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Solphos: A New Family of Efficient Biaryl Diphosphine Ligands

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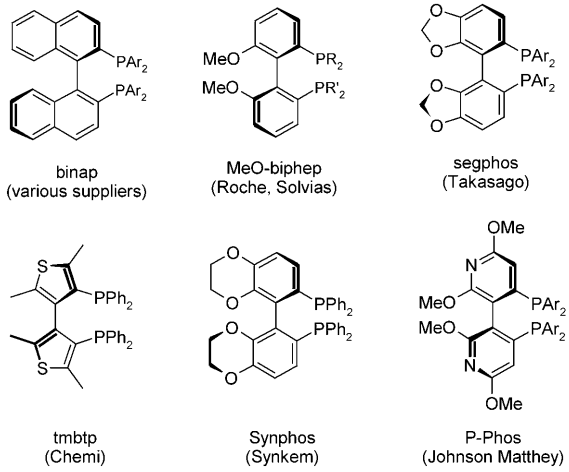
Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: Solphos (7,7′-bis(diarylphosphino)-3,3′,4,4′-tetrahydro-4,4′-dimethyl-8,8′-bis-2H-1,4-benzoxazine) is a new modular atropisomeric biaryl ligand with a very attractive activity profile. A technically feasible synthesis is described allowing the synthesis of various derivatives of enantiopure ligand on a technical scale. Very good catalytic performances have been demonstrated for the following transformations: Ru-catalyzed hydrogenation of various β-keto esters (95–99% *ee*, s/c up to 100000), of acetyl acetone (>99% *ee*, DL/*meso*>98:2), and of an exocyclic α,β-unsaturated acid (98.6% *ee*, s/c 250). In several cases, the nature of the PAr_2 moiety had a significant effect on the enantioselectivity. Furthermore, Rh and Ir Solphos complexes achieved high enantioselectivities for a novel synthesis of 3,3-disubstituted phthalides and the reductive coupling of alkynes with *N*-sulfonyl imines, respectively.

Keywords: chirality · enantioselectivity · hydrogenation · phosphine ligands · ruthenium

Introduction

Biaryl diphosphine ligands in general and binap in particular are arguably the most versatile ligands for transition- and noble-metal-catalyzed asymmetric transformations.[1] Despite the fact that a plethora of these atropisomeric ligands has been prepared, only very few are commercially available; the most important representatives are depicted in Scheme 1. As a consequence, only a handful of such ligands have been used for synthetic and/or industrial applications.[2,3] The possibility to vary the nature of the substituents at the phosphorous atoms, allowing the steric and electronic tuning of the ligands, is an important feature and is often decisive for achieving good catalyst performance. Our main motivation to undertake the preparation of novel representatives of this class of ligands was the completion of our ligand portfolio consisting mainly of ferrocene-based diphosphines and phospholanes.[4] Furthermore, existing biaryl phosphines did not always give satisfactory results, and the most effective biaryl diphosphines are patent protected and not always convenient to license.



Scheme 1. Commercially available biaryl-type phosphine ligands (*R* enantiomers).

In our assessment, the family of MeO-biphep ligands, created and owned by Roche,[5] has a very attractive performance profile and a technical synthesis has been developed.

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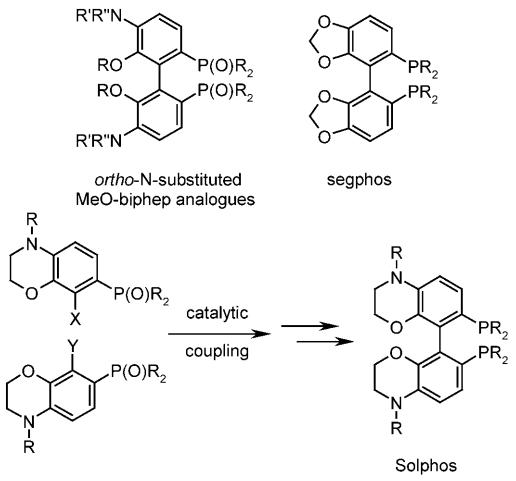
We reasoned that additional N-based substituents *ortho* to the MeO group and *para* to the phosphorus atom would make the ligand slightly more electron-rich, and should supply a handle to further tune and functionalize the ligand. Last but not least, this would provide ligands outside the numerous existing patents. When we analyzed a paper by a group at Takasago[6] on the excellent results achieved with segphos, another variation of the binap motif, we decided to concentrate on a benzoxazine structure. We assumed that a similar coupling and modular phosphine-introduction strategy as developed for the MeO-biphep ligands (Scheme 2) would be applicable. Very soon we found that things were not so simple. When we tried to couple the appropriate fragments with various X and Y substituents using a variety of catalysts, we found to our disappointment that only traces of the desired benzoxazine were formed. Since the few milligrams of the new ligand prepared by this route showed the expected excellent catalytic performance (see below), we had to devise a more promising synthetic approach.



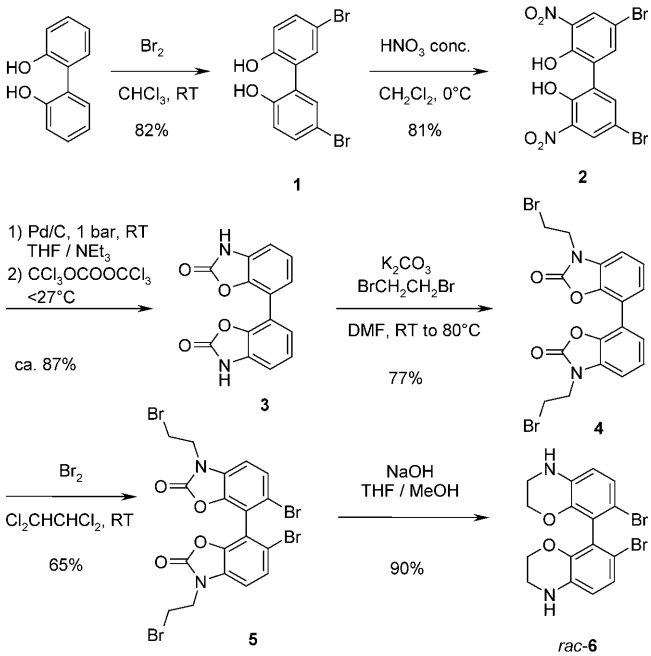
Scheme 2. Coupling strategy for Solphos.

Results and Discussion

Synthetic Approaches

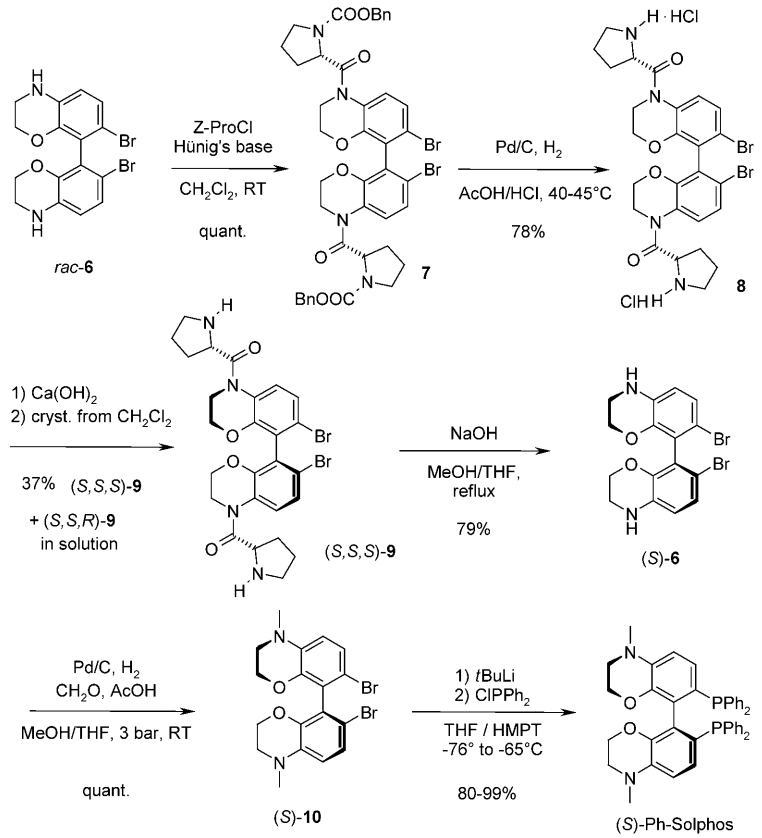
In a concerted effort involving several Solvias teams a scaleable synthesis for the Solphos ligand family was developed.[7] Since both enantiomers of the ligands were needed, the separation of a racemic intermediate by crystallization to as close to the final ligand as possible was a major consideration. Of the various variants investigated, the most convenient one, depicted in Schemes 3 and 4, was carried out on a kilogram scale.

The synthesis starts from the cheap, commercially available 2,2′-biphenyldiol. For the desired 3,3′-dinitration, the two *para* positions had to be protected first. The bromination was successful only in chloroform; other solvents afforded complex mixtures of isomers and polybrominated compounds. The nitration of **1** also required chlorinated solvents, and the best results were obtained in methylene chloride. Hydrogenation of **2** in the presence of Pd/C led to the air- and light-sensitive debrominated 3,3′-diamino biphenyldiol, which, after filtering off the Pd/C catalyst, was directly converted into the stable bis-benzoxazoledione **3**. Alkylation with 1,2-dibromoetane to **4** and subsequent bromination afforded 5 in good yield. The construction of the tetrahydrooxazine ring by opening of the oxazoledione and the subsequent nucleophilic substitution of the bromide were carried out in a one-pot reaction to give racemic **6** in crystalline form. All intermediates **1**–**6** are solids, thus allowing purification without chromatography, and the synthesis was scaled up for the multikilogram production of *rac*-**6**, the starting material for the enantiopure ligands (Scheme 4).



Scheme 3.

Since we did not succeed in finding a crystalline salt of *rac*-**6** for a classical resolution, we prepared various diastereomeric derivatives of **6**. The best results were obtained with the bis-(*S*)-proline amide **8**. The Z-protected derivative **7** (mixture of *S,S,S* and *S,S,R* diastereomers; Z = benzyloxycarbonyl) was prepared by treating *rac*-**6** suspended in dichloromethane with (*S*)-Z-ProCl, freshly prepared from (*S*)-Z-ProOH and oxalyl chloride under standard conditions at 35 °C. Hünig's base had to be added slowly to drive the reaction to completion. For deprotection, **7** was dissolved in glacial acetic acid and hydrochloric acid and hydrogenated in the presence of 5 % Pd/C at < 0.5 bar to avoid debromination or amide cleavage. After evaporation of the acetic acid the HCl adduct, **8** was isolated from ethanol by simple crystallization with seeding. Purity was essential for the crystallization to occur. The choice of $Ca(OH)_2$ was critical in the liberation of the free base **9** (mixture of *S,S,S* and *S,S,R* diastereomers). Stronger bases such as NaOH, KOH, NaOMe, or Na_2CO_3 can cleave the amide bond to give by-products which inhibit the subsequent crystallization. The diastereo-



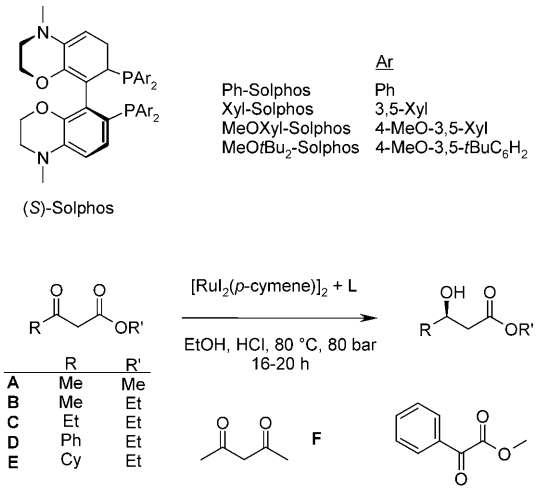
Scheme 4.

meric mixture of (*S,S,S*)-**9** and (*S,S,R*)-**9** was dissolved in the fivefold amount of dichloromethane, seeded, and stirred at room temperature for five days, resulting in a first crop of crystalline material (20% yield). Since crystallization proved to be sensitive to small impurities, the mother liquor was chromatographed, followed by a second crystallization. The total yield of (*S,S,S*)-**9** was 37%, and this was hydrolyzed at reflux with sodium hydroxide to give (*S,S,S*)-**10**. The product precipitated from solution and was washed with water. The nitrogen atom was methylated by using a reductive amination protocol with 5% Pd/C and aqueous formaldehyde in methanol/THF to give a gray foam in quantitative yield. Similar results were obtained with formaldehyde and $NaCNBH_3$.

Compounds (*S*)-**10** and (*R*)-**10** (prepared in an analogous way by using (*R*)-Z-ProCl) are the central intermediates allowing the preparation of various Solphos derivatives by Br/Li exchange and subsequent reaction with $ClPR_2$ at temperatures below −65 °C to avoid racemization. In this way, the bisphenylphosphino derivative (*S*)-Ph-Solphos (for the naming of the ligands, see Scheme 5) was obtained in 80–99% yield (for unknown reasons yields varied significantly, especially in larger batches). The resulting amorphous powder is stable under ambient conditions.

(*R*)-Ph-Solphos and both enantiomers of Xyl-Solphos, MeOXyl-Solphos, and MeO*t*Bu_2-Solphos were prepared in analogy using the corresponding $ClPAr_2$ compounds. Yields were significantly lower for the sterically more hindered derivatives.

In principle, the presence of an amine group in the Solphos ligand provides opportunities to tune the catalytic as well as the physical/technical properties. We observed, for example, that by the addition of a strong acid such as $MeSO_3H$ a Rh/Solphos complex was active in water whereas the corresponding Rh/MeO-biphep catalyst showed no activity in water under the same conditions owing to its insolubility. However, we found that increasing the size of the substituents (Me, CH_2Ph, CH_2Np) at the amine groups had only a marginal effect on the enantioselectivity for the Ru-catalyzed hydrogenation of an α,β-unsaturated acid. For this reason this issue was not pursued further.



Scheme 5. Nomenclature of Solphos ligands and hydrogenation conditions for selected ketones.

Catalytic Results

The catalytic performance of three Solphos derivatives was investigated for relevant model hydrogenation reactions (Scheme 5), and selected results are summarized in Table 1. As expected, several β-keto esters were hydrogenated with very high enantioselectivities using a Ru catalyst prepared in situ from $[RuI_2(p\text{-cymene})]_2$ (Table 1, entries 1-5). While

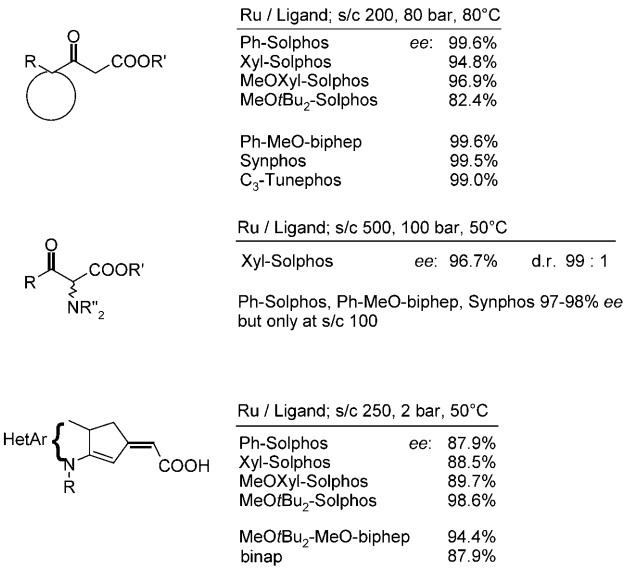
Table 1. Catalytic performance of Solphos derivatives in the hydrogenation reactions shown in Scheme 5.

Entry	Ketone	*ee* [%] Ar = Ph	*ee* [%] Ar = Xyl	*ee* [%] Ar = MeOXyl	Comments
1	**A**	97.8	98.5	99.0	Ar = Ph: s/c 100000
2	**B**	98.3	98.7	99.1	Ar = Ph: s/c 50000
3	**C**	98.2	97.3	98.0	
4	**D**	98.0	98.2	96.7	
5	**E**	96.6	96.4	95.4	
6	**F**	99.0	99.4	98.8	DL/*meso* > 98:2
7	**G**	91.6	89.8	90.0	

Reaction conditions: ethanol, s/c 200, $p(H_2)$ 60–80 bar, 80 °C.

the *ee* values were comparable to results obtained with ligands such as segphos, MeO-biphep, or Synphos,[8] the Ru/Ph-Solphos system showed extraordinarily high activity, enabling complete conversion within 20 h with substrate/catalyst ratios (s/c) up to 100000. The catalytic system is relatively insensitive to the nature of the R and R' groups in the substrate and (somewhat surprisingly) also to the nature of the Ar group of the Solphos ligand. Acetoxyacetone (**F**) is hydrogenated to 2,5-pentanediol with *ee* values around 99% and very high diastereoselectivity (Table 1, entry 6) while the α-keto ester **G** is hydrogenated with relatively modest enantioselectivities (entry 7).

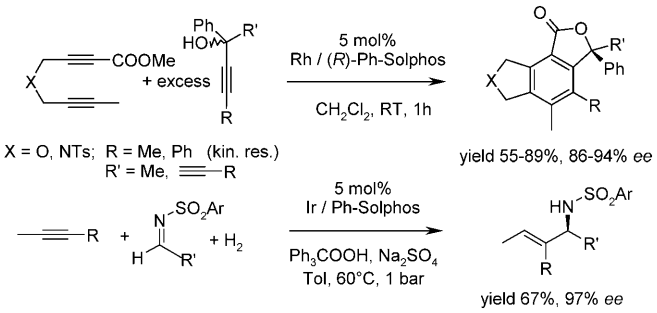
Furthermore, Solphos also showed very good performances for the hydrogenation of a number of industrial substrates, as summarized in Scheme 6 (for reasons of confidentiality, the exact structure of the substrates can not be divulged). In most cases, Solphos and MeO-biphep ligands gave the best overall performance while binap was significantly less effective. In contrast to the model studies described above, the nature of the PAr_2 moiety had a more pronounced effect in these "real-world" substrates, and especially the very bulky MeO*t*Bu_2-Solphos showed the largest



Scheme 6. Industrial applications of Solphos ligands.

deviation, either positive as for the hydrogenation of the exocyclic α,β-unsaturated acid or negative for the hydrogenation of the β-keto ester.

Solphos ligands were also applied in the two novel transformations depicted in Scheme 7. A Rh/Solphos complex was shown to be the catalyst of choice for the asymmetric one-pot transesterification and [2+2+2] cycloaddition leading to enantioenriched 3,3-disubstituted phthalides reported by Tanaka et al.[9] In the case of the unsymmetrical substrate (fivefold excess) kinetic resolution of the racemic alcohol is achieved. Very high enantioselectivities were also observed for the Ir/Solphos-catalyzed reductive coupling of alkynes with *N*-sulfonyl imines developed by the Krische group.[10]



Scheme 7. Rh- and Ir-catalyzed reactions using Solphos.

Conclusions

Solphos is a new and very effective family of biaryl diphosphine ligands. Its catalytic performance for a variety of Ru-, Rh-, and Ir-catalyzed reactions is comparable or better than that of commercially available ligands of the class of atropisomeric diphosphine ligands such as binap, MeO-biphep, segphos, or Synphos. Our results confirm that already small changes in the structure of the biaryl backbone can lead to significant differences in selectivity and/or activity. While some of these differences might be explained by differences in bite angle,[6] the electronic nature of the PAr_2 group as well as of the substituent *para* to the the PAr_2 group certainly also has an effect. However, we can not recognize a systematic trend when we compare the performance of Solphos (with one oxygen and one nitrogen substituent) with ligands with one (MeO-biphep) or two (segphos or Synphos) oxygen substituents.

The synthesis of the new ligand family was much more difficult than anticipated—again a big effect from a seemingly small structural difference. The final route is relatively complex but uses only readily available reagents, requires no expensive chromatography, and allows racemate separation right before the R and PAr_2 groups are introduced. As we have demonstrated, the synthesis can be carried out on the kilogram scale for the key intermediate **6**. However, especially the crystallization of the diastereomeric mixture is very sensitive to impurities, and also final introduction of

the PAr_2 groups is not always reproducible. For these reasons and despite the excellent catalytic results, the Solphos ligands do not meet the criteria to be included in the Solvias Ligand Portfolio at the present time.

Experimental Section

General Remarks

Unless otherwise noted, reagents were purchased either from Fluka or Merck (pa grade) and used as received. All reactions involving air-sensitive materials were conducted in an inert argon atmosphere. Chromatography was carried out with Kieselgel (Merck, 0.04–0.06 mm); HPLC was carried out on a HP Hypersyl BDS-C18 column. MS measurements were performed on a Waters ZQ 2000 ESI (desolvation; *T*: 300 °C).

Synthesis

1: A solution of Br_2 (140 mL, 2.73 mol) in 600 mL $CHCl_3$ was added over 2.5 h to 2,2′-dihydroxybiphenyl (250 g, 1.34 mol) dissolved in $CHCl_3$ (3.4 L). The reaction mixture was concentrated to 600 mL and the crystalline solid was filtered and washed twice with $CHCl_3$ (75 mL) to give dibromide **1** (379.5 g, 82 %). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.80$ (s, 2 OH), 6.85 (d, 2 H), 7.40 ppm(m, 4 H); MS: *m*/*z*: 341, 343, 345.

2: Dibromide **1** (394 g, 1.40 mol) was added to a solution of conc. HNO_3 (95.2 mL, 2.28 mol) in 3.6 L CH_2Cl_2 in portions over 25 min under cooling with ice. After stirring for 90 min at room temperature the reaction mixture was filtered and the product was washed twice with MeOH (30 mL) to give the dinitro compound **2** (400 g, 81 %) as orange crystals. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$ (d, 2 H), 8.35 (d, 2 H), 10.85 ppm (s, 2 OH); MS: *m*/*z*: 433 $[M]^+$.

3: Dibromide **2** (823 g, 1.90 mol) was dissolved in 4 L THF and triethylamine (1.06 L, 7.59 mol, 4 equiv). After addition of 62.2 g of palladium on carbon 5 %, hydrogenation was carried out to saturation in a low-pressure hydrogenation apparatus at 1 bar for 40 h (uptake of 361 L H_2, 106 %). The solution was filtered through hyflo, and half the solution was immediately processed further. Triethylamine (608 mL, 4.36 mol) was added, followed by the slow addition of triphosgene (393.9 mL, 1.33 mol) in 500 mL THF in such a way that the temperature was less than 27 °C (ca. 45 min). Then triethylamine (0.9 equiv) was added and the mixture was stirred for 1 h at room temperature. After evaporation of the solvent, the residue was treated with water/MeOH 2:1 (ca. 1 L) at 45 °C. After cooling to room temperature, HCl (37 %) was added until pH 2. The precipitate was collected by filtration and washed with MeOH, yielding bisbenzoxazole **3** (516.2 g) as a beige solid containing 13 % NEt_3·HCl (yield: 87 %). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 7.15$ (d, 2 H), 7.29 (t, 2 H), 7.35 (d, 2 H), 11.85 ppm (s, 2 H); MS: *m*/*z*: 291 $[M+Na]^+$.

4: A solution of compound **3** (510 g, 1.9 mol) in 4.0 L DMF was stirred overnight at room temperature with potassium carbonate (525 g, 3.80 mol) and 1,2-dibromoethane (1.47 L, 17 mol) and then heated to 80 °C for 1 h. The reaction mixture was evaporated and the residue was triturated overnight with water and filtered. The precipitate was washed with water and dried for 3 days at 50 °C to give as a brown solid (710 g, 77 %). ^{1}H NMR ($CDCl_3$): $\delta = 3.71$ (t, 4 H), 4.30 (t, 4 H), 7.10 (dd, 2 H), 7.32 (t, 2 H), 7.60 ppm (dd, 2 H); MS: *m*/*z*: 505 $[M+Na]^+$.

5: Bromine (225 mL, 4,39 mol) was added in one portion to a suspension of **4** (705 g, 1.46 mol) in 2.8 L tetrachloroethane. The mixture was stirred at room temperature for 21 h and then poured into 1.2 L water. After phase separation, the organic layer was washed with saturated $NHSO_3$ solution, dried with Na_2SO_4, treated with charcoal (16 g) and silica gel (200 g), and filtered. The solution was evaporated and heated to 80 °C with 2 L acetonitrile. After cooling to room temperature, the precipitate was filtered, affording **5** as a brown solid (542 g); after concentration another crop of white crystals resulted (67.7 g). Total yield of **5**: 610.3 g, 65 %. ^{1}H NMR ($CDCl_3$): $\delta = 3.70$ (t, 4 H), 4.26 (dt, 4 H), 7.13 (d, 2 H), 7.57 (d, 2 H); MS: *m*/*z*: 622 $[M+Na]^+$.

rac-**6**: Aqueous NaOH (25 %, 823 mL, 10 equiv) was added to a suspension of the tetrabromide **5** (513 g, 0.8 mol) in 3.0 L THF and 3.0 L MeOH over 15 min (exothermic, 45 °C) and then heated at reflux for 5 h. Stirring was continued overnight at room temperature. After evaporation the residue was triturated with water (1.7 L) for 10 min at 50 °C. After cooling the residue was collected and dried (14 h, 80 °C), resulting in beige crystals of *rac*-**6** (306.6 g, 90 %). ^{1}H NMR ([D$_6$]DMSO): $\delta = 3.25$ (q, 4 H), 4.00 (m, 4 H), 5.92 (s, 2 NH), 6.50 (d, 2 H), 6.91 ppm (d, 2 H); MS: *m*/*z*: 427 $[M]^+$.

7: Z-L-proline (2.02 kg, 8.1 mol) was dissolved in 12 L dichloromethane, and DMF (7 mL) was added. Oxalyl chloride (1070 mL, 12.65 mol) was added at 35 °C at a rate such that gas evolution stayed within acceptable limits (ca. 90 min). The solution was stirred for 2 h, transferred to a rotary evaporator under exclusion of humidity, and evaporated (100 mbar) until no oxalyl chloride distilled off anymore. The Z-L-proline chloride was added within 30 min at 20 °C (light cooling necessary) to *rac*-**6** (1.5 kg, 3.52 mol) suspended in 17 L dichloromethane. Then Hünig's base (1385 mL, 8.1 mol) was added over 5 h, and the mixture was stirred for 12 h. The mixture was transferred to a separation vessel and extracted twice with 3 L 2 M HCl. The combined aqueous phases were extracted with 5 L dichloromethane. The combined organic phases were washed with 10 L 5 % Na_2CO_3 solution, dried over sodium sulfate and silica gel, and evaporated completely to give **7** as a beige foam in approximately quantitative yield of (some residual dichloromethane present). MS: *m*/*z*: 907 $[M]^+$.

8: Compound **7** (1.85 kg, 0.42 mol) was dissolved in 15 L glacial acetic acid and 525 mL HCl conc. in a 50 L stainless steel autoclave with an impeller. 5 % Pd/C (200 g, Engelhard) was added, and the mixture was hydrogenated at atmospheric pressure for 24 h at 40–45 °C. The mixture was filtered and evaporated completely. To remove the acetic acid, the residue was evaporated twice with 10 L toluene and dissolved in 4 L ethanol. After evaporation of 2 L the product started to crystallize on cooling, resulting in hydrochloride salt **8** as an off-white solid (850 g, 78 %). MS: *m*/*z*: 621 $[M]^+$.

(*S,S,S*)-**9**: Hydrochloride salt **8** (1.68 kg, 2.42 mol) was dissolved in 12 L water in a 50 L separation vessel. Dichloromethane (8 L), methanol (2 L), BHT (200 mg, as radical inhibitor), and powdered $Ca(OH)_2$ (718 g, 9.7 mol) were added, and the white suspension was stirred for 60 min. Then hyflo was added, and the suspension was filtered. The organic phase was separated, and the aqueous phase was extracted with 5 L dichloromethane and 1 L methanol. The combined organic phases were dried over sodium sulfate and evaporated. The resulting foam was dissolved in 1 L dichloroethane and evaporated again to remove methanol traces. The crude product was dissolved in 8 L dichloromethane and seeded with (*S,S,S*)-**9**. The precipitate of (*S,S,S*)-**9** that formed after 5 days was collected by filtration and dried to yield colorless crystals (298 g, 20 %). The mother liquors was evaporated with 1 kg silica gel and chromatographed (8 kg silica gel, ca. 200 L dichloromethane/methanol/triethylamine 10:1:0.3, increasing polarity during elution) to give enriched fractions of (*S,S,S*)-**9** and (*S,S,R*)-**9**. A further crystallization from dichloromethane as described above yielded a second crop of crystals (248 g, 17 %). Total yield of (*S,S,S*)-**9**: 546 g, 37 %. MS: *m*/*z*: 621 $[M]^+$.

(*S*)-**6**: Compound (*S,S,S*)-**9** (660 g, 1.06 mol) was suspended in 6 L methanol and 4 L THF, and 200 mg BHT was added as a radical inhibitor. Then 30 % NaOH (655 mL) was added slowly, and the mixture was heated to reflux, resulting in dissolution of the reactant. The product started to precipitation from the reaction mixture. Water (500 mL) was added, and the organic solvents were removed on a rotary evaporator. The obtained crude product was filtered, washed thoroughly with water, and dried, yielding (*S*)-**6** as a beige solid (355 g, 79 %). ^{1}H NMR ([D$_6$]DMSO): $\delta =$ 3.25 (q, 4 H), 4.00 (m, 4 H), 5.92 (s, 2 NH), 6.50 (d, 2 H), 6.91 ppm (d, 2 H); MS: *m*/*z*: 427 $[M]^+$.

(*S*)-**10**: Compound (*S*)-**6** (450 g, 1.06 mol) was dissolved in 2.3 L methanol and 2.2 L THF. Aqueous formaldehyde (36 %, 311 mL, 3.85 equiv) and 5 % Pd/C (45 g, Engelhard) were added, and the mixture was hydrogenated at atmospheric pressure for 36 h. The suspension was filtered, and the residual water was removed by azeotropic distillation with toluene (3×2 L), yielding (*S*)-**10** as a gray foam in quantitative yield.

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^{1}H NMR ($CDCl_3$): $\delta = 2.90$ (s, 6H), 3.28 (m, 4H), 4.23 (t, 4H), 6.57 (d, 2H), 7.13 ppm (d, 2H); 477 $[M+Na]^+$.

(*S*)-Ph-Solphos: Compound (*S*)-**10** (240 g, 0.53 mol) was dissolved in 3.6 L THF and cooled to −75 °C (internal temperature). A solution of *t*BuLi (742 g, 18 % in pentane; Chemetall) was added by cannula at less than −65 °C (ca. 90 min). The mixture was stirred at −65 °C for 2 h and chlorodiphenylphosphine (232 g, 1.06 mol) diluted with 150 mL THF was added slowly at under −65 °C (ca. 45 min). The mixture was stirred for 30 min at −75 °C and then warmed to −45 °C. At this temperature the reaction was quenched with 20 mL concentrated ammonia and 50 mL water. The mixture was evaporated, and the residue was dissolved again in dichloromethane (ca. 500 mL). The cloudy solution was filtered over hyflo and evaporated. The residue was dissolved in 1100 mL THF and added at −15 °C to 7.5 L methanol, 0.5 L water, and 10 mL aqueous ammonia, resulting in the precipitation of a grainy solid that was filtered, washed with plenty of methanol/water (4:1), and dried, yielding (*S*)-Solphos (350 g, 99 %). M.p. 151 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.77$ (s, 6H), 2.85 (ddd, $^2J = 11.3$ Hz, $^3J = 3.5$ Hz, 2H), 3.13 (ddd, $^2J = 11.3$ Hz, $^3J = 3.5$ Hz, 2H), 3,41 (ddd, $^2J = 11.25$ Hz, $^3J = 7.5$, 3.5 Hz, 2H), 3.60 (ddd, $^2J = 11.3$ Hz, $^3J = 3.5$ Hz, 2H), 6.35 (d_pd, $^3J = 7.5$ Hz, $^4J = 3.5$ Hz, 2H), 6.55 (d_pd, $^3J = 15.0$, 7.5 Hz, 2H), 7.09–7.21 (m, 4H), 7.21–7.45 (m, 12H), 7.55–7.65 ppm (m, 4H); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = +30.93$ ppm; MS: *m*/*z*: 665 $[M]^+$. Elemental analysis (%) calcd for $C_{42}H_{38}N_2O_2P_2$ (664.72): C 75.89, H 5.76, N 4.21, O 4.81, P 9.32; found: C 75.68, H 5.80, N 4.22, O 4.87, P 9.18. The yields for this step were not well reproducible, varying between 40 % and 99 % for unknown reasons.

Hydrogenation

General procedure: $[RuI_2(p\text{-cymene})]_2$ (0.01 mmol) and the appropriate diphosphine ligand (0.021 mmol) were introduced into a Schlenk vessel filled with argon. Ethanol (20 mL, degassed) was subsequently added, and the solution was stirred at room temperature for 10 min. The solution was used directly for the hydrogenation. The ketone (2 mmol) and degassed ethanol (5 mL) were introduced in succession into a Schlenk vessel filled with argon. This solution and the freshly prepared catalyst solution were then transferred in succession with a steel capillary into a 50 mL steel autoclave filled with argon. The s/c (substrate/catalyst) ratio was 200. The autoclave was closed, and a pressure of 50 bar was set using four flushing cycles (pressurization with 20 bar of hydrogen). The autoclave was then heated to 80 °C, and after 30 min the reaction pressure was set to 80 bar. The autoclave mixture was stirred for 21 h. The heating was subsequently switched off, and the autoclave was cooled to room temperature. The conversion was determined by means of GC and ^{1}H NMR spectroscopy. Removal of the solvent on a rotary evaporator gave a quantitative yield of the corresponding alcohol, and the enantiomeric purity was determined by HPLC; column: Chiralcel OD-H, 250 mm, hexane/isopropanol 93:7, flow rate: 0.8 mL min^{-1}.

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