dropwise addition, the reaction was completed according to TLC (AcOEt, UV detection). The reaction mixture was treated with 100 mL of a saturated $Na_2S_2O_5$ aqueous solution following which, peroxide could no longer be detected. THF was then distilled off under reduced pressure, and 500 mL of dichloromethane was added. After stirring for 15 min, the aqueous phase was separated, and the organic phase extracted with 150 mL of 1 N hydrochloric acid. The aqueous phase was separated and back-extracted with 250 mL of dichloromethane. The combined organic phases were partially concentrated by distillation under vacuum, and 800 mL of dioxane was added. The concentration of the reaction mixture was continued until 600 mL of dioxane remained. The suspension was subsequently heated to 90 °C for solubilisation, cooled within 45 min to 45 °C, maintained at 45 °C for 30 min, cooled to 20 °C within 1 h, and maintained at 20 °C for 1 h. The white crystals were filtered off under suction, washed with 100 mL of dioxane, and dried at 45 °C in vacuo overnight to provide 105.7 g (56.3%) of compound **3** as a white solid. From the mother liquor, dioxane was distilled off under reduced pressure until 200 mL remained. The suspension was subsequently heated to 60 °C for solubilisation and slowly cooled to 20 °C in 1 h and maintained at 20 °C for 1 h. The white crystals were filtered off under suction, washed with 20 mL of dioxane, and dried at 45 °C in vacuo overnight to provide 40.9 g (21.8%, combined yield 78.1%) of compound **3** as a white solid. Mp = 150−155 °C. $^1$H NMR ($CDCl_3$): $\delta$ = 4.26 (m, 4H), 6.95 (dd, $J$ = 11.8, 3.1 Hz,1H), 7.09−7.18 (m, 2H), 7.42−7.54 (m, 6H), 7.61−7.72 (m, 4H). $^{13}$C NMR ($CDCl_3$): $\delta$ = 64.1, 64.4, 117.6 (d, $J$ = 14.6 Hz), 121.2 (d, $J$ = 12.1 Hz), 125.5 (d, $J$ = 10.3 Hz), 128.2, 128.4, 131.7, 131.8, 132.0, 133.6, 143.3, 146.7. $^{31}$P NMR ($CDCl_3$): $\delta$ = 30.10. CI-MS (pos) $m/z$ 337 $(M + H)^+$.

**(2-Iodo-3,4-ethylenedioxyphenyl)diphenylphosphine Oxide 6.** Compound **3** (50 g, 0.149 mol) and 500 mL of dry THF were placed under nitrogen in a 1-L three-necked flask provided with a thermometer, stirring bar, and dropping funnel with pressure compensation. After cooling to −75 °C, 81.8 mL (0.164 mol) of lithium diisopropylamide (2 N solution in heptane/THF/ethylbenzene) was added dropwise with the temperature being held below −70 °C. After stirring at −75 °C for 3.5 h, the reaction mixture was cannulated at −10 °C over 30 min in a 2.5-L three-necked flask (provided with a thermometer and a stirring bar) containing 75.5 g (0.297 mol) of iodine and 500 mL of dry THF. After stirring for 1 h at −10 °C, the reaction mixture was heated to 20 °C, held for 1 h at 20 °C, and hydrolyzed with 400 mL of 20% aqueous solution of $Na_2S_2O_5$. After stirring for 15 min the aqueous phase was separated, and the organic phase was distilled off under reduced pressure. The crude residue was dissolved in 500 mL of dichloromethane, and 300 mL of 1 N sodium hydroxide was added. After stirring for 15 min the aqueous phase was separated, and the organic phase extracted with 150 mL of 1 N hydrochloric acid. After the aqueous phase was separated, the organic phase was evaporated under reduced pressure to give 70 g of a thick brown oil. ($^1$H NMR ratio **3/6** = 16/84). $^1$H NMR ($CDCl_3$): $\delta$ = 4.31 (m, 4H), 6.69 (dd, $J$ = 12.7, 8.7 Hz, 2H), 6.81(dd, $J$ = 8.7, 2.8 Hz, 2H), 7.47−7.58 (m, 6H), 7.63−7.77 (m, 4H). $^{31}$P NMR ($CDCl_3$): $\delta$ = 34.42. CI-MS $m/z$ 463 $(M + H)^+$.

**[(5,6),(5′,6′)-Bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine oxide), SYNPHOSO$_2$ 4 from compound 3.** To a solution of **3** (30 g, 87 mmol) in dry THF (600 mL) was added dropwise *t*-BuLi (65 mL, 1.5 M solution in pentane, 90 mmol) at −100 °C. During 30 min, the reaction temperature was raised to −70 °C, and the resulting red solution was stirred for an additional 3 h at this temperature. Anhydrous $FeCl_3$ (19.8 g, 121.8 mmol) was then added in one portion under a flow of argon at −70 °C. The reaction temperature quickly rose to 10 °C, and the brown mixture was stirred overnight at room temperature. The solution was concentrated in vacuo, and the brown residue was diluted with $CH_2Cl_2$ (500 mL) and treated with 50 mL of 1 N aqueous NaOH. After stirring for 30 min, the resulting suspension was filtered on Celite, and the filter cake was washed with $CH_2Cl_2$ (100 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting brown solid, containing 50% of starting material **3**, was dissolved in $CHCl_3$ (150 mL), and a solution of racemic dibenzoyltartaric acid (15.8 g, 44 mmol) in AcOEt (180 mL) was added. In a few minutes, a precipitate was formed. After filtration (the filtrate was concentrated in vacuo to give starting material **3** (15 g, 50%) as a pale yellow solid), the solids were suspended in $CH_2Cl_2$ (200 mL) and treated with 100 mL of 1 N aqueous KOH. After stirring for 30 min, the clear organic layer was separated, washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to afford pure *rac*-**4** (15 g, 50%) as a white solid. Mp > 260 °C. $^1$H NMR ($CDCl_3$): $\delta$ = 3.42 (m, 2H), 3.70 (m, 2H), 3.92 (m, 2H), 4.06 (m, 2H), 6.64 (dd, $J$ = 13.3, 8.5 Hz, 2H), 6.77 (dd, $J$ = 8.5, 3.1 Hz, 2H), 7.26−7.31 (m, 4H), 7.35−7.55 (m, 12H), 7.65−7.70 (m, 4H). $^{13}$C NMR ($CDCl_3$): $\delta$ = 63.3, 63.9, 115.9 (d, $J$ = 14.6 Hz), 121.2, 124.5, 127.7, 127.9, 130.8, 132.1, 132.2, 132.4, 135.5, 141.0, 145.8. $^{31}$P NMR ($CDCl_3$): $\delta$ = 30.97. CI-MS $m/z$ 671 $(M + H)^+$. HRMS: calcd for $C_{40}H_{32}O_6P_2$ (M + H) 671.1752; found 671.1755.

**[(5,6),(5′,6′)-Bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine oxide), SYNPHOSO$_2$ 4 from Compound 6.** Sixty-eight grams of crude compound **6** (88% purity, 0.129 mol) and 300 mL of DMF were placed under nitrogen in a 0.5-L three-necked flask provided with a

thermometer and a stirring bar. The reaction mixture was heated to 110 °C, and 24.7 g (0.388 mol, 45 $\mu$m) of copper powder were added. After stirring for 2.5 h at 110 °C the reaction mixture was cooled to 20 °C and filtered, and the solid residue was washed with 50 mL of DMF. The solvent was distilled off from the filtrate under reduced pressure, and the resulting oily residue was diluted in 300 mL of $CH_2Cl_2$, washed successively with 100 mL of saturated $NH_4Cl$ solution and 100 mL of water. The solvent was distilled off under reduced pressure to give 51.5 g of a thick brown oil (HPLC ratio **3**/**4** ≈ 20/80).

**Resolution of SYNPHOSO$_2$ 4.** To a 1-L three-necked flask provided with a thermometer, stirring bar, and dropping funnel with pressure compensation were added 34 g (80% purity, 40.6 mmol) of *rac*-SYNPHOSO$_2$ **4** and 340 mL of $CHCl_3$ under nitrogen. A solution of 16.8 g (46.9 mmol) of (−)-*O*,*O*-dibenzoyltartaric acid in 800 mL of AcOEt was added dropwise to the reaction mixture at 20 °C. After stirring at 20 °C for 2 h, the white suspension was cooled to 0 °C, stirred a further 1 h at 0 °C, and filtered at 0 °C. The resulting solid was washed with 100 mL of AcOEt and dried under vacuum at 30 °C overnight to give a 50/50 mixture (according to HPLC) of both (−)-(*S*)-**4**/(−)-DBTA and (+)-(*R*)-**4**/(−)-DBTA complexes (39.6 g, 95%). The resulting solid was then mixed with 490 mL of $CH_2Cl_2$ in a 1-L three-necked-flask provided with a thermometer and a stirring bar. After stirring for 2 h at 20 °C, the suspension was filtered, and the filtrate was stored for the recovery of the other enantiomer. The resulting solid was washed with 50 mL of $CH_2Cl_2$ and dried at 30 °C under vacuum to give 17.8 g of a white solid. An aliquot of the resulting white solid was suspended in $CH_2Cl_2$ and treated with 1 N aqueous KOH. After stirring for 15 min, the clear organic layer was separated, washed with water, and evaporated to afford a white solid (ee = 94.4% according to HPLC). The solid was once again mixed with 200 mL of $CH_2Cl_2$ in a 0.5-L three necked flask provided with a thermometer and a stirring bar. After stirring for 1.5 h at 20 °C, the suspension was filtered, and the filtrate was stored for the recovery of the other enantiomer. The resulting solid was washed with 40 mL of $CH_2Cl_2$ and dried at 30 °C under vacuum to give 16.3 g of a white solid. The resulting white solid was then suspended in 200 mL of $CH_2Cl_2$ and treated with 150 mL of 1 N aqueous KOH. After stirring for 30 min, the clear organic layer was separated, washed with 100 mL of water, and evaporated to afford 10.74 g (79.0% based on theory) of enantiopure (+)-(*R*)-**4** (ee > 99.9% according to HPLC) as a white solid. $[\alpha]^{20}_D$ = (+) 143 (*c* = 1, $CHCl_3$). All other analytical data were identical to those of racemic **4**.

The combined filtrates were concentrated under vacuum and treated as described above (1 N KOH and usual workup). The resulting white solid (15.5 g) was then treated, similary, with (D)-(+)-dibenzoyltartaric acid (7.7 g, 21.4 mmol) and finally 10.64 g (78.2% based on theory) of (−)-(*S*)-**4** (ee > 99.9% according to HPLC) was obtained as a white solid. $[\alpha]^{20}_D$ = (−) 142 (*c* = 1, $CHCl_3$). All other analytical data were identical to those of racemic **4**.

**[(5,6),(5′,6′)-Bis(ethylenedioxy)biphenyl-2,2′-diyl]bis-(diphenylphosphine), SYNPHOS 5.** To a 0.25-L three-necked flask provided with a thermometer, a stirring bar, and a dropping funnel with pressure compensation were added under nitrogen 10 g of compound **4** (14.8 mmol), 100 mL of dry xylene, and 15.2 g of tributylamine (82.0 mmol). To the resulting suspension were added dropwise at 20 °C 10.1 g of trichlorosilane (74.6 mmol). The resulting mixture was then heated at 130 °C for 14 h. The reaction mixture was cooled to 0 °C, and 100 mL of degassed 4 N aqueous NaOH was added dropwise. After stirring for 30 min the reaction mixture was heated to 20 °C, and 300 mL of degassed $CH_2Cl_2$ was added. The reaction mixture was stirred for 30 min. The organic layer was isolated, washed with 100 mL each of degassed distilled water and degassed brine, and concentrated in vacuo. MeOH (100 mL) was then added, and a white precipitate formed. The solid was filtered at 20 °C under nitogen and dried in vacuo for 3 h to afford 8.57 g (90.0%) of SYNPHOS **5** as a white solid.

(−)-(*S*)-SYNPHOS **5**: mp > 260 °C. $[\alpha]^{20}_D$ = (−) 44 (*c* = 0.1, $C_6H_6$). $^1$H NMR ($CDCl_3$): $\delta$ = 3.35 (m, 2H), 3.83 (m, 4H), 4.13 (m, 2H), 6.62 (dd, *J* = 8.0, 3.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 7.05−7.10 (m, 4H), 7.20−7.25 (m, 8H), 7.27−7.32 (m, 8H). $^{31}$P NMR ($CDCl_3$): $\delta$ = −14.30. ESI-MS *m*/*z* 639 $(M + H)^+$. HRMS: calcd for $C_{40}H_{32}O_4P_2$ (M + H) 639.1854; found 639.1844.

(+)-(*R*)-SYNPHOS **5**: mp > 260 °C. $[\alpha]^{20}_D$ = (+) 32 (*c* = 0.1, $CHCl_3$). All other analytical data were identical to those of compound (−)-(*S*)-SYNPHOS **5**.

**Typical Procedure for Asymmetric Hydrogenation.** (*S*)-SYNPHOS (7.1 mg, 0.011 mmol) and (COD)Ru($\eta^3$-$(CH_2)_2CCH_3)_2$ (3.2 mg, 0.01 mmol) were placed in a 10-mL flask, and 1 mL of degassed anhydrous acetone was added dropwise. A methanolic solution of HBr (122 $\mu$L, 0.18 M) was added dropwise to the suspension. The reaction mixture was stirred at room temperature for about 30 min, and a resulting orange suspension was observed. The solvent was removed under vacuum. The brown solid residue was used without further purification as a catalyst for the hydrogenation reaction of the desired substrate (1 mmol) in 2 mL of MeOH or EtOH. The reaction vessel was placed in a 500-mL stainless steel autoclave, which was pressurized at the desired pressure and warmed to the desired temperature for 24 h. The methanol was concentrated, and the crude product was filtered on a short pad of silica gel (cyclohexane/AcOEt, 1:1). Conversion and ee were determined by $^1$H NMR and chiral GC.

**Multigram-Scale Asymmetric Hydrogenation of Methyl Acetoacetate.** In a 0.5-L flask, in situ catalyst "((*R*)-SYNPHOS)RuBr$_2$" (77.5 mg, 0.086 mmol) was prepared according to the previously described typical procedure. Methyl acetoacetate (100 g, 0.861 mol) and 200 mL of methanol were degassed and added to the catalyst via cannula under a flow of argon. The reaction vessel was introduced in a 600-mL stainless steel autoclave, which was pressurized at 20 bar and warmed to 50 °C for 3 days. The methanol was evaporated in vacuo, and the crude product was filtered on silica gel (cyclohexane/AcOEt, 1:1). (3*R*)-Methyl hy-

droxybutanoate was obtained as a colorless oil with 91% yield (92.6 g) and ee > 99% according to GC (Lipodex A, 35 °C, hold for 30 min, ramp to 100 °C at 1 °C/min, retention time: 45.34 min (*S*); 48.00 min (*R*)).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