Synthesis of the Dibenzofuran-Based Diphosphine Ligand BIFAP and Its Water-Soluble Derivative BIFAPS and Their Use in Ruthenium-Catalyzed Asymmetric Hydrogenation.[±]

Arjan E. Sollewijn Gelpke,[a] Huub Kooijman,[b] Anthony L. Spek,[b] and Henk Hiemstra*[a]

Abstract: The syntheses of both enantiomers of the novel diphosphine ligand 2,2′-bis(diphenylphosphanyl)-1,1′-bidibenzofuranyl (BIFAP, **1**) and the water-soluble analogue (−)-2,2′-bis(diphenylphosphanyl)-1,1′-bidibenzofuranyl-8,8′-disulfonic acid dipotassium salt (BIFAPS, **2**) are reported. Advantage is taken of the very high regioselectivity in ring functionalisation of the 1,1′-bidibenzofuranyl backbone. These ligands are used in the ruthenium-catalysed hydrogenation of methyl acetoacetate and (*Z*)-acetamidocinnamic acid in methanol and water. In methanol both BIFAP and BIFAPS give the products in very high enantiomeric excess. With BIFAPS in water a slight drop in the *ee* of the products is observed. When BIFAPS is used with either water or methanol as the solvent the addition of a small amount of acid turns out to be essential for a fast reaction and high asymmetric induction.

Keywords: asymmetric synthesis · atropisomerism · dibenzofuran · enantioselectivity · hydrogenations · P ligands

Introduction

Atropisomeric, C_2-symmetric phosphine ligands have played a crucial role in the development of asymmetric catalysis. The first and so far most successful of these is the well-known BINAP ligand, first reported in 1980.[1] BINAP induces very high *ee*'s in several transition metal catalysed processes, such as hydrogenations, hydrosilylations, hydrocyanations, Heck reactions and enamine isomerisations.[2–4] The discovery of this ligand was followed by the development of several other atropisomeric ligands based on the biphenyl, binaphthyl or other biaryl backbones.[4–20]

The dibenzofuran skeleton has been studied extensively in heteroaromatic chemistry.[21–24] An important synthetic aspect of the dibenzofuran moiety is the directing effect of the furan oxygen on ring functionalisation. This oxygen atom activates the *para* positions towards electrophilic substitution. Thus, Friedel–Crafts acylation and alkylation, halogenation, and sulfonation give predominantly the *para*-substituted products. In contrast, treatment with nitric acid in a mixed acid system exclusively yields the *meta*-nitrated product.[23, 25] Metallation of dibenzofuran selectively occurs at the *ortho*-positions, because of the complexation of the metal with the dibenzofuran oxygen.

As a result of the selectivity in functionalisation, the dibenzofuran can serve as a skeletal basis in ligand synthesis. A few examples of dibenzofuran-based ligands for transition metal catalysis have been reported.[26–30] To the best of our knowledge, the diphosphine BIBFUP is the only atropisomeric biaryl ligand based on dibenzofuran described in literature.[18] No functionalised analogues of this ligand have been reported so far.

We recently published on the synthesis and resolution of 1,1′-bidibenzofuranyl-2,2′-diol (BIFOL).[31] This configurationally stable biaryl served as an efficient chiral auxiliary in the α-alkylation of phenylacetic acid, much like BINOL. Furthermore it was shown that this compound could be functionalised with high regioselectivity.

We then envisaged that the 1,1′-bidibenzofuranyl unit could also serve as a novel backbone for several atropisomeric diphosphine ligands. These ligands are expected to be comparable with the 1,1′-binaphthyl ligands regarding geometry and asymmetric induction, but with the additional feature of high selectivity on introducing functionality by electrophilic aromatic substitution.

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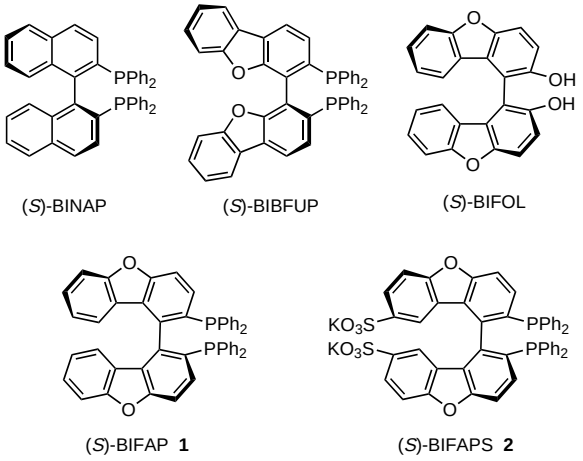
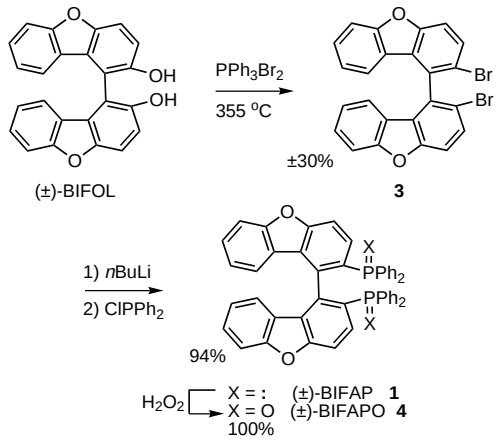


This paper reports i) the synthesis of enantiopure (*R*)- and (*S*)-2,2′-bis(diphenylphosphanyl)-1,1′-bidibenzofuranyl [(*R*)- and (*S*)-BIFAP], ii) the sulfonation of (*R*)- and (*S*)-BIFAP to yield the water-soluble analogues (*R*)- and (*S*)-2,2′-bis(diphenylphosphanyl)-1,1′-bidibenzofuranyl-8,8′-disulfonic acid dipotassium salt [(*R*)- and (*S*)-BIFAPS], iii) structural information on BIFAP derived from crystal structures and iv) a study on asymmetric ruthenium-catalysed hydrogenations in methanol and water.

Results and Discussion

Synthesis of BIFAP: The synthesis of BIFAP was accomplished in a five step procedure starting from racemic BIFOL[31] (Scheme 1), in the same manner as the original

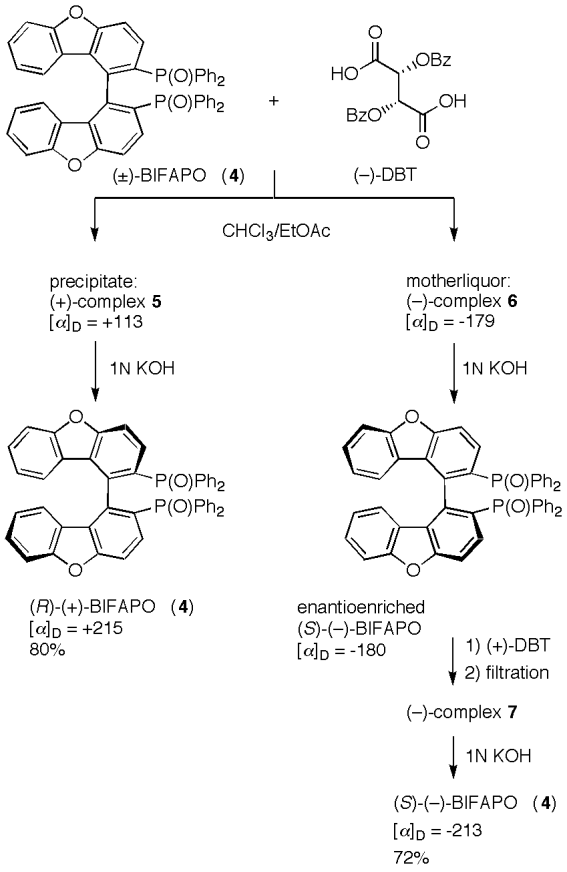


Scheme 1. Conversion of BIFOL to racemic BIFAPO.

synthesis of BINAP developed by Noyori and co-workers.[3, 4] The first aim was the synthesis of racemic diphosphine oxide BIFAPO (**4**), which after resolution and reduction should give both enantiomers of BIFAP (**1**).

The synthesis started with the transformation of racemic BIFOL into dibromide **3** (Scheme 1). This reaction turned out to be difficult, so that careful control of reaction conditions was pivotal for obtaining the desired product in a reasonable yield. Best results were obtained when preformed PPh_3Br_2 was used instead of the adduct formed in situ. In this way the presence of free bromine could be prevented. Furthermore, vigorous mixing and a gradual rise of the reaction temperature were important. The final reaction temperature had to lie between 345 and 360 °C. Lower reaction temperatures mainly gave the monobrominated product. Reaction temperatures exceeding 360 °C gave rise to tarry mixtures from which no product could be isolated. The dibromide was once obtained in a yield of 55 %, but a yield of approximately 30 % was more usual. Dibromide **3** was then lithiated by lithium-halogen exchange with two equivalents of *n*-butyllithium at −78 °C in THF. The stable 2,2′-dilithio-1,1′-bidibenzofuranyl was obtained as a green suspension. Reaction with 2.1 equivalents of $ClPPh_2$ gave racemic BIFAP (**1**) as a pale yellow, slightly oxidation-sensitive solid in high yield. Purification of the product was not necessary at this stage. Instead, it was quantitatively converted into the diphosphine oxide BIFAPO by stirring with an excess of aqueous hydrogen peroxide in THF. The oxidation was fast and crude BIFAPO (**4**) was obtained as a pale yellow solid.

Racemic BIFAPO was resolved[3, 4] with *O*,*O*-dibenzoyl tartaric acid [(+)- or (−)-DBT] in a very easy and efficient precipitation procedure, as depicted in Scheme 2. A solution



Scheme 2. Resolution of BIFAPO.

of racemic BIFAPO in chloroform and a solution of (−)-DBT in ethyl acetate were mixed. After a few seconds the solution became cloudy and precipitation of a 1:1 complex **5** of

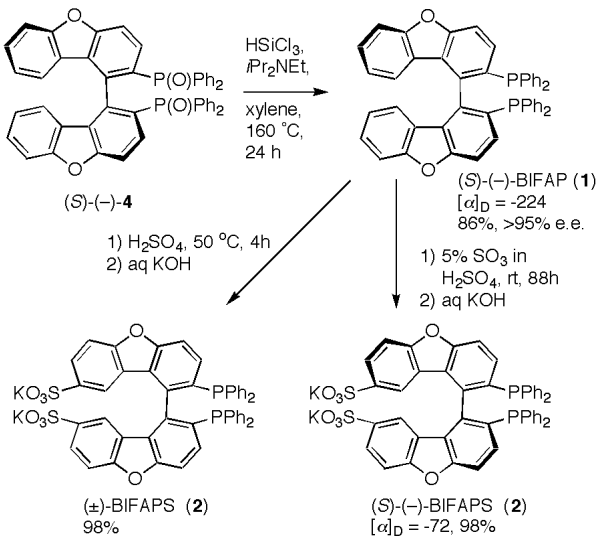
(−)-DBT and (+)-BIFAPO as a white crystalline solid was observed. This solid was filtered off, suspended in dichloromethane and treated with 1N KOH to break up the complex. Aqueous work up and evaporation of the solvent yielded pure (*R*)-(+)-BIFAPO (**4**) in high yield. The saponified DBT was washed away during the basic, aqueous work-up.

The solid **6** obtained by concentrating the mother liquor in vacuo was also treated with 1N KOH to give enantiomerically enriched (*S*)-(−)-BIFAPO, as could be concluded from the optical rotation and ^{31}P NMR spectroscopy (vide infra). This enantiomerically enriched BIFAPO was treated with one equivalent of (+)-DBT to give the 1:1 complex **7** of (+)-DBT and (*S*)-(−)-BIFAPO as a white solid. A small amount of this complex was recrystallised from chloroform/ethyl acetate to give colourless, cube-shaped crystals for X-ray analysis. The rest of the complex was treated with 1N KOH as before, to furnish enantiopure (*S*)-(−)-BIFAPO (**4**) in 72% overall yield.

The enantiopurity of the (*R*)-(+)- and (*S*)-(−)-BIFAPO was determined by ^{31}P NMR spectroscopy. The ^{31}P NMR spectrum of a 1:1 mixture of (−)-DBT and racemic BIFAPO in $CDCl_3$ showed two singlets at $\delta = 33.7$ and 33.4, which correspond to the diastereomeric (−)-DBT/(*R*)-(+)-BIFAPO and (−)-DBT/(*S*)-(−)-BIFAPO complexes, respectively. This feature could in principle make it possible to determine the enantiopurity, but the solubilities of the precipitated (−)-DBT/(*R*)-(+)-BIFAPO and the (+)-DBT/(*S*)-(−)-BIFAPO complexes in $CDCl_3$ were too low to obtain spectra with a sufficient signal to noise ratio. Therefore, small amounts of free (+)- and (−)-BIFAPO were complexed with (+)-DBT and (−)-DBT, respectively, to give the readily soluble (+)/(+) and (−)/(−) complexes. These complexes exhibited single signals in their ^{31}P NMR spectra; this proved >95% enantiomeric purity of both (*S*)-(−)- and (*R*)-(+)-BIFAPO. Furthermore, the specific rotations of (*S*)-(−)- and (*R*)-(+)-BIFAPO were of the same magnitude with opposite sign, within an error range of 1%.

The next step in the synthetic route was the reduction of BIFAPO. This was accomplished by treatment of BIFAPO with trichlorosilane in refluxing *p*-xylene.[3, 4] In this way (*S*)-(−)-BIFAPO was converted into BIFAP (**1**) in good yield, as depicted in Scheme 3. However, the enantiopurity of the product obtained from this reaction turned out to be only 70%. This was apparent from the ^{31}P NMR spectrum of a diastereomeric palladium complex (vide infra). Hence, under the applied reaction conditions, partial racemisation took place. This partial racemisation of BIFAP in the reduction with trichlorosilane was prevented by addition of ethyldiisopropylamine to the reaction mixture. This base scavenges the liberated HCl, which we believe to play a role in the racemisation. In this way enantiopure (*S*)-(−)- and (*R*)-(+)-BIFAP were obtained in high yield. The >95% enantiopurity was proven by ^{31}P NMR of a diastereomeric Pd complex (vide infra). The optical rotations of these compounds are of the same magnitude with opposite sign, within an error range of 1%.

To obtain the water-soluble analogue BIFAPS (**2**), (*S*)-(−)-BIFAP was dissolved in sulfuric acid and stirred at room temperature for more than two days. After this period

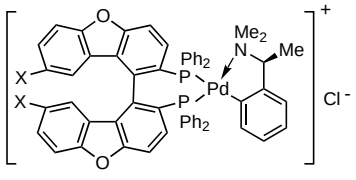


Scheme 3. Reduction and sulfonation.

sulfonation was still incomplete; this was concluded after isolation of a considerable amount of monosulfonated product. Raising the reaction temperature to 50 °C gave BIFAPS after 4 h in 98% yield. Surprisingly, a virtually racemic product was obtained, as determined by ^{31}P NMR spectroscopy (vide infra). Running the reaction at lower temperatures and with a stronger sulfonating reagent prevented this racemisation. After 88 h at room temperature with 5% SO_3 in H_2SO_4 enantiopure (*S*)-(−)-BIFAPS was obtained almost quantitatively as an off-white solid. (*R*)-(+)-BIFAP was converted to (*R*)-(+)-BIFAPS in the same way.

The solubility of BIFAPS in water was determined to be 90 g L^{-1}. In warm water more BIFAPS could be dissolved, but on cooling the solution solidified to form a gel.

Determination of enantiopurity: The enantiopurity of BIFAP and BIFAPS was determined by ^{31}P NMR spectroscopy of the diastereomeric complexes **8** and **9**. These palladium complexes were prepared by stirring BIFAP or BIFAPS with one equivalent of di(μ-chloro)bis[(*S*)-dimethyl(α-methylbenzyl)aminato-C^2N]dipalladium(II) in methanol for about 15 min at room temperature.[32] The (*S*,*S*) and (*R*,*S*) diastereomers of both **8** and **9** showed two separate sets of doublets in the ^{31}P NMR spectrum. From the integrals the enantiopurity of the diphosphines could be calculated. The appearance of a single set of doublets confirmed a >95% enantiopurity of the diphosphines.



8 X = H
9 X = SO_3K

Racemisation of the 1,1′-bidibenzofuranyl backbone: The optical activity of biaryl compounds originates from the

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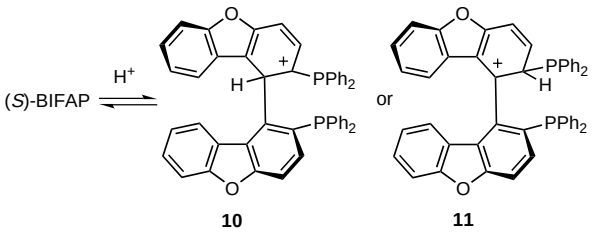
hindered rotation about the central C–C bond. Sufficient steric hindrance is essential for optical stability at room temperature and in practice most 2,2′,6,6′-tetrasubstituted biaryls meet this requirement. However, some reports on loss of optical activity of these type of compounds are known.[33–36] As was discussed previously, partial racemisation of the 1,1′-bidibenzofuranyl skeleton was observed in two different steps of the synthesis. We believe that strongly acidic conditions together with elevated temperatures caused this unexpected and remarkable behaviour.

We expect the rotational barriers of 1,1′-bidibenzofuranyl-2,2′-substituted compounds to be at least of the same magnitude as the 1,1′-binaphthyl-2,2′-substituted compounds and probably larger, because of the larger steric bulk of the dibenzofuran units. To account for rotation, and hence racemisation, a much more flexible intermediate has to be formed in which the rotational barrier is lowered drastically. Two conceivable ways in which this might be accomplished are 1) tilting one or both dibenzofuran planes by protonation at C1 and/or C1′ and 2) bending away one or both PPh_2 groups by protonation at C2 and/or C2′. Structures **10** and **11** demonstrate these situations (Scheme 4). The protonated

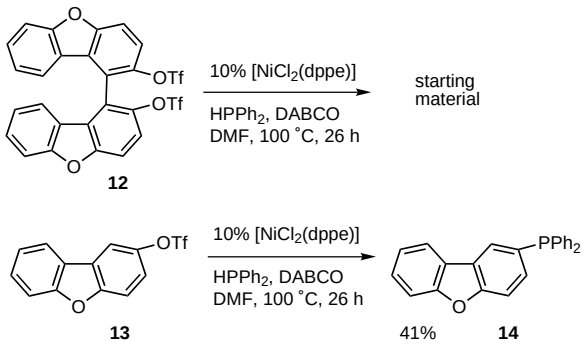


Scheme 4. Racemisation intermediates.

carbons C1 and C2 are changed from sp^2 to sp^3 hybridisation, giving rise to a greater flexibility in the molecule, causing the observed racemisation.

A shorter route: The described syntheses of BIFAP and BIFAPS are practical. However, a disadvantage is the difficult conversion of BIFOL to dibromide **3**. Therefore, we tried to circumvent this reaction by the direct transformation of ditriflate **12** to BIFAP, similar to a recently reported short route to BINAP.[17, 37] Unfortunately, the nickel-catalysed phosphorylation of the ditriflate **12**[31] could not be accomplished. Even after prolonged reaction times, raised reaction temperatures, use of stoichiometric amounts of [$NiCl_2$(dppe)] and use of other catalysts (i.e., $NiCl_2$, $Pd(OAc)_2$/dppp) the starting material was recovered almost quantitatively. The oxidative addition of the triflate to the nickel is probably sterically hindered in **12**. In contrast, the more accessible triflate group in 2-(trifluoromethanesulfonyloxy)dibenzofuran **13**[31] is reactive and gives monophosphine **14** in moderate yield (Scheme 5).

Crystal structures: Structural information about BIFAP, such as absolute configuration and geometry, was obtained from crystal structures of the free ligand (*S*)-(−)-**1**, of the BIFAPO/DBT complex **7**, and of [(bifap)$PdCl_2$] (**15**).



Scheme 5. Direct introduction of diphenylphosphine.

The 1:1 complex **7** of (*S*)-(−)-BIFAPO and (+)-(2*S*,3*S*)-DBT was crystallised from ethyl acetate/chloroform yielding colourless crystals, suitable for X-ray analysis. The crystal structure, depicted in Figure 1, unambiguously proved the absolute configuration of (−)-BIFAPO to be *S* with respect to the known configuration of (+)-DBT. The two dibenzofuran units in BIFAPO are positioned almost perpendicular to each other with an angle of 89.6(2)° between both planes. Furthermore, it can be seen that the interaction between neighbouring molecules in the complex originates from hydrogen bonding between the carboxylic acid and the phosphine oxide moieties. The BIFAPO molecules are linked in this way by DBT units to form strands of regularly alternating BIFAPO and DBT molecules. The distance between the carboxylic oxygen and the oxygen on the phosphorus is 2.50 Å. A similar polymeric structure has been reported for a complex of a BINAP derivative and DBT. It is believed that the low solubility of this type of complex can be attributed to their linear polymeric structures.[5] Remarkably, in contrast to BINAPO, derivatives of BINAPO, and other biaryl phosphine oxides, the stereochemical correlation of DBT and BIFAPO is opposite. The *S* enantiomer of BIFAPO precipitates with (+)-DBT, while the *S* enantiomer of BINAPO precipitates with (−)-DBT.[4, 11, 20]

To investigate the geometry of BIFAP, (*S*)-(−)-BIFAP was recrystallised from EtOAc and pentane to provide crystals suitable for X-ray analysis. In the crystal structure, depicted in Figure 2, an almost perpendicular positioning of the two dibenzofuran units is observed. The angle between these two planar moieties is 81.40(6)°. The P(1)–P(2) distance is 3.8913(8) Å. Furthermore, it is clear that the two phenyl rings at each phosphorus atom are inequivalent. The two equatorial phenyls A and B point away from the 1,1′-bidibenzofuranyl backbone. The two axial phenyl groups C and D are positioned more or less parallel with the counter dibenzofuran unit. We believe that the equatorial phenyls A and B dictate the chiral induction.[42]

Unfortunately, the crystal structure data of free BINAP are not included in the Cambridge Crystallographic Database. Therefore, comparison of structural features of BIFAP and BINAP, based on the crystal structures of the free ligands, was not readily possible. This problem could be overcome by determining the crystal structure of the [(bifap)$PdCl_2$] complex. The crystal structure of [(binap)$PdCl_2$] is published,[42] making possible a comparison of both ligands.

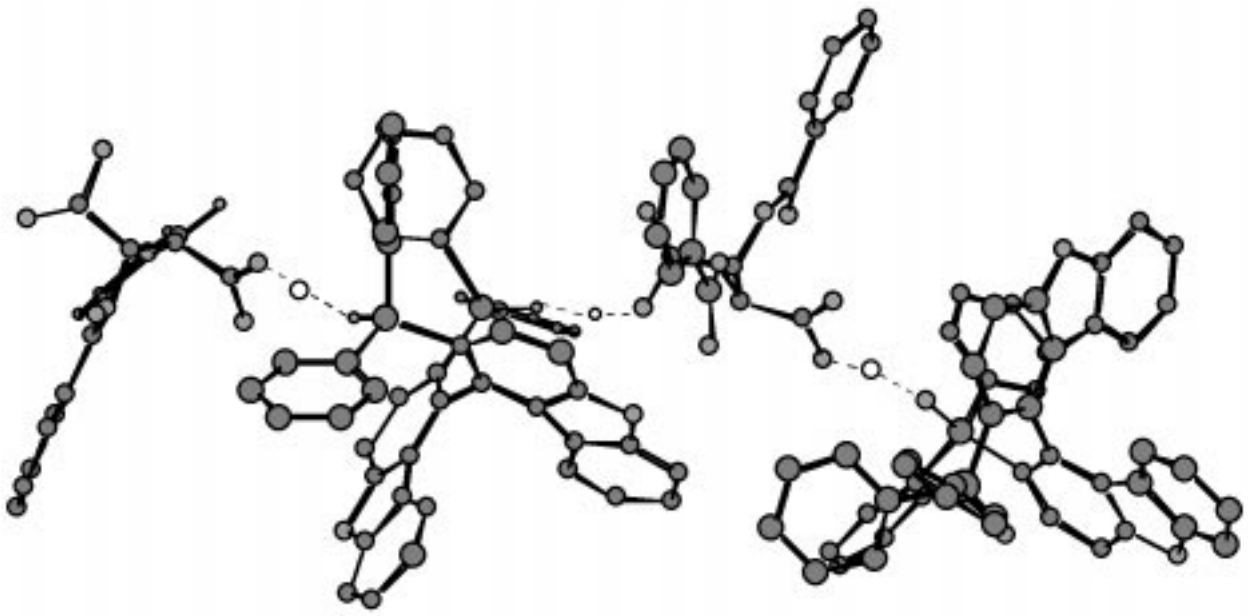


Figure 1. Chem 3D view of the crystal structure of the 1:1 (S)-(−)-BIFAPO/(+)-(2S,3S)-DBT complex **7**. The crystal consists of polymeric chains of alternating BIFAPO and DBT molecules, connected by hydrogen bonds.

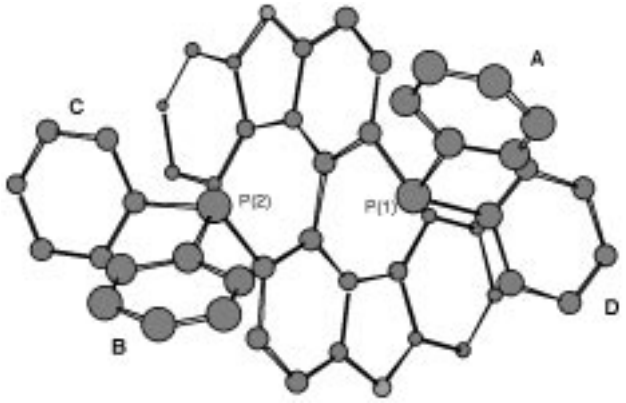


Figure 2. Chem 3D view of the crystal structure of (S)-(−)-**1**.

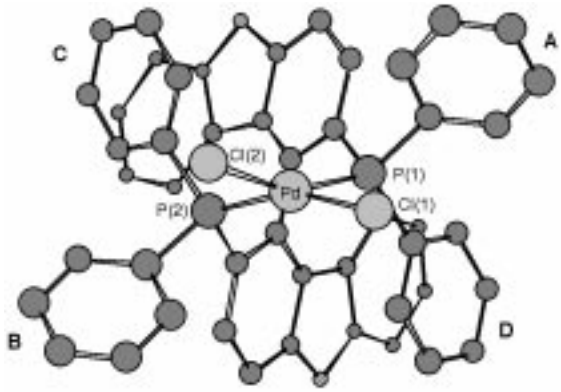


Figure 3. Chem 3D view of the crystal structure of racemic **15**.

Racemic [(bifap)$PdCl_2$] complex (**15**) was synthesised by mixing solutions of racemic BIFAP and $PdCl_2(MeCN)_2$ in benzene at room temperature. An orange precipitate was formed and this solid was recrystallied by slow diffusion of pentane into dichloromethane. Racemic **15** was obtained as orange plates, suitable for X-ray analysis.

As in the crystal structure of the free ligand, two of the phenyl rings (C and D) have an axial orientation and apparent arene–arene interactions with the parallel dibenzofuran moiety (Figure 3). The other two phenyls (A and B) have an equatorial orientation, extruded towards the coordination sites of the chlorine atoms. The steric bulk of these phenyls causes the chlorine atoms to be situated above and below the P(1)–Pd–P(2) plane, giving rise to a distorted square-planar coordination of the palladium atom. Most bond lengths, angles, and other structural features in **15** are comparable with those found in the [(binap)$PdCl_2$] complex[42] and other dichloropalladium complexes.[43] However, the central, connecting C–C bond is somewhat longer in **15** (1.499(3) Å) than in [(binap)$PdCl_2$] (1.48(1) Å). The P(1)–Pd–P(2) bite angle of 94.39(2)° in **15** is also larger than the corresponding 92.69(8)° angle in (binap)$PdCl_2$.

When the crystal structures of **15** and (*S*)-BIFAP are compared (Figures 3 and 2), it becomes clear that the angle between the two dibenzofuran planes is much smaller in **15** than in the free ligand (76.24(3)° and 81.40(2)°, respectively). The P(1)–P(2) distance in **15** is 3.2937(10) Å, versus 3.8913(8) Å in the free BIFAP . It can be concluded that chelation to the palladium atom causes squeezing of the 1,1′-bidibenzofuranyl unit. Furthermore, the positioning of the axial and equatorial phenyl rings in **15** is different from BIFAP. In the free ligand the lone pairs of the phosphorus atoms point diagonally in opposite directions and are not properly positioned for bidentate ligation. To allow chelation of the lone pairs of both phosphorus atoms to the palladium atom, the lone pairs have to be in the same plane. Hence, rotations around the P(1)–C(1) and P(2)–C(24) bonds are necessary. As a result, the axial phenyl rings C and D more closely overlap the parallel dibenzofuran moieties, while the equatorial rings A and B are bent backwards.

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Asymmetric hydrogenations: Aqueous-phase asymmetric hydrogenations are the best documented asymmetric, aqueous-phase, transition metal catalysed reactions in literature.[10, 14, 44–53, 55, 56] The aqueous-phase hydrogenations of olefins, ketones, α-and β-unsaturated acids and imines have been reported. Generally, sulfonated analogues of successful chiral ligands are used. The enantioselectivities observed in aqueous-phase hydrogenations are usually lower than the enantioselectivities of the same transformations in organic media, although some exceptions are known. An overview of the results obtained for aqueous-phase hydrogenations up to 1997 has been published.[56]

Using the diphosphines BIFAP and BIFAPS as ligands, we investigated the ruthenium-catalysed hydrogenations of (*Z*)-acetamidocinnamic acid[48, 57] and methyl acetoacetate[53, 59, 60] in a stepwise fashion by 1) running the reaction in methanol with BINAP as the ligand according to the literature, 2) running the reaction in methanol with BIFAP, 3) running the reaction in methanol with BIFAPS and 4) running the reaction in water or a two-phase system with BIFAPS.

Following a known procedure[59] a mixture of complexes $[RuCl_2((R)\text{-binap})(dmf)_2]$ and $[\{RuCl_2((R)\text{-binap})(dmf)\}_n]$ (**16**) was prepared. A mixture of complexes $[RuCl_2((S)\text{-bifap})(dmf)_2]$ and $[\{RuCl_2((S)\text{-bifap})(dmf)\}_n]$ (**17**) was prepared in a similar way. The complex [RuCl(benzene)((*R*)-bifaps)]Cl (**18**) was prepared by stirring $[\{RuCl_2(benzene)\}_2]$ and (*R*)-BIFAPS in methanol at room temperature.[61] After filtration and removal of the solvent in vacuo, **18** was obtained as an orange solid. These complexes were used without further purification.

The hydrogenations of (*Z*)-acetamidocinnamic acid were carried out in a constantly shaken pyrex flask at 4 atm H_2 pressure and room temperature. The hydrogenations of methyl acetoacetate were carried out in a stainless steel autoclave, equipped with a liquid/gas stirring rod, at 100 atm H_2 pressure and 70 °C. As catalyst precursors two equivalents of the ligand were used with either the preformed ruthenium complexes **16**, **17** or **18** or complexes of $[\{RuCl_2(benzene)\}_2]$ formed in situ. The solvents used were degassed by passing argon through them for about 15 min. The conversions were determined by ^{1}H NMR spectroscopy. The enantiomeric excesses of the products were determined by chiral HPLC or by measuring optical rotations. The results are given in Tables 1 and 2.

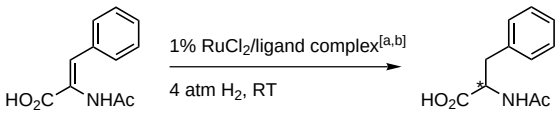
The hydrogenation of (*Z*)-acetamidocinnamic acid (Table 1) with BINAP resulted in a product with high *ee*, similar to the literature value (entry 1).[49] The hydrogenations with BIFAP showed a somewhat lower enantioselectivity (entry 2). Use of BIFAPS as the ligand resulted in product with 72 % *ee* in methanol as well as in a 1:1 water/ethyl acetate mixture. (entries 3 and 4). The reaction rate in water/ethyl acetate was low; this was most likely due to the poor mixing of (*Z*)-acetamidocinnamic acid, catalyst and hydrogen gas in this three-phase system.

The hydrogenation of methyl acetoacetate (Table 2) with BINAP proceeded as described in the literature[59] (entry 1). The reaction with BIFAP yielded the product in 100 % *ee* (entry 2). When BIFAPS was used as the ligand (entries 3 and 4), an intriguing observation was made. When the reaction was run under identical conditions (entry 3) as the reactions with BINAP and BIFAP, incomplete conversion was observed. After prolonged reaction times (68 h) 82 % conversion of the starting material was observed. The *ee* of the product was only 11 %. Because the medium in the previously described hydrogenation of (*Z*)-acetamidocinnamic acid in methanol is intrinsically acidic, we decided to add some acid to the reaction mixture. After addition of 1 % of sulfuric acid, the results drastically improved (entry 4) and the product was obtained in 100 % *ee*.

This spectacular effect from the addition of a small amount of acid was also observed in the reactions run in water (entries 5, 6 and 7). Without acid the reactions were slow and the enantioselectivities low (entry 5), but addition of 1 % of H_2SO_4 or HCl resulted in high reaction rates (entries 6 and 7). The products were obtained with high enantiomeric excess (86 % and 85 %, respectively). This drop in enantiomeric excess on going from methanol to water is in line with literature findings.[46, 47]

In order to test whether the presence of potassium sulfonate groups negatively affects the reactions, we performed the reaction with BIFAP in methanol with the addition of potassium tosylate to the mixture. However, the reaction

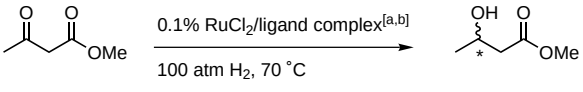
Table 1. Hydrogenation of (*Z*)-acetamidocinnamic acid.



	ligand	solvent	time [h]	conversion[c]	*ee*[d]
1	(*R*)-(+)-BINAP	MeOH	24	100 %	87 % (*R*)
2	(*S*)-(−)-BIFAP	MeOH	100	100 %	82 % (*S*)
3	(*R*)-(+)-BIFAPS	MeOH	48	100 %	72 % (*R*)
4	(*R*)-(+)-BIFAPS	H_2O/EtOAc	48	18 %	72 % (*R*)

[a] The complexes **16**, **17** and **18** were used as the catalyst precursor. [b] Reactions were performed on 1 mmol scale in 0.1 M solutions. [c] Conversions were determined with ^{1}H NMR. [d] *ee*'s of the products were determined with chiral HPLC and absolute configurations are given in parentheses.

Table 2. Hydrogenation of methyl acetoacetate.



	ligand	solvent	additive	time [h]	conversion[c]	*ee*[d]
1	(*R*)-(+)-BINAP	MeOH	–	2	100 %	99 % (*R*)
2	(*S*)-(−)-BIFAP	MeOH	–	2	100 %	100 % (*S*)
3	(*R*)-(+)-BIFAPS	MeOH	–	68	82 %	11 % (*R*)
4	(*R*)-(+)-BIFAPS	MeOH	1 % H_2SO_4	2	100 %	100 % (*R*)
5	(*R*)-(+)-BIFAPS	H_2O	–	2	58 %	22 % (*R*)
6	(*R*)-(+)-BIFAPS	H_2O	1 % H_2SO_4	2	100 %	86 % (*R*)
7	(*R*)-(+)-BIFAPS	H_2O	1 % HCl	2	100 %	85 % (*R*)
8	(*S*)-(−)-BIFAP	MeOH	0.4 % TsOK	2	100 %	100 % (*S*)

[a] Both preformed complexes **16**, **17**, **18** (procedure A, all entries), and complexes formed in situ (procedure B, entries 1, 2, 4 and 6) were used as the catalyst, with identical results where both procedures were compared. [b] Reactions were performed in duplo on 17 mmol scale in 1 M solutions. [c] Conversions were determined by ^{1}H NMR. [d] See ref. [62], absolute configurations are given in parentheses. [e] See ref. [63].

was not affected and the product was obtained in the same, very high enantiomeric excess (entry 8).

Although there are some reports on certain beneficial effects of the addition of acid in hydrogenations,[67, 68] the nature of these effects remains unclear. Possibly, the acid is required for breaking up catalytically inactive, trinuclear ruthenium-species formed under the reaction conditions.[69] Studies on the nature of the acid effect are currently underway.

Conclusion

From the reported results the following conclusions can be drawn.

1) Both enantiomers of the atropisomeric diphosphine BIFAP, based on the novel 1,1′-bidibenzofuranyl backbone, have been synthesised. The absolute configuration was determined from the X-ray analysis of a single BIFAPO/DBT complex. The conformation of BIFAP is similar to BINAP, as concluded from comparison of the crystal structure of [(bifap)$PdCl_2$] with the crystal structure of [(binap)$PdCl_2$], known in the literature.
2) The direct sulfonation of BIFAP to obtain the water-soluble BIFAPS is completely regioselective and high yielding. A single disulfonate is obtained without phosphine oxide formation. Herewith the value of the dibenzofuran skeleton as a substitute for the phenyl ring to allow ready and regioselective sulfonation is established.
3) These ligands allow investigation of transition metal catalysed asymmetric reactions in organic and aqueous media.
4) BIFAP and BIFAPS gave high *ee*'s in the ruthenium-catalysed hydrogenations of (*Z*)-acetamidocinnamic acid and methyl acetoacetate in methanol, similar to BINAP. When water is used as the solvent the enantioselectivity is slightly lower.
5) The rate and asymmetric induction in the hydrogenation of methyl acetoacetate with BIFAPS in water as well as methanol is considerably enhanced by the addition of a small amount of acid to the reaction mixture. Studies on the nature of this effect are currently underway.

Experimental Section

General information. All reactions were carried out under an inert atmosphere of dry nitrogen and followed by TLC, except for the sulfonation reactions. Glassware was flame dried before use. Standard syringe techniques were applied to transfer dry solvents and reagents. Infrared (IR) spectra were obtained from $CHCl_3$ solutions or NaCl plates with a Perkin–Elmer 1310 spectrophotometer. ^{1}H NMR and ^{13}C NMR (APT) spectra were determined in $CDCl_3$ (unless stated otherwise) with a Bruker ARX 400 (400 and 100.6 MHz, respectively) spectrometer. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. ^{31}P NMR spectra were recorded on a Bruker 300 AMX NMR (121.5 MHz) spectrometer. Chemical shifts (δ) are given in ppm downfield from 85 % H_3PO_4. Mass spectra and accurate mass measurements were carried out with a VG Micromass ZAB-2HF instrument. Elemental analyses were performed on a Vario EL. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in a 1 dm cell (2 mL) in the indicated solvent at the indicated concentration, temperature, and wavelength. Melting points are uncorrected. Flash chromatography was performed as described in the literature by use of Acros silica gel (0.035–0.07 mm, ca. 6 nm pore diameter).[70] THF was freshly distilled from sodium/benzophenone ketyl under a nitrogen atmosphere. CH_2Cl_2 was distilled from CaH_2 under a nitrogen atmosphere and stored over 4 Å molecular sieves. Ethyl acetate and petroleum ether (PE, bp 60–80 °C) were distilled before use. Benzene and *p*-xylene were distilled from CaH_2 and stored over 4 Å molecular sieves under nitrogen. MeOH and methyl acetoacetate were distilled before use and stored under nitrogen. DMF was distilled from 4 Å molecular sieves before use and stored under nitrogen. *i*Pr_2NEt and Et_3N were distilled from KOH pellets and stored over KOH pellets under nitrogen. $ClPPh_2$ was vacuum distilled before use and stored under nitrogen at 4 °C. All other chemicals were used as obtained from Aldrich or Acros. For sulfonations 99.999 % pure sulfuric acid was used. Hydrogenation experiments were performed with 99.999 % hydrogen gas, purchased from Air Liquide.

2,2′-Dibromo-1,1′-bidibenzofuranyl (3): Racemic BIFOL[31] (8.5 g, 23.2 mmol) and triphenylphosphine dibromide (19.6 g, 46.4 mmol) were thoroughly mixed in a 100 mL three-neck flask. While mechanically stirred, the mixture was heated to 240 °C over 20 min. After 10 min at this temperature, the mixture was further heated to 355 °C over 20 min. [Careful control of the reaction temperature is essential in this reaction. When the mixture was stirred at temperatures lower than 355 °C, the monobrominated product, 2-bromo-2′-hydroxy-1,1′-bidibenzofuranyl, mainly was isolated. When the temperature was raised too quickly or when the temperature exceeded 360 °C, the yield dropped dramatically.] After being stirred for 1 h at 355 °C, the mixture was cooled to about 200 °C and approximately 5 g of Celite was added. After cooling to room temperature, the dark brown mass was extracted with CH_2Cl_2 and filtered over silica gel. The dark filtrate was stirred with 30 % H_2O_2 for 30 min to oxidise the triphenylphosphine. The organic layer was washed with water and evaporated. The resulting dark brown mass was extracted with EtOAc/PE 1:3 (6 × 200 mL). The organic layers were filtered over silica gel, combined and evaporated. The resulting off-white solid was recrystallised from EtOAc/PE 1:4, to give 3.5 g of white crystalline solid (31 %). M.p. 233–237 °C; ^{1}H NMR: δ = 6.68 (d, J = 7.8 Hz; H9, H9′), 6.96 (dt, J = 7.8, 0.5 Hz; H8, H8′), 7.34 (dt, J = 8.4, 0.8 Hz; H7, H7′), 7.53 (d, J = 8.3 Hz; H6, H6′), 7.67 (d, J = 8.7 Hz; H3, H3′), 7.90 (d, J = 8.7 Hz; H4, 4′); ^{13}C NMR: δ = 111.5, 113.2, 116.8, 121.4, 122.8, 123.1, 124.4, 127.8, 130.8, 133.0, 155.2, 156.5; IR (NaCl) $\tilde{\nu}$ = 3070, 1460, 1412, 1219, 1026 cm^{-1}; HRMS (FAB+): calcd for $C_{24}H_{12}O_2{}^{81}Br_2$ $[M+H]^+$ 493.9163, found 493.9163.

Spectral data of 2-bromo-2′-hydroxy-1,1′-bidibenzofuranyl, isolated from a product mixture by flash chromatography (silica gel, EtOAc/PE 1:2) after incomplete reaction. ^{1}H NMR: δ = 4.95 (br s, OH), 6.61 (dd, J = 7.8, 0.6 Hz, 1H), 6.66 (dd, J = 7.9, 0.6 Hz, 1H), 6.92 (dt, J = 8.0, 0.8 Hz, 1H), 6.97 (dt, J = 8.1, 0.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.30 (dt, J = 8.4, 1.3 Hz, 1H), 7.35 (dt, J = 8.5, 1.3 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H).

2,2′-Bis(diphenylphosphanyl)-1,1′-bidibenzofuranyl (BIFAP, 1): Compound **3** (1.78 g, 3.62 mmol) was azeotropically dried with dry toluene (2 × 10 mL) and dissolved in THF (26 mL). At −78 °C, *n*BuLi (4.53 mL, 1.6 M in hexanes) was slowly added to the solution. A yellow solution was obtained that slowly turned into a green suspension. After stirring for 2 h at −78 °C, chlorodiphenylphosphine (1.30 mL, 7.24 mmol) was slowly added. The mixture was allowed to warm to room temperature overnight. The resulting light yellow solution was worked up with CH_2Cl_2/water, washed with brine and water and dried over $MgSO_4$. After evaporation of the solvents, a light yellow solid was obtained, which was triturated with methanol (5 mL). Filtration yielded 2.34 g of light yellow crystalline solid (92 %). M.p. 257–260 °C; ^{31}P NMR: δ = −16.6; ^{1}H NMR: δ = 6.02 (d, J = 7.7 Hz; H9, H9′), 6.62 (t, J = 7.5 Hz; H8, H8′), 6.90 (m, 4H; PhH-*meta*), 6.99 (m, 6H; PhH-*ortho*+*para*), 7.16 (m; 10PhH, H7, H7′), 7.40 (d, J = 8.2 Hz; H6, H6′), 7.52 (dt, J = 8.4, 1.3 Hz; H3, H3′), 7.68 (d, J = 8.5 Hz; H4, H4′); ^{13}C NMR: δ = 110.8, 111.8, 122.1, 122.4, 123.2, 123.8 (t, J = 5.5 Hz), 128.0, 128.3, 131.6 (dd, J = 5.6, 3.4 Hz), 132.8 (t, J = 10.0 Hz), 133.6, 134.3 (t, J = 11.2 Hz), 137.1 (dd, J = 7.2, 5.0 Hz), 137.8 (dd, J = 6.6, 4.9 Hz), 140.0 (m), 156.2, 156.5; IR (NaCl): $\tilde{\nu}$ = 3070, 1584, 14.60, 1418, 1193, 908 cm^{-1}; HRMS (FAB+): calcd for $C_{48}H_{33}O_2P_2$ $[M+H]^+$ 703.1956, found 703.1981.

2,2′-Bis(diphenylphosphinoyl)-1,1′-bidibenzofuranyl (BIFAPO, 4): A 30 % aqueous H_2O_2 solution (2 mL) was added to a solution of BIFAP (2.34 g, 3.33 mmol) in THF (20 mL) at 0 °C. After stirring for 30 min, the reaction was worked up with CH_2Cl_2, water and brine. After drying over $MgSO_4$ the solvents were evaporated and a light yellow solid was obtained (2.44 g,

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100%). M.p. 203–210°C; ^{31}P NMR: $\delta = 30.2$; ^{1}H NMR: $\delta = 5.86$ (d, $J =$ 7.5 Hz; H9, H9′, 6.49 (t, $J = 7.3$ Hz; H8, H8′), 7.03 (dt, $J = 7.6$, 2.8 Hz; 4PhH), 7.13 (dt, $J = 8.4$, 1.2 Hz; H7, H7′), 7.13 (m; 2PhH), 7.25 (m; 4PhH), 7.38 (m; 6PhH, H6, H6′), 7.56 (dd, $J = 12.6$, 8.8 Hz, H3, H3′), 7.65 (dd, $J =$ 8.6, 1.9 Hz; H4, H4′), 7.73 (m; 4PhH); ^{13}C NMR: $\delta = 110.7$, 110.8, 122.0, 122.4, 123.2, 124.0 (d, $J = 12.7$ Hz), 125.5 (d, $J = 105.2$ Hz), 126.7, 127.5 (d, $J = 11.8$ Hz), 127.9 (d, $J = 12.4$ Hz), 130.7 (d, $J = 2.5$ Hz), 131.1 (d, $J =$ 2.5 Hz), 131.8 (d, $J = 9.3$ Hz), 132.0, 132.5 (d, $J = 10.5$ Hz), 132.8 (d, $J =$ 102.6 Hz), 134.1 (d, $J = 105.2$ Hz), 134.2, 138.5 (dd, $J = 8.2$, 3.8 Hz), 156.1, 157.0 (d, $J = 2.8$ Hz); IR (NaCl): $\tilde{\nu} = 3053$, 1575, 1436, 1193, 1118 cm^{-1}; HRMS (FAB+): calcd for $C_{48}H_{33}O_4P_2$ $[M+H]^+$ 735.1854, found 735.1911.

Resolution of BIFAPO (4): A solution of (−)-*O*,*O*′-dibenzoyl tartaric acid (1.06 g, 2.80 mmol) in EtOAc (50 mL) was added to a stirred solution of (±)-BIFAPO (**4**) (2.06 g, 2.80 mmol) in $CHCl_3$ (20 mL). After approximately 1 min, a white precipitate was formed. This 1:1 complex **5** of (*R*)-(+)-BIFAPO and (−)-DBT was filtered off and dried in vacuo. M.p. 217–222°C; ^{31}P NMR: $\delta = 33.7$; ^{1}H NMR: δ 3.0 (brs; 2COO*H*), 5.87 (d, $J =$ 7.5 Hz; H9, H9′), 5.90 (s; 2H–COBz), 6.56 (dt, $J = 7.3$, 0.7 Hz; H8, H8′), 6.88 (m; 4H), 7.08 (dt, $J = 7.4$, 0.9 Hz, 2H), 7.17 (m, 6H), 7.26 (m, 4H), 7.36 (m, 8H), 7.53 (m, 2H), 7.60 (dd, $J = 7.4$, 1.6 Hz, 4H), 7.68 (ddd, $J = 12.4$, 7.1, 1.3 Hz, 4H), 8.03 (d, $J = 7.1$ Hz, 4H). The mother liquor was evaporated to obtain a light-yellow solid **6**. ^{31}P NMR: $\delta = 33.4$, 33.7 in a ±10:1 ratio.

Complex **5** was suspended in CH_2Cl_2 (30 mL) and stirred with 1N aqueous KOH (30 mL). After 1 h the white solid was dissolved completely. The organic layer was separated, washed with brine and water and dried over $MgSO_4$. After evaporation, (*R*)-(+)-BIFAPO was obtained as a white solid (824 mg, 80%). M.p. 189–191°C; $[\alpha]_D^{20} = +215$ ($c = 1$ in $CHCl_3$); Spectral data were identical to racemic BIFAPO. To check the enantiopurity of the product by ^{31}P NMR, (*R*)-(+)-BIFAPO (12.6 mg) and (+)-DBT (6.5 mg) were mixed in $CDCl_3$. ^{31}P NMR: $\delta = 33.4$ (single signal).

The light yellow solid **6** was dissolved in CH_2Cl_2 (30 mL) and stirred with aqueous KOH (1N, 30 mL). After 30 min the organic layer was separated, washed with brine and water and dried over $MgSO_4$. After evaporation enantioenriched BIFAPO was obtained as a light yellow solid. This solid was dissolved in $CHCl_3$ (10 mL). A solution of (+)-*O*,*O*′-dibenzoyl tartaric acid (560 mg, 1.48 mmol) in EtOAc (25 mL) was added and a white precipitate was formed instantly. This 1:1 complex **7** of (*S*)-(−)-BIFAPO and (+)-DBT was filtered off and dried in vacuo. Spectral data are identical to the complex of (*R*)-(+)-BIFAPO and (−)-DBT. About 10% of this complex was recrystallised from $CHCl_3$/EtOAc 1:1 to obtain crystals suitable for X-ray analysis. The rest of **7** was suspended in CH_2Cl_2 (30 mL) and stirred with aqueous KOH (1N, 30 mL). After 1 h, when the white solid had disappeared, the organic layer was separated, washed with brine and water and dried over $MgSO_4$. After evaporation, (*S*)-(−)-BIFAPO was obtained as a white solid (742 mg, 72%). M.p. 190–193°C; $[\alpha]_D^{20} = -213$ ($c = 1$ in $CHCl_3$); Spectral data were identical to racemic BIFAPO. To check the enantiopurity of the product by ^{31}P NMR, (*S*)-(−)-BIFAPO (12.0 mg) and (−)-DBT (6.3 mg) were mixed in $CDCl_3$. ^{31}P NMR: $\delta = 33.4$ (single signal).

(*S*)-(−)-BIFAP (1): Diisopropylethyl amine (5.3 mL, 30 mmol) and trichlorosilane (3.06 mL, 30 mmol) were added to a stirred solution of (*S*)-(−)-BIFAPO (1.1 g, 1.49 mmol) in *p*-xylene (20 mL) in a sealed tube. The tube was closed and heated at 160°C for 24 h. After cooling the reaction mixture was worked up with CH_2Cl_2 and aqueous KOH (1N), washed with water and brine and evaporated. The solids were dissolved in CH_2Cl_2 (10 mL) and EtOH (20 mL) was added. CH_2Cl_2 was slowly distilled off and the product precipitated. (*S*)-(−)-BIFAP was obtained as a white crystalline solid (900 mg, 86%). M.p. 120–123°C; $[\alpha]_D^{20} = -224$ ($c = 0.5$ in C_6H_6); HRMS (FAB+): calcd for $C_{48}H_{33}O_2P_2$ $[M+H]^+$ 703.1956, found 703.1913. Spectral data were identical to (±)-BIFAP.

(*R*)-(+)-BIFAP (1): (*R*)-(+)-BIFAPO (980 mg, 1.33 mmol) was treated in the same manner as described for the synthesis of (*S*)-(−)-BIFAP. The product was obtained as a white crystalline solid (862 mg, 92%). M.p. 120–125°C; $[\alpha]_D^{20} = +226$ ($c = 0.5$ in C_6H_6); HRMS (FAB+): calcd for $C_{48}H_{33}O_2P_2$ $[M+H]^+$ 703.1956, found 703.1967. Spectral data were identical to (±)-BIFAP.

(*S*)-(−)-2,2′-Bis(diphenylphosphanyl)-1,1′-bidibenzofuranyl-8,8′-disulfonic acid dipotassium salt ((*S*)-(−)-BIFAPS, 2): (*S*)-(−)-BIFAP (208 mg, 0.296 mmol) was dissolved in sulfuric acid (0.75 mL) at 0°C to obtain a brown viscous solution. A 10% solution of SO_3 in sulfuric acid (0.75 mL) was added and the mixture was stirred at room temperature for 80 h. The reaction was followed by ^{31}P NMR. The mixture was cooled again to 0°C and distilled water (3 mL) was added. A white sticky precipitate was formed. 30% aqueous KOH was added until the pH of the mixture was between 7.0 and 7.3. The milky mixture was evaporated and the resulting white solid was extracted with MeOH (3 × 5 mL) and filtered. The combined fractions were evaporated and the off-white solid was extracted with EtOH (3 × 2 mL). After evaporation of the combined fractions, the optically pure product was obtained as an off-white solid (272 mg, 98%). M.p. > 365°C; $[\alpha]_D^{20} = -74$ ($c = 0.5$ in MeOH/H_2O 1:1); ^{31}P NMR (CD_3OD): $\delta = -14.0$; ^{1}H NMR (CD_3OD): $\delta = 6.67$ (d, $J = 1.5$ Hz; H9, H9′), 6.85 (t, $J = 7.2$ Hz, 2H; Ph-*para*), 6.96 (t, $J = 7.3$ Hz, 4H; Ph-*meta*), 7.02 (m, 4H; Ph-*ortho*), 7.31 (m, 10H; PhH), 7.35 (d, $J = 8.6$ Hz; H6, H6′), 7.41 (dt, $J = 8.5$, 1.4 Hz; H3, H3′), 7.65 (dd, $J = 8.5$, 1.7 Hz; H7, H7′), 7.67 (d, $J = 8.6$ Hz; H4, H4′); ^{13}C NMR (CD_3OD): $\delta = 111.7$, 113.0, 121.7, 123.7, 125.1 (t, $J = 5.4$ Hz), 126.5 (m), 133.5 (t, $J = 5.3$ Hz), 134.4 (t, $J = 11.4$ Hz), 135.0, 135.5 (t, $J = 10.5$ Hz), 136.6 (t, $J = 5.4$ Hz), 139.3 (t, $J = 6.5$ Hz), 140.1 (m), 140.9, 158.3, 158.6; IR (Kbr): $\tilde{\nu}$ 3448 (br), 3069, 1624, 1570, 1433, 1228, 1099, 1025 cm^{-1}; $C_{48}H_{30}O_8P_2S_2K_2 \cdot 3H_2O$ (993.08): calcd C 58.06, H 3.66, S 6.45; found C 58.05, H 3.73, S 6.57.

(*R*)-(+)-2,2′-Bis(diphenylphosphanyl)-1,1′-bidibenzofuranyl-8,8′-disulfonic acid dipotassium salt ((*R*)-(+)-BIFAPS, 2). (*R*)-(+)-BIFAP (170 mg, 0.242 mmol) was treated in the same manner as described for the synthesis of (*S*)-(−)-BIFAPS. Optically pure (*R*)-(+)-BIFAPS was obtained as an off-white solid (220 mg, 97%). M.p. > 365°C; $[\alpha]_D^{20} = +72$ ($c = 0.5$ in MeOH/H_2O 1:1); HRMS (FAB+): calcd for $C_{48}H_{31}O_8P_2S_2K_2$ $[M+H]^+$ 939.0210, found 939.0218; Spectral data were identical to (*S*)-(−)-BIFAPS.

Preparation of 2-(diphenylphosphine)dibenzofuran (14) by nickel catalysis. Diphenylphosphine (100 μL, 0.57 mmol) was added to a solution of [$NiCl_2$(dppe)] (53 mg, 0.1 mmol) in DMF (2 mL). The mixture was heated at 100°C for 30 min. To this was added a solution of 2-(trifluoromethanesulfonyloxy)dibenzofuran (317 mg, 1 mmol) and DABCO (450 mg, 4 mmol) in DMF (1.5 mL). The dark green solution was kept at 100°C. After 2, 4, and 6 h extra portions of diphenylphosphine were added (3 × 50 μL, 0.28 mmol). After 2 d, the precipitate was filtered off and washed with 2 × 1 mL methanol. This afforded the product in 41% yield (145 mg). Spectral data are identical to literature data;[71] ^{31}P NMR: $\delta = -3.70$; ^{1}H NMR: $\delta = 7.98$ (dd, $J = 7.7$, 1.1 Hz, 1H; H9), 7.85 (dd, $J = 7.7$, 0.5 Hz, 1H; H1), 7.54–7.58 (m, 2H; H4, H6), 7.43–7.48 (m, 2H; H7, H8), 7.35–7.39 (m, 10H; Ph*H*), 7.30 (dt, $J = 0.7$, 7.7 Hz; H3).

[(bifap)$PdCl_2$] (15): A solution of (±)-BIFAP (40 mg, 57 μmol) in benzene (1 mL) was added to a stirred yellow solution of $PdCl_2(MeCN)_2$ (15 mg, 57 μmol) in benzene (1 mL). An orange precipitate formed and after stirring overnight this precipitate was filtered off and dried in vacuo. The yield was 49 mg of orange crystals (99%). The complex was recrystallised from CH_2Cl_2/pentane to obtain crystals suitable for X-ray crystallographic analysis. M.p. 318–320°C; ^{31}P NMR: $\delta = 27.7$; ^{1}H NMR: $\delta = 7.80–7.60$ (m, 8H; ArH), 7.50–7.42 (m, 8H; ArH), 7.36–7.28 (m, 6H; ArH), 6.95 (t, $J =$ 7.3 Hz, 2H; ArH), 6.76 (t, $J = 7.5$ Hz, 2H; H8, H8′), 6.52 (brs, 4H; ArH), 6.11 (d, $J = 7.9$ Hz, 2H; H9m, H9′); ^{13}C NMR: $\delta = 157.8$, 156.2, 135.3 (m), 134.9 (m), 134.4 (m), 132.8 (m), 131.1 (d, $J = 13$ Hz), 129.2 (d, $J = 62$ Hz), 128.3, 127.8 (m), 127.6 (m), 125.3 (m), 123.8 (d, $J = 60$ H), 123.2, 123.1 (dd, $J = 54$, 4 Hz), 122.9, 121.5, 111.8 (m), 111.6.

$RuCl_2$/(*S*)-(−)-bifap complex (17): (*S*)-(−)-BIFAP (100 mg, 142 μmol) and [{$RuCl_2$(benzene)}$_2$] (34 mg, 67 μmol) were dissolved in degassed DMF (2.3 mL). This dark brown mixture was heated at 100°C for 10 min. The mixture was cooled to room temperature and concentrated in vacuo. The air-sensitive mixture of complexes was obtained as a reddish brown solid.

[RuCl(benzene)(*R*)-(+)-bifaps]Cl (18). (*R*)-(+)-BIFAPS (100 mg, 106 μmol) and [{$RuCl_2$(benzene)}$_2$] (23 mg, 46 μmol) were dissolved in degassed MeOH (5 mL). The orange solution was stirred overnight at room temperature, filtered and concentrated in vacuo. An air-sensitive complex was obtained as an orange solid. ^{31}P NMR (MeOH): $\delta = 39.7$ (d, $J =$ 63.2 Hz), 32.3 (d, $J = 64.0$ Hz).

Hydrogenation of methyl acetoacetate

Procedure A, with preformed $RuCl_2$/ligand complex. A solution of methyl acetoacetate (1.85 mL, 17.0 mmol) in solvent (17 mL) was degassed by bubbling through argon for 10 min (pH 3.5). To this mixture was added $RuCl_2$/ligand complex **16**, **17**, or **18** (16.0 μmol), which was quickly weighed in air. The solution was stirred at room temperature for about 2 min and

turned yellow. If indicated, sulfuric acid (9 μL, 169 μmol), HCl (1N, 170 μL, 170 μmol) or potassium tosylate (16 mg, 68 μmol) was added. The mixture was transferred through a cannula into a stainless steel 100 mL autoclave, which was previously evacuated and filled with nitrogen 3 times. The mixture was stirred at 600 rpm, pressurised with hydrogen gas, and heated at 70 °C for 2 h. The autoclave was cooled to room temperature, depressurised and opened. The resulting orange solution was concentrated in vacuo when methanol was used as the solvent or extracted with CH_2Cl_2 and then concentrated in vacuo when water was used as the solvent. The conversion was checked by ^{1}H NMR. Bulb-to-bulb distillation (100–150 °C, 20 mbar) yielded the pure product as a colourless liquid in 70–95% isolated yield. The optical purity was determined by dividing the measured rotation by the literature rotation of the *R* product. $[\alpha]_D^{20} = -23.5$ (neat);[59] ^{1}H NMR: $\delta = 4.19$ (m, 1H; C*H*OH), 3.70 (s, 3H; OCH_3), 3.0 (br s, 1H; OH), 2.49 (dd, $J = 16.5$, 3.6 Hz, 1H; C*H*HC=O), 2.42 (dd, $J = 16.3$, 8.6 Hz, 1H; CH*H*C=O), 1.21 (d, $J = 6.3$ Hz, 3H; CH_3CHOH); ^{13}C NMR: $\delta = 173.0$, 64.0, 51.3, 42.8, 22.3.

Procedure B, with in situ formed $RuCl_2$/ligand complex. A solution of methyl acetoacetate (1.85 mL, 17.0 mmol) in solvent (17 mL) was degassed by bubbling through argon for 10 min. [{$RuCl_2$(benzene)}$_2$] (4.0 mg, 8.0 μmol) and ligand (17.0 μmol) were added to this mixture. The solution was stirred for 30 min and the mixture turned yellow. The reaction was further carried out as described in procedure A.

Hydrogenation of (*Z*)-acetamidocinnamic acid. In a 100 mL pyrex flask solvent (10 mL) was degassed by bubbling through argon for 10 min. (*Z*)-acetamidocinnamic acid (205 mg, 1.0 mmol) and $RuCl_2$/ligand complex **16**, **17** or **18** (0.01 mmol, quickly weighed in air) were added and the yellow mixture was stirred for 5 min at room temperature. The flask was pressurised with hydrogen gas (4 atm) and firmly shaken at room temperature. After 24–100 h the flask was depressurised and opened. The reaction mixture was concentrated in vacuo when methanol was used as the solvent. When a water/ethyl acetate mixture was used, the organic layer was separated and concentrated in vacuo. The conversions were determined by ^{1}H NMR: $\delta = 7.30$–7.23 (m, 3H; ArH), 7.16 (d, $J = 6.6$ Hz, 2H; ArH), 6.12 (br s, 1H; N*H*), 4.88–4.84 (m, 1H; C*H*NHAc), 3.22 (dd, $J =$ 14.0, 5.5 Hz, 1H; ArCH*H*), 3.12 (dd, $J = 14.0$, 6.1 Hz, 1H; ArCH*H*), 1.98 (s, 3H; CH_3C=O).

Part of the crude product was methylated for determination of enantiomeric excess. About 10% of the crude product was dissolved in methanol and treated with an excess of freshly distilled diazomethane solution in diethylether.[72] The resulting mixture was quenched with acetic acid and concentrated in vacuo. The methylated product was purified by flash chromatography (EtOAc/PE 1:1) and the enantiomeric excess was checked by chiral HPLC (Daicel OD, heptane/*i*PrOH 9:1, 0.5 mL min^{-1}, UV 254 nm: t_R 10.0 and 12.3). ^{1}H NMR: $\delta = 7.30$–7.22 (m, 3H; ArH), 7.08 (d, $J = 6.6$ Hz, 2H; ArH), 5.99 (br d, $J = 6.9$ Hz, 1H; N*H*), 4.90–4.85 (m, 1H; C*H*NHAc), 3.72 (s, 3H; CH_3O_2C), 3.17–3.06 (m, 2H; ArCH_2), 1.97 (s, 3H; CH_3C=O).

X-ray structure determination of 7, (*S*)-(−)-1 and 15: Crystals suitable for X-ray diffraction were glued to the tip of a glass capillary. Complexes **7** and **15** were mounted on an Enraf–Nonius CAD4-T diffractometer with a rotating anode. Compound (*S*)-(−)-**1** was measured on a Enraf–Nonius κ-CCD with a rotating anode. All diffraction experiments were carried out using graphite monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Accurate unit-cell parameters and an orientation matrix were determined by least-squares fitting of the setting angles of a limited set of reflections (SET4-centered[38] on the CAD4). The unit-cell parameters were checked for the presence of higher lattice symmetry.[39] Crystal data and details on data collection and refinement are collected in Table 3. Data were corrected for Lorentz and polarisation effects, but not for absorption. The CAD4 data were also corrected for the observed linear instability of the reference reflections. F_c values of (*S*)-(−)-**1** were corrected for secondary extinction by refinement of an empirical isotropic parameter: $F_c = F_c k[1+xF_c^2\lambda 3/\sin(2\theta)]^{-1/4}$, where $x = 11.1(10)10^{-6}$ and k is the overall scale factor.

All structures were solved by automated direct methods (SHELXS 97[41] for **7**; SHELXS 86[40] for (*S*)-(−)-**1** and **15**). The structures were refined on F^2, using full-matrix least-squares techniques (SHELXL 97-2);[54] no observance criteria were applied during refinement. Hydrogen atoms were included in the refinement on calculated positions, riding on their carrier atoms, except for the hydroxyl hydrogen atoms of complex **7**, which were located on a difference Fourier map and whose coordinates were included in the refinement as parameters.

The crystal structures of complexes **7** and **15** contain disordered solvent areas. The BYPASS procedure,[58] as implemented in the program PLATON,[66] was used to take the corresponding electron density into account. For complex **7** two separate solvent areas were found in the unit cell. Each area has a volume of 335 Å^3 and contains 122 electrons. The unit cell of complex **15** contains a total solvent area of 567 Å^3, with a contents of 157 electrons per unit cell.

The non-hydrogen atoms were refined with anisotropic atomic displacement parameters. The hydrogen atoms were refined with a fixed isotropic displacement parameter related to the value of the equivalent isotropic displacement parameter of their carrier atoms by a constant factor of 1.5 for the hydroxyl hydrogen atoms and a factor of 1.2 for all other hydrogen atoms.

The absolute configuration of **7** was assigned in accordance with the known configuration of (+)-DBT (i.e., *S* configuration for the chiral carbon atoms). The Flack parameter (x),[64] derived during the final structure-factor calculation, amounts to 0.1(3) for this configuration. After refinement of the alternative chirality a value of 0.6(3) was derived. For (*S*)-(−)-**1** the absolute structure was set equal to the one observed in complex **7**. The x parameter was calculated to be 0.05(6). Inversion of the structure gave $x =$ 0.95(7) after refinement. Neutral atom scattering factors and anomalous dispersion corrections were taken from the International Tables for Crystallography.[65]

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-112762 (compound **7**), CCDC-112763 (compound (*S*)-(−)-**1**) and CCDC-112764 (compound **15**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, (UK) (fax: (+44) 1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

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Table 3. Crystallographic data for **7**, (S)-(−)-**1** and **15**.

	7	(*S*)-(−)-**1**	**15**
Crystal data			
formula	$C_{48}H_{32}O_4P_2 \cdot C_{18}H_{14}O_8$[a]	$C_{48}H_{32}O_2P_2$	$C_{48}H_{32}Cl_2O_2P_2Pd$[a]
M_w	1093.03	702.73	880.05
crystal system	orthorhombic	monoclinic	triclinic
space group	$P2_12_12_1$ (No. 19)	$P2_1$ (No. 4)	$P\bar{1}$ (No. 2)
a [Å]	12.7075(8)	11.3816(3)	12.1177(14)
b [Å]	18.9911(14)	9.4766(2)	13.7260(18)
c [Å]	24.4726(13)	17.4564(5)	15.314(2)
α [°]	–	–	103.246(12)
β [°]	–	97.827(11)	110.931(11)
γ [°]	–	–	93.335(10)
V [Å^3]	5906.0(7)	1865.29(8)	2288.1(5)
ρ_{calcd} [g cm^{-3}]	1.229[a]	1.251	1.277[a]
Z	4	2	2
$F(000)$	2272[a]	732	892[a]
μ [$Mo_{K\alpha}$, mm^{-1}]	0.14[a]	0.16	0.63[a]
crystal size [mm]	0.1 × 0.1 × 0.1	0.25 × 0.25 × 0.30	0.1 × 0.2 × 0.2
Data collection			
T [K]	200	295	150
θ_{min}, θ_{max} [°]	0.8, 25.0	1.6, 27.5	1.5, 27.5
Cell determination			
(no. refln/θ-range)	25/9.9–13.6	450/2.0–20.0	21/11.4–14.0
scan type	ω	–	ω
refined mosaicity	–	0.286(1)	–
X-ray exposure time [h]	27	9	60
h, k, l ranges	0–15, 0–22, 0–29	−14–14, −11–11, −22–22	−15–15, −17–17, −19–19
total no. reflns	5977	26900	25932
unique reflns	5746	8248 [$R_{int} = 0.0554$]	10526 [$R_{int} = 0.0554$]
Refinement			
parameters	727	470	496
final R[b]	0.0783 [2621 $I > 2\sigma(I)$]	0.0411 [5532 $I > 2\sigma(I)$]	0.0360 [8660 $I > 2\sigma(I)$]
final $wR2$[c]	0.1681	0.0914	0.0819
goodness of fit	0.912	0.966	1.039
w^{-1}[d]	$\sigma^2(F^2) + (0.0641P)^2$	$\sigma^2(F^2) + (0.0445P)^2$	$\sigma^2(F^2) + (0.0334P)^2 + 0.53P$
$(\Delta/\sigma)_{ave}/(\Delta/\sigma)_{max}$	0.000/0.001	0.000/0.001	0.000/0.004
min./max. residual density [e Å^{-3}]	−0.24/0.29	−0.15/0.14	−0.40/0.98 [near Pd]

[a] Without disordered solvent contribution (see text). [b] $R = \Sigma || F_o | - | F_c || / \Sigma | F_o |$. [c] $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$. [d] $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$.

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