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P-Chirogenic Xantphos Ligands and Related Ether Diphosphines – Synthesis and Application in the Rhodium Catalyzed Asymmetric Hydrogenation

Jens Holz,*[a] Katharina Rumpel,[a] Anke Spannenberg,[a] Rocco Paciello,[b] Haijun Jiao,[a] Armin Börner*[a,c]

[a] Leibniz-Institut für Katalyse e.V., A.-Einstein-Str. 29a, 18059 Rostock (Germany)

[b] BASF SE, GCB/H - M313, 67056 Ludwigshafen (Germany)

[c] Institut für Chemie, Universität Rostock, A.-Einstein-Str. 3a, 18059 Rostock (Germany)

ABSTRACT: A series of *P*-chirogenic Xantphos ligands and related diarylether diphosphines have been synthetized by a modification of the well-established Jugé method. The approach consists in the *in situ* deboranation of the chiral ephedrine-based phosphinite before the P-C-coupling takes place. The stereochemical integrity of the stereocenters of the diphosphines during synthesis, long-time storage and catalytic application was evaluated. In the rhodium catalyzed asymmetric hydrogenation of isophorone as a model substrate for industrially relevant prostereogenic enones with some of the diphosphines almost complete conversion, high chemoselectivity and 96 %ee were achieved.

Keywords: *chiral ligands, P-chirogenic phosphines, long-term stability, rhodium, chemoselective hydrogenation, asymmetric hydrogenation*

1. INTRODUCTION

Trivalent phosphorus compounds play a pivotal role as ligands in homogeneously metal catalyzed reactions.[1] Due to their diversity in terms of steric and electronic properties, they are ideally suited as ligands for a variety of metals and enable a wide array of catalytic applications. In extension of this behaviour chiral phosphorus ligands can induce chirality in the prochiral substrate, which is the precondition for the generation of enantioenriched products.[2] Up to now, the design of new ligands is mainly based on a few well-established empiric principles.[3] Geometric features of phosphorus ligands can be evaluated by the Tolman angle[4] or the natural bite angle (α) first suggested by Casey and Whiteker.[5] In general, these heuristic rules are based on conclusions collected with a large number of slightly differing individuals. Some particularly useful ligands are called 'privileged ligands'.[6] They are characterized by a broad applicability on different metal catalyzed reactions, high efficiency and superior productivity in the relevant metal catalysts. Moreover, some of them show a high robustness during long-term storage.

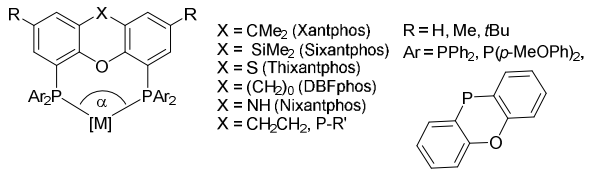


Figure 1. Xantphos and some related ligands.

One of the most eminent examples in this regard is the diphosphine Xantphos (Figure 1). This bidentate ligand and its numerous variations (like Sixantphos, Thixantphos, DBFphos or Nixantphos) served van Leeuwen, Kamer and colleagues to develop and to broaden the natural bite angle concept.[7] The concept was first proven in the *n*-regioselective hydroformylation,[8] but in turn it was also successfully applied to a wide range of other metal catalyzed transformations. A current SciFinder-search gave more than 1200 hits, where Xantphos and its derivatives have been employed for tuning the properties of Pd-, Rh-, Ir-, Ru-, Ni- or Cu-complexes used as catalysts in C-C- or C-N-bond formation reactions, isomerizations or hydrogenations.[9] Taking this feature in mind Xantphos can be considered as one of the most successful diphosphine ligand ever developed.

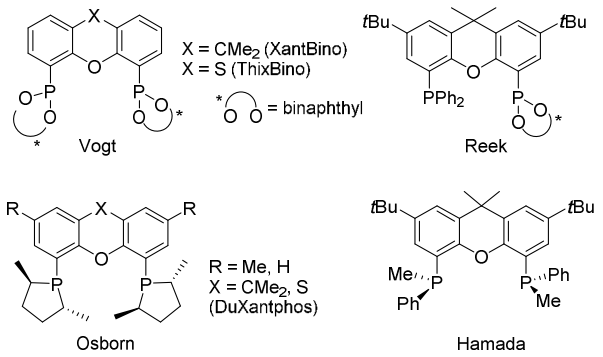


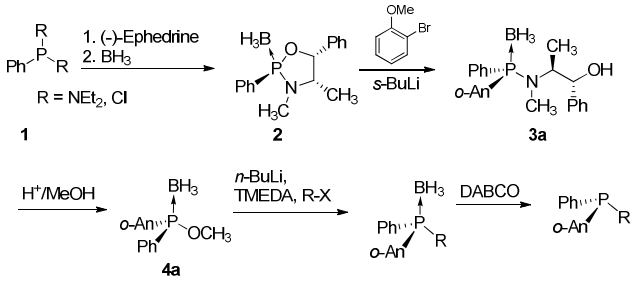
Figure 2. Examples for chiral ligands related to Xantphos.

We were rather surprised to notice that up to now only very few chiral ligands have been described being more or less related to Xantphos (Figure 2). Such unique examples concern chiral diphosphonites (XantBino and ThixBino) synthesized by Vogt and co-workers and tested in various asymmetric reactions, like hydrocyanation,[10] hydrogenation or hydroformylation.[11] Hybrid phosphine phosphonites with the xanthene backbone were used for the hydroformylation of unsaturated heterocycles by the Reek group.[12] Two C_2-symmetric bisphospholanes with a 9*H*-xanthene or phenoxathiine backbone, later collected under the short name DuXantphos, were developed by Osborn and

colleagues and investigated in detail in the palladium catalyzed asymmetric alkylation.[13]

The closest relation to Xantphos itself represents *P*-chirogenic diphosphines with the relevant backbone.[14] Remarkably for such *P*-chirogenic Xantphos-type ligands only a single individual exists in the literature described by Hamada et al. in 1997.[15] The compound was prepared starting by a non-stereoselective phosphorylation of the relevant xanthene dibromide with two equivalents of chloromethylphenylphosphine. From the resulting diastereomeric mixture, containing also the undesired *meso*-compound in almost 50 % yield, the racemic compound was isolated. After oxidation, kinetic resolution of the diphosphine oxide and reduction, the enantiopure diphosphine was obtained in ca. 10 % overall yield. Its catalytic performance was tested in the palladium catalyzed allylic alkylation wherein 87 %ee was achieved. Although the low yield of the diphosphine could be slightly enhanced in a subsequent partial epimerization of the residual *meso*-diphosphine oxide the chosen multi-step route is not applicable in large scale. Moreover, this tedious pathway is not suitable for the generation of a broad class of slightly differing ligands. Therefore, we looked for a more facile and general protocol.

One of the most common pathways for the generation of *P*-chirogenic phosphines was established by Jugé and co-workers.[14c,16,17] In this method the chiral *P*-center is created by the assistance of (-)-ephedrine as stereoinductor (Scheme 1).



Scheme 1. Jugé's approach for the synthesis of *P*-stereogenic phosphines.

The synthesis is based on the diastereoselective opening of an oxazaphospholidine **2** prepared by condensation of aryl dichlorophosphines or aryl phosphinediamides of the general formula **1** with (-)-ephedrine. Opening of the heterocycle can be conducted for example with *ortho*-anisyl lithium to give **3a**. In the subsequent step the stereoinducing ephedrine moiety is displaced via substitution with methanol to give the enantiopure phosphinite **4a**. In order to fix the stereochemistry at the chirogenic phosphorus center over the whole course of the substitution steps via **2** and **3**, it is continuously protected as BH_3-adduct. The *P*-chirogenic phosphinite borane complex such as **4a** can be coupled subsequently with a range of C-nucleophiles. At the end of the sequence, the borane group is usually removed.

Our intention was to use this methodology for the construction of a large set of *P*-chirogenic diarylether diphosphines and to screen them as ligands in the rhodium catalyzed asymmetric hydrogenation. As prochiral substrate isophorone was chosen which represents a model compound for the chemoselective and asymmetric hydrogenation of industrially important α,β-unsaturated ketones or aldehydes, such as neral, geranial or citral.[18] Due to the cyclic structure isophorone is configurationally stable. Therefore it does not undergo *Z/E*-isomerization and is therefore of particular value as model substrate for the hydrogenation of acyclic enones widely employed as perfumery ingredients.[18c] Up to now the hydrogenation of isophorone was mainly in the focus of heterogeneous palladium catalyzed hydrogenation using chiral modifiers.[19]

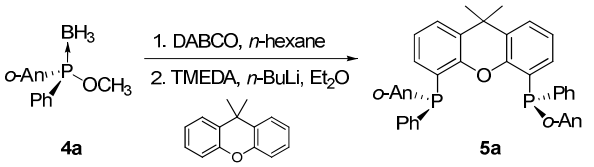
2. RESULTS AND DISCUSSION

2.1. Synthesis of *P*-Chirogenic Diphosphines.

When we tried to apply Jugé's methodology on 4,5-dilithiated 9,9-dimethyl-9*H*-xanthene besides some other by-products only the monophosphine (^{31}P NMR ($CDCl_3$): δ = -25.4 ppm) was obtained in low yield.[20] Under these conditions even the BH_3 group was lost (see Supporting Information). Unexpectedly, we found that also the reaction of the dilithiated diphenyl ether (DPE) with two equivalents of BH_3-protected chiral methyl phosphinites (like **4a**) failed, although the compound is conformationally more flexible. The same problem was faced with the corresponding dibenzo[*b*,*d*]furan derivative in hand.

This situation strongly resembles results of trials with *ortho*-substituted benzene diphosphines, where only monophosphine borane adducts yielded in the reaction of the diphosphines with BH_3.[21,22] Only recently, Bayardon and Jugé were able to overcome this challenge with benzene derivatives by using an aryne as reactive intermediate, which has been prepared from *ortho*-1,2-bromobenzene.[23] Moreover, the second phosphine unit was introduced after prior deboranation of the *P*-chirogenic phosphinite borane complex, which was realized in a separate step.

Now, we found that the tricky coupling of the xanthene backbone with two *P*-chirogenic units can be realized in a one-pot reaction under the precondition that the BH_3 groups have been removed *in situ* before the coupling reaction takes place (Scheme 2).



Scheme 2. The modified Jugé's approach for the synthesis of *P*-stereogenic Xantphos derived diphosphines.

In a preliminary trial we removed the BH_3 group from the phosphinite **4a** at 40 °C with DABCO. After retreatment with BH_3 the stereochemical purity of the product was proved by HPLC. In this manner evidence was given that no racemization occurred. This gave us hope that the stereoselectivity will remain also in a subsequent P-C-coupling reaction. Indeed, we were pleased to see, that complete deboranation of phosphinite **4a** could be realized *in situ* at 40 °C in *n*-hexane, accompanied by quantitative precipitation of the created DABCO*BH_3 complex. After filtration and subsequent addition of the phosphinite to the solution of dilithiated xanthene at -45 °C the *P*-chirogenic diphosphine **5a** was obtained in 60% yield (Table 1).

In order to verify the enantiomeric integrity for comparison we performed the same reaction with racemic **4a**. The ^{31}P NMR spectrum of the product displayed three signals (Figure 3a). Besides the signal of the formed monophosphine (δ = -25.5 ppm) a large signal at δ = -26.5 ppm was found, that corresponds to the racemic mixture of (*S*,*S*)/(*R*,*R*)-**5a**. The smaller signal at δ = -26.6 ppm results from the *meso*-compound (*R*,*S*)-**5a**. On the other hand, we were pleased to see that in the ^{31}P NMR spectrum of (*S*,*S*)-**5a** only a single resonance was found, indicating that no *meso*-compound was created and therefore no epimerization took place during the synthesis (Figure 3b).

By application of this new methodology 17 *P*-chirogenic Xantphos derivatives **5a-t** were derived in yields ranging from 10-86%.[24]

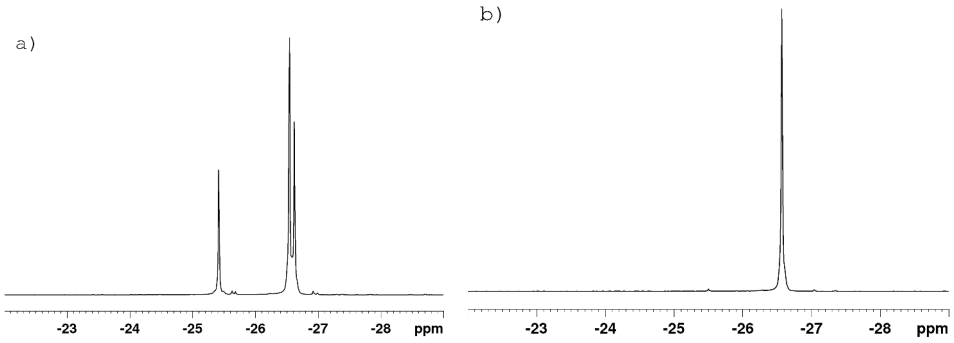


Figure 3. ^{31}P NMR spectra in $CDCl_3$ of a) racemic mixture of Xantphos derivative **5a** and b) enantiomerically pure (*S,S*)-**5a**.

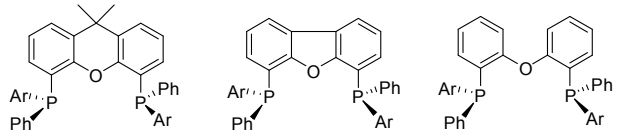
Moreover, by application of the new approach also three *P*-chirogenic dibenzofuran diphosphines **6a,g,h** of the DBFphos-type were prepared in good yields (Table 1). Further investigations showed that by using 4,6-dibromo-dibenzofuran as starting material improved yields can be achieved by conducting the dilithiation with *n*-butyllithium.

A further literature research revealed that also *P*-chirogenic DPEphos congeners are not available up to now, although a Sci-Finder search listed more than 700 hits, where this achiral diphosphine ligand has been used in metal catalyzed homogeneous reactions. Some of these reactions may take benefit from chiral DPEphos ligands. [25]

As already mentioned above, the simultaneous incorporation of two phosphine-borane units in this backbone likewise failed although its conformational flexibility is greater than that of xanthene or dibenzofuran. In contrast, our new coupling approach also allowed the synthesis of such *P*-chirogenic diphosphines like **7a-t** (Table 1).

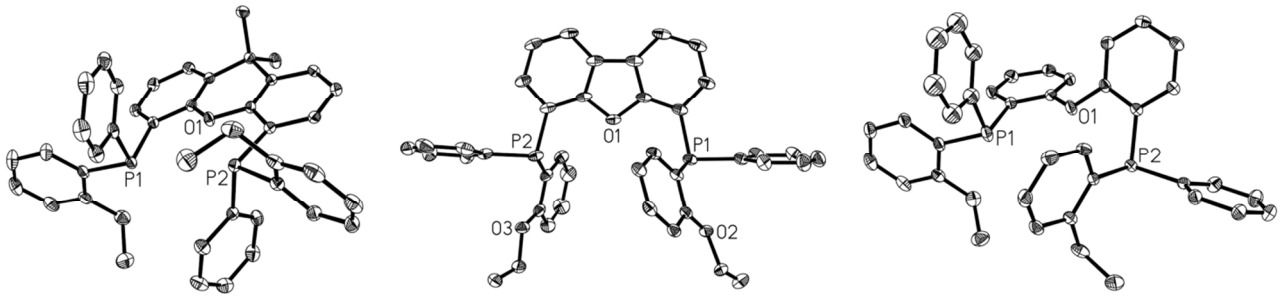
In Figure 4 three representative molecular structures of each type of diphosphines are depicted for illustration.[26] The expected (*S*)-configuration at *P*-atoms in **5j**, **6g** and **7j** was confirmed. Due to the pyran ring of the xanthene derivatives of type **5** their backbone is not fully planar.

Table 1. New *P*-chirogenic diphosphines. ^{31}P NMR resonances and isolated yields.



	Ar	Type **5** ^{31}P NMR (yield)	Type **6** ^{31}P NMR (yield)	Type **7** ^{31}P NMR (yield)
a	2-MeO-Ph	-26.6 (60%)	-27.3 (70%)	-25.7 (18%)
b	3-MeO-Ph	-16.5 (12%)		-15.6 (47%)
c	4-MeO-Ph	-18.8 (53%)		-17.6 (61%)
d	2-Me-Ph	-24.5 (54%)		-24.0 (37%)
e	3-Me-Ph	-17.4 (33%)		-16.3 (65%)
f	4-Me-Ph	-18.2 (33%)		-17.1 (65%)
g	2-EtO-Ph	-25.7 (85%)	-25.7 (90%)	-24.4 (58%)
h	3-EtO-Ph	-16.5 (45%)	-16.3 (76%)	-[a]
i	4-EtO-Ph	-18.8 (72%)		-17.8 (21%)
j	2-Et-Ph	-26.5 (10%)		-26.0 (33%)
k	3-Et-Ph	-[a]		-[a]
l	2-*i*PrO-Ph	-25.6 (52%)		-[a]
m	3-*i*PrO-Ph	-16.5 (76%)		-15.7 (40%)
n	2-*i*Pr-Ph	-[a]		-27.0 (59%)
o	3-*i*Pr-Ph	-[a]		-[a]
p	3,5-MeO-Ph	-14.9 (48%)		-14.2 (80%)
q	1-Naphthyl	-25.3 (56%)		-23.1 (40%)
r	2-Naphthyl	-16.4 (63%)		-15.5 (39%)
s	9-Phenantryl	-23.0 (44%)		-22.6 (51%)[b]
t	4-DBF[c]	-28.9 (63%)		-28.5 (22%)

[a] Diphosphines could not be separated from the monosubstituted phosphine derivatives with sufficient purity.
[b] The opposite enantiomer was synthesized. [c] 4-DBF = Dibenzo[*b,d*]-furan-4-yl.



5j **6g** **7j**

Figure 4. Molecular structure of diphosphines with a different backbone.[27] Displacement ellipsoids correspond to 30% probability. Hydrogen atoms are omitted for clarity. For **6g** and **7j** only one of the two molecules of the asymmetric unit is shown.

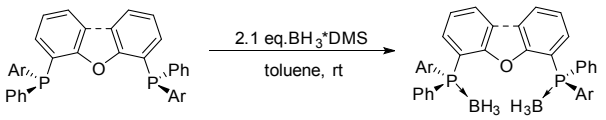
Table 2. Comparison of natural bite angles of selected *P*-chirogenic diether phosphines with those of parent achiral diphosphines.

	5j	Xantphos	**6g**	DBFphos	**7j**	DPEphos
Bite angle [°]	120.0	119.1	118.2	118.2	115.3	114.2

For example in structure **5j** a deviation from the planarity, indicated by the folding angle was found to be 171.24(3)°. In contrast, the furan ring in **6g** caused an almost planar geometry of the backbone (mean deviation of the best plane defined by all atoms of the DBF-moiety: 0.01 Å and 0.03 Å for both molecules in the asymmetric unit). As expected the backbone of **7j** is conformational entirely flexible. Thus, the aromatic rings of the DPE-backbone are twisted around the oxygen by 79.9(1)° and 59.7(1)°, respectively (for more details see Supporting Information).

In order to compare the geometric feature of these new *P*-chirogenic diphosphines, the natural bite angles on the basis of the definition by van Leeuwen were estimated.[7c,d] Since different methods and programs may give different bite angles for the same ligand, it is necessary to model the bite angles of all ligands in a series with the same program and the same parameter set:[5c] Herein, we used the molecular mechanics methods implemented in Spartan '08 program.[28] As shown in Table 2, there are only marginal differences between chiral and achiral diphosphines. In general, the natural bite angles of chiral compounds with different backbone follow the same trend as found with achiral compounds.

While in diphosphines of type **5** the small distance between the *P*-atoms (e.g. in **5j**: 4.2 Å in the solid state) permitted only the incorporation of a single BH_3 unit, in diphosphines of type **6** and **7** both *P*-atoms easily reacted with BH_3*DMS (DMS = dimethyl sulfide) (Scheme 3). Obviously the larger spatial distances (in **6g**: 5.6/5.9 Å, **7j**: 4.9/5.4 Å) allow the conversion of both phosphine groups. Thus, e.g. the DBFphos-derivative **6g** has been cleanly converted into **6g'** (δ_P = +15.7 ppm). This result is again rather surprising, because as already mentioned above all attempts failed to couple two equivalents of BH_3 protected methyl phosphinite **4g** to the corresponding backbone.



6g, **7e**, **7g** **6g'**, **7e'**, **7g'**

Scheme 3. Reaction of DBF- and DPE-derivatives with BH_3*DMS.

Also diphosphines with DPE-backbone **7e** and **7g** were transformed into their bis-borane adducts **7e'** and **7g'** by addition of 2.1 eq. of BH_3*DMS. The ^{31}P NMR spectra showed a typical broad signal at +19.1 ppm for **7e'**.[29]

2.2. Epimerization studies of the diphosphines.

For the successful and broad application of *P*-chirogenic diphosphines as ligands in asymmetric catalysis their stereochemical integrity is of crucial importance. This stability is not only indispensable for the catalytic reaction itself, but also for the long-time storage as usually demanded in industrial labs when e.g. high-throughput screening is routinely used.

In contrast to tertiary amines with three different substituents compounds with a *P*-chirogenic center own a significantly higher inversion barrier. In general, phosphines have high, but not insurmountable, barriers to inversion. Typical alkyl and/or aryl substituted acyclic trivalent phosphines have inversion barriers of around 120-150 kJ/mol.[30] With increasing number of aryl groups at the phosphorus the inversion energy drops. Baechler and Mislow found that the free energy of activation for the inversion of trialkyl phosphines ($\Delta G^{\ddagger}_{inv}$) is ca. 36 kcal/mol, for dialkyl aryl phosphines ca. 33 kcal/mol, and for alkyl diaryl phosphines ca. 30 kcal/mol.[31] The trend suggests that the barrier for triaryl phosphines should be ca. 27 kcal/mol.[32] However up to now, only few data can be found in the literature beyond these results. Moreover, in the most cases non-chiral triarylphosphines were investigated.[33]

In order to clarify this situation, we investigated the long-term stability of some of our diphosphines over a period of about two years. In Figure 5 the relevant ^{31}P NMR spectra of compound **5r** are shown exemplarily. After 25 months of storage under argon at room temperature an additional signal at slightly higher field appeared which corresponds to the formed *meso*-derivative of **5r** (Figure 5b). It is remarkable that another batch of **5r** isolated by crystallization from dichloromethane/hexane and stored under the same conditions did not racemize at all. After 23 months only one signal in ^{31}P NMR spectrum of (*S*,*S*)-**5r** was visible (Figure 5a). This phenomenon was observed repeatedly: *P*-Chirogenic derivatives isolated by crystallization are more stable at ambient temperature over a long period while compounds which have been isolated by column chromatography and isolated as amorphous solids undergo slow epimerization.

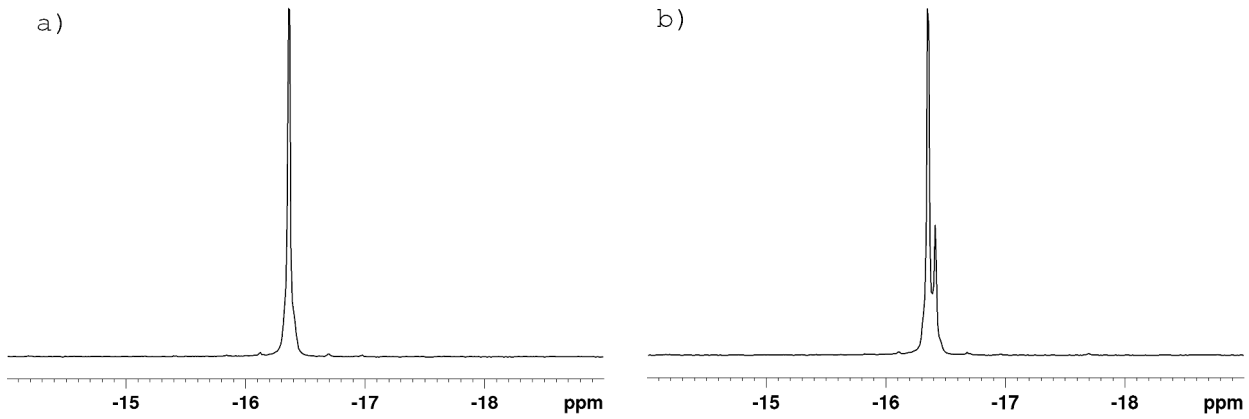


Figure 5. ^{31}P NMR spectra of compound **5r** a) After isolation by column chromatography and b) after 25 months storage at ambient temperature under Ar-atmosphere (ratio ~77:23).

Thus for example precipitated diphosphines like **5a, 5d, 5q, 5s, 7d** and **7r** kept its optical purity over several months and even years. But compounds purified by column chromatography like **5g** changed to a mixture with a ratio of 90:10 after 4 months. Diphosphine **7c** was transformed into a nearly 1:1 mixture of chiral (*S,S*)/(*R,R*)-**7c** and (*R,S*)-**7c** within two years. We explain these differences by assuming traces of acids remaining from silica used for chromatography.

It is known that the epimerization is dependent on the temperature. Therefore, 2-methoxyphenyl derivative **5a** was dissolved in toluene-d_8 at 70°C. After 15 minutes at this temperature only one signal at δ -26.6 ppm was visible in the ^{31}P NMR spectrum. After three days at this temperature, the resonance split up into two signals with a ratio of nearly 55:45 at ca. -26.5 ppm corresponding to the (*S,S*)/(*R,R*)-enantiomers and the signal of the (*R,S*)-compound (Figure 6a). A differentiation between the chiral and the achiral compounds could also be made by ^{1}H NMR spectroscopy. Thus, the enantiopure compounds displayed only a single signal for both methyl groups of the isopropylidene group (C(CH_3)$_2$) while in case of the *meso*-compound each methyl group was characterized by its own NMR shift. After subsequent treatment of the mixture of **5a** with 1.2 equivalents of BH_3*DMS the ^{31}P NMR spectrum afforded a joint broad signal at +20.6 ppm (50%) for the protected *P*-atoms and two sharp signals at -29.4 ppm (27%) and -30.1 ppm (23%), characterizing the unprotected *P*-atoms of the chiral and the *meso*-compound of **5a'**, respectively (Figure 6b).

A similar behaviour was noted for compound **6a** (see Supporting Information). In contrast, the DPEphos derivative **7e** did not epimerize within 96 hours at 50°C. Heating a sample of **6g** at 50°C epimerization forged ahead ($\delta_{P,meso}$ = -25.9 ppm; 18% after 24 h and 38% after 96 h). Under the same conditions the enantioselectivity of **6g'** retained but partial loss of borane was observed.[34]

2.3. Asymmetric hydrogenation of isophorone.

In order evaluate the stereodifferentiating properties of the new chiral diphosphines we screened them as ligands in the rhodium catalyzed asymmetric hydrogenation of isophorone **8** (Scheme 4).

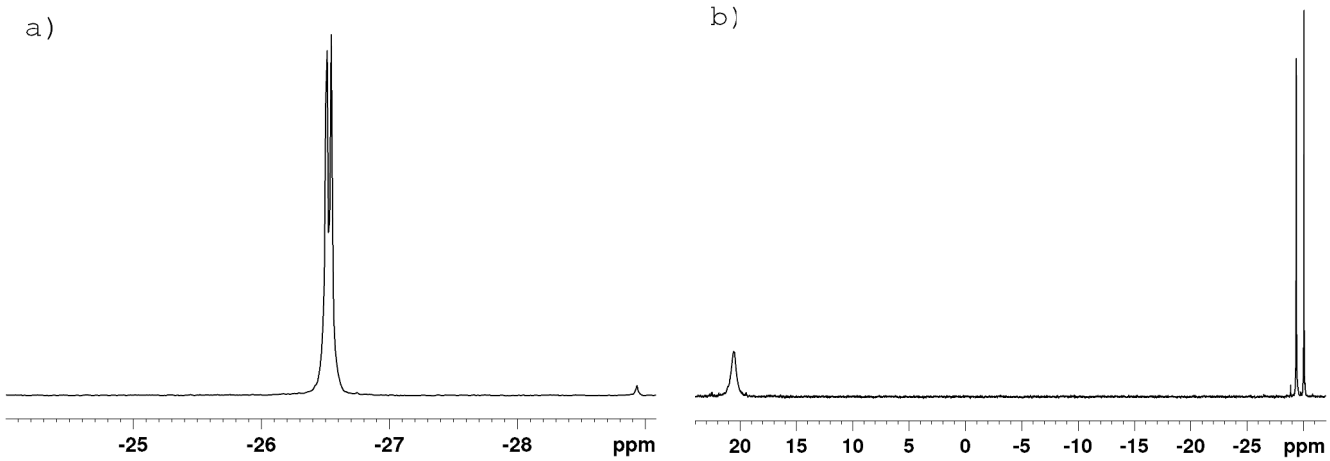
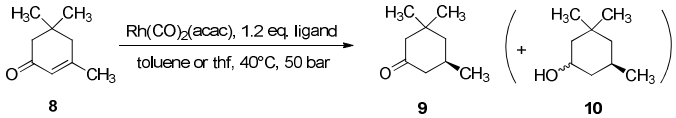


Figure 6. ^{31}P NMR spectrum of **5a** a) after 3 days at 70°C and b) after subsequent addition of 1.2 equivalents of BH_3*DMS.



8 9 10

Scheme 4. Asymmetric hydrogenation of isophorone 8 to chiral ketone 9 and alcohol 10.

A particular challenge with this enone is not only the achievement of high enantioselectivity, but also the chemoselectivity for the hydrogenation of the C=C-double bond without touching the carbonyl group. In the beginning we tested two Rh sources e.g. Rh(cod)(acac) (cod = 1,5-cyclooctadiene) and $Rh(CO)_2(acac)$ (acac = acetyl acetonate). These preliminary trials showed that in general with the latter significantly higher enantioselectivities can be obtained.

In dependence of the reaction time, parts of the formed chiral ketone may be transferred into the corresponding alcohol by hydrogenation of the ketone. Fortunately, with our catalysts in hand, this reaction is significantly slower as the hydrogenation of the olefin and can be therefore conveniently suppressed by termination of the gas supply.

Table 3 summarizes all results of the asymmetric hydrogenation.[35] In general, a catalyst/substrate ratio of 1:200 was used. Some remarkable differences in the performances of the new ligands can be derived: In general, the results are only marginally dependent on the solvent used: toluene or tetrahydrofuran. High conversions and good chemoselectivity were noted with rhodium catalysts based on ligands **5a** (Run 2) and **5c** (Run 4), **5d** (Runs 5 and 6) and **7a** (Run 22) in a period of 4-20 hours. The enantioselectivities are in the range from 0-96%.

Already a shift of substituents into the *meta*-position caused a serious decrease of the activity e.g. **5d** (Runs 5 and 6) vs. **5e** (Runs 7 and 8) and **5q** (Runs 13 and 14) vs. **5r** (Runs 15 and 16). When *para*-aryl substituted ligands like **5f** (Runs 9 and 10) were tested then the hydrogenation activity was extremely low.

The table illustrates nicely that the highest enantioselectivities can be reached by using ligands owing substituents in *ortho*-position of the *P*-aryl groups. Thus, **5a** (Runs 1 and 2), **5d** (Runs 5 and 6), **5q** (Runs 13 and 14), and **5s** (Runs 17 and 18) induced enantioselectivities between 80% and 96%. Worthy of note is the fact that the hydrogenation of isophorone with the rhodium catalyst of the DBF-ligand **6g** gave only 24%ee (Run 21). Moreover, the conformationally flexible DPE-ligands of type **7** induced lower conversions accompanied by poor enantioselectivities (Runs 26-28).

In order to make sure that no epimerization of the ligands during the catalytic reaction took place, in a separate trial the hydrogenation with ligand **5a** (Run 2, Table 3) was interrupted after certain stages of conversion. Analysis of the ee-values after 45, 90, 135, and 180 min, respectively, showed no effect on the enantioselectivity.

Table 3. Rhodium catalyzed asymmetric hydrogenation of isophorone (8).[a]

Run	Ligand (Ar)	solvent	*t* [h]	conv. [%][b]	%ee of **9**[c]
1	**5a** (2-MeO-Ph)	toluene	20	100 (81)	85 (*S*)
2	**5a** (2-MeO-Ph)	tetrahydrofuran	20	100 (91)	84 (*S*)
3	**5c** (4-MeO-Ph)	toluene	8	45 (81)	2 (*S*)
4	**5c** (4-MeO-Ph)	tetrahydrofuran	8	94 (98)	1 (*S*)
5	**5d** (2-Me-Ph)	toluene	4	97 (99)	96 (*S*)
6	**5d** (2-Me-Ph)	tetrahydrofuran	4	95 (99)	96 (*S*)
7	**5e** (3-Me-Ph)	toluene	4	74 (99)	13 (*S*)
8	**5e** (3-Me-Ph)	tetrahydrofuran	4	87 (99)	10 (*S*)
9	**5f** (4-Me-Ph)	toluene	8	19 (99)	2 (*S*)
10	**5f** (4-Me-Ph)	tetrahydrofuran	4	20 (99)	rac
11	**5p** (3,5-MeO-Ph)	toluene	4	20 (99)	26 (*S*)
12	**5p** (3,5-MeO-Ph)	tetrahydrofuran	4	50 (97)	25 (*S*)
13	**5q** (1-Naphthyl)	toluene	4	87 (98)	92 (*S*)
14	**5q** (1-Naphthyl)	tetrahydrofuran	4	84 (98)	92 (*S*)
15	**5r** (2-Naphthyl)	toluene	20	50 (99)	17 (*S*)
16	**5r** (2-Naphthyl)	tetrahydrofuran	20	57 (97)	20 (*S*)
17	**5s** (9-Phenantryl)	toluene	4	89 (98)	92 (*S*)
18	**5s** (9-Phenantryl)	tetrahydrofuran	4	89 (98)	92 (*S*)
19	**5t** (4-DBF)	toluene	4	81 (99)	38 (*S*)
20	**5t** (4-DBF)	tetrahydrofuran	8	47 (99)	14 (*S*)
21	**6g** (2-EtO-Ph)	tetrahydrofuran	6	75 (99)	24 (*S*)
22	**7a** (2-MeO-Ph)	toluene	4	100 (99)	59 (*S*)
23	**7c** (4-MeO-Ph)	toluene	8	10 (99)	1 (*S*)
24	**7d** (2-Me-Ph)	toluene	4	10 (99)	33 (*S*)
25	**7f** (4-Me-Ph)	toluene	8	0	-
26	**7p** (3,5-MeO-Ph)	toluene	4	3 (99)	6 (*S*)
27	**7q** (1-Naphthyl)	toluene	4	32 (99)	28 (*S*)
28	**7r** (2-Naphthyl)	toluene	8	5 (99)	1 (*S*)

[a] Conditions: 1 mmol isophorone (138.2 mg), 5 µmol $Rh(CO)_2(acac)$ (1.29 mg), 6 µmol ligand, 3 mL solvent, 40°C, 5 MPa.
[b] In parenthesis parts of ketone **9**. [c] Estimated by GC.

3. CONCLUSIONS

In conclusion, we have discovered an easy and versatile access to enantiomerically pure *P*-chirogenic Xantphos ligands and related diarylether diphosphines. By application of the new protocol more than 35 *P*-chirogenic ligands were prepared in a convenient and efficient manner, which is the precondition for their application in a broad range of asymmetric transformations. The stereochemical integrity of the chirogenic centers over a period of two years was proved. By commonly applied storage under argon in a refrigerator no racemization takes place. In a first evaluation concerned to the asymmetric hydrogenation of isophorone using corresponding rhodium complexes with some of the ligands high conversion, almost perfect chemoselectivity and enantioselectivities by up to 96% were achieved.

AUTHOR INFORMATION

Corresponding Authors

jens.holz@catalysis.de

armin.boerner@catalysis.de

ASSOCIATED CONTENT

Supporting Information

Preparation procedures, NMR spectra of hydrolysis experiments, hydroformylation details, X-ray crystallographic data, DFT calculation results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) It is remarkable that the molecule lost its symmetry due to this manipulation. In the ^{1}H NMR and ^{13}C NMR spectra the signals have been doubled but in ^{31}P NMR only a joined broad signal became visible (see supplementary material). In case of compound **7g'** the signals are also doubled but in ^{31}P NMR now two broad signals at δ = +17.3/+16.0 ppm were observed. In both cases the integrals of signals belonging together are only nearly in a 1:1 ratio. It can also be assumed that the bis-borane adduct is formed in two symmetrical species. But NMR investigations of **7g'** in a temperature interval of -60 to +60°C did not show any interconversions because the ratio between integrals and positions of NMR signals kept quite constant. Removal of the BH_3-groups by treatment of **7g'** with DABCO yielded compound **7g** with the same enantiomerically purity as before. That means that no epimerization occurred.

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(34) In the ^{31}P NMR spectrum 30 mol-% of mono-BH_3-adduct of **6g** was observed at δ_P = +13.8/-29.6 ppm. The deprotection was verified by the reaction of **6g** with only one equivalent of BH_3*DMS. Under these conditions epimerization at the unprotected chiral *P*-atom did not take place.

(35) General procedure for the asymmetric hydrogenation: All reactions were carried out using an automatic device [HPChemScan, Fa. HEL Ltd.] which allows the parallel hydrogenation in up to eight mini-autoclaves (16 mL). Every autoclave was equipped with a proper glass vial and loaded with 0.5 µmmol (1.29 mg) of Rh(acac)(cod) and 0.6 µmol of ligand. After assembling of autoclaves into the device isophorone (1 mmol, 3 ml of a 0.333 M stock solution) was added under argon atmosphere. The autoclaves were purged three times with argon (0.6 MPa) and then three times with hydrogen (1 MPa). The autoclaves were heated to 40°C under ambient pressure. Then hydrogen pressure was adjusted to 5 MPa. When the reaction was finished the system was cooled down and after release of pressure the autoclaves were purged again with argon (5 cycles). The conversion and parts of product and undesired alcohol were estimated by NMR. The enantioselectivities were determined by gas chromatography.

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