DOI: 10.1002/adsc.200800363

Impact of Incorporating Substituents onto the P-*o*-Anisyl Groups of DiPAMP Ligand on the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of Olefins

Borut Zupančič,[a] Barbara Mohar,[a,*] and Michel Stephan[a,b,*]

[a] Laboratory of Organic and Medicinal Chemistry, National Institute of Chemistry, Hajdrihova 19, SI-1001 Ljubljana, Slovenia
Fax: (+386)-1-476-0300; e-mail: michel.stephan@ki.si
[b] PhosPhoenix SARL, 115, rue de l'Abbé Groult, 75015 Paris, France
E-mail: mstephan@phosphoenix.com

Received: June 11, 2008; Published online: August 19, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800363.

Abstract: The introduction of 1,2-bis[(*o*-anisyl)-(phenyl)phosphino]ethane (DiPAMP) as a *P*-stereogenic ligand for rhodium(I)-catalyzed hydrogenation by Knowles et al. came after their evaluation of several diphosphines. However, no in-depth study was carried out on incorporating various substituents on its P-*o*-anisyl groups. In this work, we have prepared a large series of enantiopure and closely related DiPAMP analogues possessing various substituents (MeO, TMS, *t*-Bu, Ph, fused benzene ring) on the *o*-anisyl rings. The new ligands were evaluated in rhodium-catalyzed hydrogenation of several model substrates: methyl α-acetamidoacrylate, methyl (*Z*)-α-acetamidocinnamate, methyl (*Z*)-β-acetamidocrotonate, dimethyl itaconate, and atropic acid. They displayed enhanced activities and increased enantioselectivities, particularly the P-(2,3,4,5-tetra-MeO-C_6H)-substituted ligand (4MeBigFUS). Interestingly enough, 88% *ee* was obtained in the hydrogenation of atropic acid using the Rh-(4MeBigFUS) catalyst under mild conditions (10 bar H_2, room temperature) versus 7% *ee* using Rh-DiPAMP. Conversely, the ligand possessing P-(2,6-di-MeO-C_6H_3) groups proved to slow down considerably the hydrogenation. X-Ray structures of their corresponding Rh complexes are presented and discussed.

Keywords: asymmetric catalysis; enantioselectivity; hydrogenation; P ligands; rhodium

Introduction

Ecological and readily scalable asymmetric hydrogenations catalyzed by soluble transition-metal complexes have been proven to be a key technology. Mediated by Rh-, Ru- or Ir-based catalysts, they enable the effective preparation of the desired enantiomers of bioactive ingredients.[1]

After the inspiring achievement of Dang and Kagan employing the L-tartaric acid-derived *cis*-chelating 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) diphosphine ligand,[2] Nobel co-laureate Knowles' and co-workers' *P*-stereogenic 1,2-bis[(*o*-anisyl)(phenyl)phosphino]-ethane (DiPAMP) ligand exhibited superior enantioselectivities and activities in the Rh(I)-catalyzed hydrogenation of β-substituted dehydro-α-alanines, and α-substituted enol esters, etc.[3] These discoveries spawned a myriad of C_2-symmetrical diphosphines. Nevertheless, since then diphosphines with a stereogenic hydrocarbon backbone continue to constitute the larger pool of available chiral phosphines compared to *P*-stereogenic ligands.

Spurred on by an economic stimulus in our quest for phosphine ligands with boosted efficiency,[4] we were interested in optimizing existing privileged phosphines for practical use instead of devising brand new ones. Hence, we were prompted to investigate further the key findings reported by Knowles et al. since mid-1970s as there appeared to be potential for tuning. Located in close proximity to the substrate coordinated to Rh, *P*-chirality is an ideal point to tackle. As a matter of fact, their initial investigation pointed to the marked effect of the environment around the Rh core, which was ascribed to the influence of the *ortho*-substituents of the P-aryl groups. They high-

lighted that 'the power of the system' resides in the presence of P-*o*-anisyl (P-*o*-An) groups leading to high TOFs and *ee*s. However, no in-depth study was conducted by systematically modifying the P-*o*-An rings either by incorporating substituents onto the ring or by altering the methyl of its methoxy group.[3,5]

Following later breakthroughs in access routes to *P*-stereogenic phosphines,[6] a number of research groups prepared various C_2-symmetrical DiPAMP-like ligands, wherein Knowles' 'tacitly recommended' P-*o*-An group is always present.[7a–g] Dissymmetrical hybrid *P*-stereogenic diphosphines or specially tailored monophosphines were synthesized as well.[7h–k] In rare cases one can find *P*-stereogenic ethane-bridged tetraaryl diphosphines wherein the phosphorus atom bears a Ph group and an aryl group other than an *o*-An.[6b–e,8]

Some X-ray crystal structures[9] or mechanistic NMR studies[10] by the groups of Heller and Brown demonstrated that a methoxy substituent on DiPAMP could coordinate with the Rh or intervene at a late stage in the hydrogenation cycle. However, although the role or effect of the P-*o*-An methoxy group in the (Rh-DiPAMP)-catalyzed hydrogenation has not been decisively clarified, Imamoto et al. suggested that a steric factor rather than a weak coordinative interaction of the oxygen atom is most likely behind the asymmetric induction.[8a]

We undertook the task of investigating extensively the effect of electronic and steric alterations to the P-*o*-An groups of DiPAMP on Rh(I)-catalyzed asymmetric hydrogenations viz. by incorporating substituents onto the P-*o*-An rings.[11] We targeted the synthesis of a series of closely related analogues of DiPAMP with different substitution patterns on the P-*o*-An groups with substituents such as: MeO, TMS, *t*-Bu, Ph, or a fused benzene ring.

Results and Discussion

Ligand Synthesis

The targeted ligands were prepared *via* the Jugé–Stephan phosphine-*P*-borane asymmetric route starting from the enantiomerically pure 1,3,2-oxazaphospholidine-2-borane complex (**1**).[6b,c,e] This synthon has already been applied in the asymmetric synthesis of DiPAMP. The adopted synthetic strategy relies upon the sequential displacement of the ephedrine auxiliary of **1** with organolithium reagents (Scheme 1). Both P-configurations can be attained starting from either (+)- or (−)-ephedrine. To build the ethane bridge, we applied two established routes, which call upon either oxidative homocoupling of P-($LiCH_2$)-phosphine-*P*-boranes (*Route A*, step d)[6a] or displacement of the P-OMe groups of 1,2-bis(phosphinito-*P*-borane)ethane (*Route B*)[6d,e] yielding the opposite P-configuration.

Following the expedient *Route A*, enantiomerically pure (*R*,*R*)-DiPAMP [(*R*,*R*)-**6a**] and its new analogues (*R*,*R*)-**6b**, **d–m** were obtained in 12–64% overall yield starting from (−)-**1** and the corresponding aryllithium reagent.[12] An alternate methodology to obtain a functionalized P-*o*-An ring from the aminophosphine-*P*-borane **2a** was explored as well. Exploiting the directed *ortho*-lithiation property of the arylic MeO group, the (*O*-methyl)-protected **2fa** was easily formed through *s*-BuLi metallation of (*O*-methyl)-protected **2aa** followed by TMSCl quench; the structure of **2fa** was confirmed independently by *O*-methylation of **2f**. Next, H^+-catalyzed methanolysis of either **2f** or **2fa** furnished the methyl phosphinite-*P*-borane **3f** with identical optical purities. We reverted to *Route B* for the synthesis of **6c** [yielding the (*S*,*S*)-enantiomer] as when following *Route A*, the by-product[13] formed during the P-OMe-displacement stage (step c) hampered the purification. Moreover, we prepared enantiomerically pure (*S*,*S*)-DiPAMP [(*S*,*S*)-**6a**] *via Route B*.

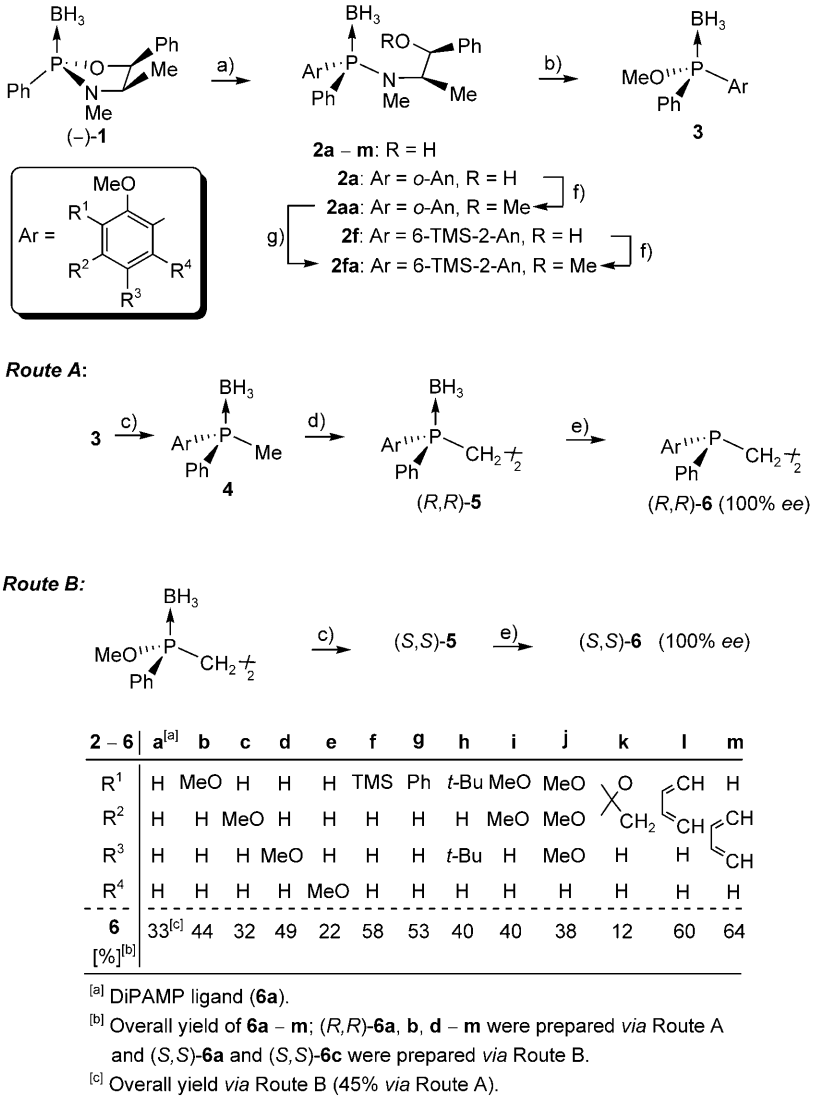
Hydrogenation Results

The assessment of the efficiency of the DiPAMP extended family members **6b–m** in comparison with DiPAMP (**6a**) in Rh(I)-catalyzed hydrogenation, was performed on the following conventional benchmark substrates: methyl α-acetamidoacrylate (MAA), methyl (*Z*)-β-acetamidocinnamate (MAC), methyl (*Z*)-β-acetamidocrotonate (*Z*-MAB), dimethyl itaconate (DMI), and atropic acid (AA) (Table 1; results correspond to unoptimized reaction conditions).

The sense of stereoselection in hydrogenation using the DiPAMP analogues **6b–m** is the same as observed with DiPAMP for all the tested substrates. The proposed empirical 'quadrant rule' is valid: (*S*)-α-amino acids were obtained using (*R*,*R*)-**6** ligands.[3b,8a,c] However, the overall performance of the new ligands was in general appreciably better than the original parent DiPAMP:[14] enhanced activities and increased enantioselectivities were obtained in almost all cases, particularly with the P-(2,3,4,5-tetra-MeO-C_6H)-substituted ligand **6j** which we dubbed '4MeBigFUS'. Exceptionally, the P-(2,6-di-MeO-C_6H_3)-substituted ligand **6e** furnished the most sluggish catalyst and yielded low *ee* values.

Hydrogenation of MAA

Regardless of the added group (MeO, TMS, *t*-Bu, Ph, or a fused benzene ring) on the P-*o*-An rings, increased reaction rates (up to 5-fold) were observed



2 – 6	a[a]	b	c	d	e	f	g	h	i	j	k	l	m
R^1	H	MeO	H	H	H	TMS	Ph	*t*-Bu	MeO	MeO	O, CH_2	CH, CH	H
R^2	H	H	MeO	H	H	H	H	H	MeO	MeO	CH_2	CH	CH
R^3	H	H	H	MeO	H	H	H	*t*-Bu	H	MeO	H	H	CH
R^4	H	H	H	H	MeO	H	H	H	H	H	H	H	H
6 [%][b]	33[c]	44	32	49	22	58	53	40	40	38	12	60	64

[a] DiPAMP ligand (**6a**).
[b] Overall yield of **6a** – **m**; (*R,R*)-**6a**, **b**, **d** – **m** were prepared *via* Route A and (*S,S*)-**6a** and (*S,S*)-**6c** were prepared *via* Route B.
[c] Overall yield *via* Route B (45% *via* Route A).

Scheme 1. Synthesis of ligands **6a**–**m**. Reagents and conditions: a) ArLi, THF or Et_2O, −20 °C→r.t.; b) MeOH, H_2SO_4, r.t.; c) MeLi (*Route A*) or ArLi (*Route B*), THF, −20 °C→r.t.; d) *s*-BuLi, THF, −30 °C then $CuCl_2$, −30 °C; e) Et_2NH or morpholine, 55–60 °C; f) NaH, MeI, THF, r.t.; g) *s*-BuLi, THF, −78→−20 °C then TMSCl, −20 °C→r.t.

with a significant increase in the induction (up to ≥99% *ee*) especially with ligands **6b**, **6f**, **6g**, **6h**, **6i**, **6j**, and **6l**. Ligands possessing $R^1 \neq H$ favoured an increase in the *ee*; for example, **6b** performed better than **6c** (or **6d**), but interestingly, the enantioselectivity was identical with **6a**, **6c** and **6d**. Also, the *ee* increased with increase in the bulkiness of R^1 going from MeO < Ph = $(CH=)_2$ < TMS < *t*-Bu. With ligand **6k**, wherein the oxygen atom of R^1 is part of a fused dihydrofuran ring, the *ee* remained unchanged but the rate increased by a factor of 2.5. Multiplication of the MeO-functionality on the P-*o*-An rings resulted in both faster reaction rates and higher *ee*s within the series **6a** < **6b** < **6i** = **6j**.

Hydrogenation of MAC

Higher *ee*s (up to 99%) as well as boosted reaction rates (up to 6-fold) were attained with the majority of the screened ligands, especially with **6f**, **6g**, **6h**, **6i**, **6j**, and **6l**. Multiplication of the MeO-substituents on the P-*o*-An led to an increase in the *ee* going from **6a** < **6b** < **6i** < **6j**. The *ee* was slightly affected with the increased steric bulk of R^1: MeO < Ph = *t*-Bu < TMS = $(CH=)_2$. With ligand **6k**, a 2.5-fold faster reaction rate was observed compared to **6a**, however with an identical *ee*. Interestingly, ligand **6b** (R^1 = MeO) led to a significantly faster reaction rate compared to **6a**, **6c** (R^2 = MeO) or **6d** (R^3 = MeO).

Table 1. $[Rh(\mathbf{6})(MeOH)_2]BF_4$ catalyzed hydrogenation of model substrates.[a]

	MAA			MAC			Z-MAB			DMI			AA		
6	Conv. [%]	*t* [min]	*ee* [%]	Conv.[%]	*t* [min]	*ee* [%]	Conv. [%]	*t* [h]	*ee* [%]	Conv. [%]	*t* [min]	*ee* [%]	Conv. [%]	*t* [h]	*ee* [%]
a	100	15	94	100	18	95	>99	16	66	100	8	85	100	3	7
b	100	8	97	100	3	97	75	16	81	100	6	76	100	3	61
c	100	6	94	100	15	97	70	16	65	100	23	88	30	3	34
d	100	6	94	100	13	96	98	16	77	100	10	88	100	3	31
e	100	360	62	100	480	56	–	–	–	–	–	–	27	17	8
f	100	4	>99	100	4	99	56	16	72	100	9	86	30	3	79
g	100	3	98	100	3	98	58	16	64	100	9	85	44	3	71
h	100	3	>99	100	12	98	57	16	72	100	24	83	69	3	5
i	100	4	99	100	4	98	86	16	76	100	4	91	100	3	38
j	100	4	99	100	4	99	100	16	80	100	5	87	100	3	88
k	100	6	94	100	7	95	89	16	69	100	3	82	21	3	48
l	100	6	98	100	3	99	38	16	70	100	14	73	100	3	43
m	100	5	95	100	11	97	100	16	58	100	7	89	100	3	43

[a] For an optimal comparison of catalyst activities, the induction period was eliminated by preforming the catalyst.[15] Runs were carried out under 1 bar of H_2 (10 bar for AA) in MeOH at room temperature with a substrate/catalyst molar ratio (S/C) of 100 for MAC, *Z*-MAB, DMI, AA, and 200 for MAA, for the time indicated.[16] Conversion and *ee* were determined by chiral GC; with (*R*,*R*)-**6**, *S*-configured hydrogenation products were obtained except with DMI.

Hydrogenation of *Z*-MAB

The inspection of hydrogenation data did not reveal particular trends upon modification of the P-*o*-An rings, but within the screened ligand set conversions were in general inferior to the one with **6a**. Conversely, ligands **6b** and **6j** afforded the highest enantioselectivity (*ca.* 80% *ee*) with the latter resulting in a complete conversion.

Hydrogenation of DMI

The analysis of the overall results revealed that the R^1 substituents exert virtually no or an unfavourable influence on the induction as was the case with **6b** and **6l**. Conversely, R^2 or R^3 substituents seemed to play a favourable role as was the case with ligands **6i** and **6m** whereby the former led to 91% *ee* in a 2-fold higher reaction rate compared to **6a**. Notably, for the best efficiency, the optimum number of MeO groups on the P-*o*-An was reached in ligand **6i** (3Me-BigFUS).[17]

Hydrogenation of AA

The screening results of the new DiPAMP analogues with this substrate revealed a pronounced and striking improvement of the *ee* in the majority of cases. As high as 88% *ee* was attained using **6j** *vs.* 7% *ee* with **6a**. Ligand **6h** ($R^1=R^3=t$-Bu) furnishing 5% *ee* with 69% conversion, performed as poorly as **6a**. By contrast, ligands **6b** (R^1=MeO), **6f** (R^1=TMS), and **6g** (R^1=Ph) led to 61%, 79%, and 71% *ee*, respectively.

Mechanistic Considerations

Chirality transfer from stereogenic DPPE-derived ligands (for example DiPAMP) to α-amino acids became a textbook example of the Rh(I)-catalyzed asymmetric hydrogenation. Some studies were conducted as well on β-dehydroamino acids, itaconates and α-arylacrylates.[18] Intimate mechanistic aspects of the proposed operative pathways were substantiated by a combination of exhaustive detailed conformational analyses resorting to *in situ* ^1H, ^{13}C, and ^{31}P NMR spectroscopy, X-ray crystallography, kinetic methods, molecular mechanics computations, etc. Informative data could be obtained from the single-crystal X-ray structure analyses of the diphosphine-Rh(I)-diene precatalyst, or from the advanced intermediate diphosphine-Rh(I)-substrate adduct (predominant diastereomer). Figure 1 displays the single-crystal X-ray diffractions of catalyst precursors $\{Rh[(R,R)\text{-P*P*}](nbd)\}BF_4$ of the extreme

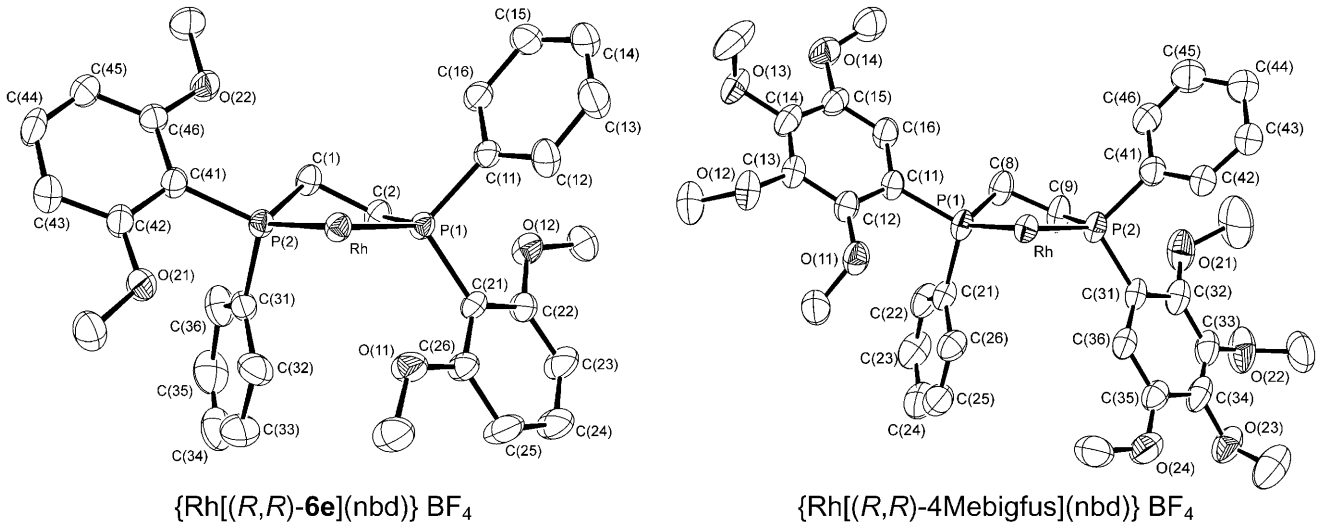


Figure 1. ORTEP drawings in elevation-view into the coordination-plane. Coordinated NBD and counter-anion (BF_4^-) are omitted for clarity. Relevant bond lengths or interatomic distances (Å) and angles (°) for {Rh[(*R*,*R*)-**6e**](nbd)}BF_4: Rh–P(1) 2.292(2), Rh–P(2) 2.297(2), Rh···O(11) 2.850(5), Rh···O(21) 3.742(5), P(1)–Rh–P(2) 83.69(5) (bite angle), Rh–P(1)–C(2) 109.8(1), Rh–P(1)–C(11) 114.6(2), Rh–P(1)–C(21) 115.1(2), Rh–P(2)–C(1) 106.0(2), Rh–P(2)–C(31) 116.0(2), Rh–P(2)–C(41) 119.3(2), γ_1 −72.8, γ_2 18.7, γ_3 2.7, γ_4 77.7; for {Rh[(*R*,*R*)-4Mebigfus](nbd)}BF_4: Rh–P(1) 2.288(1), Rh–P(2) 2.295(1), Rh···O(11) 3.795(4), Rh···O(21) 5.243(5), P(1)–Rh–P(2) 83.20(5) (bite angle), Rh–P(1)–C(8) 106.1(2), Rh–P(1)–C(11) 120.4(2), Rh–P(1)–C(21) 114.1(2), Rh–P(2)–C(9) 110.0(2), Rh–P(2)–C(31) 114.9(2), Rh–P(2)–C(41) 115.3(3), γ_1 −69.7, γ_2 20.0, γ_3 2.0, γ_4 81.5.

cases, wherein P*P* = **6e** (*left*) or 4MeBigFUS (**6j**, *right*).

The analysis of these complexes reveals profound similarities in terms of dissymmetry in the chelate cycles of these C_2-symmetrical (*R*,*R*)-P*P* ligands.[19] It shows the 5-membered chelate ring in an envelope with λ-conformation where one backbone CH_2 is at the flap of the envelope, and the other CH_2 is situated slightly out-of-plane. Also, the bulky P-(*o*-substituted)-phenyl and the P-phenyl at the fold of the envelope occupy equatorial (face/out) and axial (edge) positions, respectively. This arrangement places the substituents on the other phosphorus atom in less differentiated positions. The aryls are in a face-edge-edge-face disposition in accordance with the averaged torsion angles $\gamma_{1\text{-}4}$ [Rh–P–C_{ipso}–C_{ortho}] of aryls going from top left to top right. This is in sharp contrast with the envelope δ-conformation encountered in the rare cases of {Rh[(*R*,*R*)-dipamp](nbd)}PF_6[18f] and {Rh[(*R*,*R*)-(Ph{*o*-Tol}PCH_2)$_2$](nbd)}PF_6.[20]

Ligand (*R*,*R*)-**6e** with its P-(2,6-di-MeO-C_6H_3) substituents performed noticeably worse than (*R*,*R*)-DiPAMP, but still gave a predominance of the (*S*)-enantiomer. Ensuing the atypical hydrogenation outcome obtained with this ligand, an X-ray structure determination of its [Rh(**6e**)(nbd)]BF_4 complex confirmed our presumption that the 'forced' favoured positioning of one oxygen atom of a methoxy in this case hindered the appropriate binding of the substrate (e.g., enamide) to the Rh atom. The Rh, P(1), C(21), C(26), O(11) atoms are coplanar with a Rh···O(11) = 2.850(5) Å. This explanation is supported by the fact that the pale-yellow colored [Rh(**6e**)$(MeOH)_2$]BF_4 solvate solution did not yield the typical red-brown colour upon addition to MAC. Moreover, the ^{31}P NMR spectrum of [Rh(**6e**)$(MeOH)_2$]BF_4 in the absence or presence of MAC was almost unchanged, contrary to the spectra relative to ligand **6j**.

The steric requirements of the P-aryls and the favoured puckered-conformation of the 5-membered chelate ring induce a preferential chiral P-aryls array around the Rh(I). This in turn affects the coordination of the prochiral substrate. In the distorted square-planar Rh(I) complex, the coordinated enamide (a bidentate substrate) is orthogonal to the coordination-plane ligated *via* π-bonding of the alkene and σ-bonding of the amide oxygen atom which is nearly in-plane. The [Rh(P*P*)(enamide substrate)]$^+$ exists in two diastereomeric interchangeable forms arising from the binding of either C_α-*si* or C_α-*re* enantiotopic olefin faces. A major:minor ratio of ~10:1 for DiPAMP is formed with MAC at room temperature [(*R*,*R*)-DiPAMP yields the (*S*)-enantiomer]. Landis et al.[18f] have shown that, in solution, the chiral P-aryls orientations in [Rh(dipamp)]$^+$ are supple. In response to the steric requirements imposed by the incoming substrate, conformational changes occur through rotation of P–C_{ipso} bonds (variation of torsion angles), half-chair to envelope or λ to δ interconversions, etc. Also, the chiral P-aryls array changes on going from the major diastereomer (more favourable conformation of the chelate ring) to the minor diaste-

reomer (less favourable conformation). And the flux of catalysis is born by the minor species by its virtue of exceeding the reactivity of the major one toward the H_2 oxidative *cis*-addition. This shift towards an octahedral Rh(III)-dihydrido complex constitutes the rate- and enantio-determining step, and the main enantioselectivity occurs between the (enamide) substrate and the proximal P-phenyl H_{ortho}. Thus, the reaction rate and stereoselectivity are regulated by the relative concentration and reactivity of the two diastereomeric adducts in their resting state.[21]

The mechanism of asymmetric hydrogenation of α- and β-dehydroamino acids or itaconates (at the low H_2 pressure applied) could be different from the case of AA.[18] The striking enhancement of *ee* using the new analogues compared to DiPAMP in the hydrogenation of AA, attests the spectacular effect of judicious changes in ligand design on catalysis.[22] Up to 88% *ee* was attained with 4MeBigFUS *vs.* 7% *ee* with DiPAMP under mild conditions. Such a level of enantioselectivity constitutes a particularly respectable result in the Rh(I)-catalyzed hydrogenation of this substrate.[1a] It is quite noticeable how ligand **6h** (Ar = 4,6-di-*t*-Bu-2-An) furnished the same order of low *ee* value as DiPAMP unlike ligand **6f** (Ar = 6-TMS-2-An), which afforded 79% *ee*. A stringent explanation of these results is not available at the moment.

Overall, ligand 4MeBigFUS turned out to be the optimum ligand affording the highest *ee* values and rates. The P-(2,3,4,5-tetra-MeO-C_6H) groups increase the steric requirements of the phosphine and may favour increase in affinity of its Rh(I) complex to H_2 or facilitate the H_2 oxidative addition, which is the turnover-limiting and enantio-determining step (for enamides under 1 atm H_2 at room temperature). With MAC at room temperature, 4MeBigFUS yielded a major:minor ratio of ~3:1 influencing the observed enhanced reaction rate. Further mechanistic studies are in progress.

From all precedent investigations in the area including the present one, it transpires that the prime role of the (oxygen-containing or not) substituents of the P-(*o*-substituted)-phenyls is to induce a well pronounced chiral environment. Although in the solid state the oxygen atoms of P-*o*-An groups in Rh(I)-DiPAMP complexes (except the ones in ref.[9]) are not within a close interaction distance with the Rh center, this situation could be different during catalysis (in solution); the MeO group could serve an additional role.

Conclusions

We have prepared a large series of optically pure DiPAMP analogues possessing various substitution patterns on the P-*o*-An rings with substituents such as: MeO, TMS, *t*-Bu, Ph, or a fused benzene ring. This also included the DiPAMP analogue **6e** having an extra MeO in positon 6 of the P-*o*-An rings. The overall performance of the new ligands rivals the original parent DiPAMP ligand in the Rh(I)-catalyzed asymmetric hydrogenation. Increased activity and enantioselectivity were accomplished on the model substrates: MAA, MAC, *Z*-MAB, DMI, and AA.

Ligand **6e** furnished an extremely sluggish catalyst and yielded low *ee* values. Conversely, swapping the P-*o*-An groups with P-(2,3,4,5-tetra-MeO-C_6H) groups led to the optimum ligand in the series, 4MeBigFUS. Faster reaction rates (from 2- to 5-fold) were obtained, and up to 99% and 88% *ee*s were attained in the hydrogenation of dehydroamino acids and atropic acid, respectively. These results are bound to broaden the scope of the application of [Rh(P*P*)] which was limited to the hydrogenation of dehydroamino acids and closely related alkenes under mild conditions.

Despite current works based on the search for a rational manner of matching substrates with catalysts, the empirical design of ligands and catalysts still remains a must. Although DiPAMP was once the optimum design for *P*-stereogenic tetraaryl ligands, the overall outperformance of these new easily accessible analogues is evident. Ongoing progress in our group in this area shall be communicated shortly.

Experimental Section

For full chemical names related to phosphine and diene acronyms, see the Supporting Information.

General Procedure for the Synthesis of (Aryl)(*N*-ephedrino)(phenyl)phosphine-*P*-Boranes (2b–m)

To a cold (0 °C) solution of the corresponding bromomethoxyarene (or methoxyarene) (1.3 mol equiv.) in an appropriate solvent (ether, cyclohexane or THF) is added under stirring the appropriate BuLi (*n*, *s* or *t*) (1.3 mol equiv.). The mixture is left at room temperatuere until the transmetallation is complete. To this mixture at −30 °C, a THF (100 mL) solution of (−)-**1** (1 mol equiv.) is slowly added and the resulting mixture left to warm up to room temperature. After overnight stirring, the reaction is quenched with H_2O (5 mL). The concentrated residue is partitioned between CH_2Cl_2 (30 mL) and H_2O (100 mL), and the organic layer is dried over Na_2SO_4 then concentrated. The crude is purified on silica gel.

General Procedure for the Synthesis of Methyl (Aryl)-(phenyl)phosphinite-*P*-Boranes (3b–m)

To the (aryl)(*N*-ephedrino)(phenyl)phosphine-*P*-borane (**2b–m**) in MeOH (or MeOH/CH_2Cl_2) is added under stirring H_2SO_4 (96%, ≤ 1 equiv.) at room temperature and the mixture is left overnight. The reaction mixture is filtered

through a short bed of silica gel and concentrated. To the residue H_2O (100 mL) is added and extracted with CH_2Cl_2 (3×30 mL). The organic layer is dried over Na_2SO_4 and concentrated. Purification on silica gel eluting with toluene (**3j**: toluene/EtOAc 95:5) and/or by recrystallization afforded products **3**.

General Procedure for the Synthesis of (Aryl)-(methyl)(phenyl)phosphine-*P*-Boranes (4b, d–m)

To a cold (−20 °C) solution of methyl (aryl)-(phenyl)phosphinite-*P*-borane (**3b, d–m**) in THF is added MeLi (1.2–2.0 mol equiv.). The resulting mixture is left to warm up to room temperature. After stirring overnight, the reaction is hydrolyzed with H_2O (5 mL) and concentrated. To the residue H_2O (100 mL) is added and extracted with CH_2Cl_2 (3×30 mL). The organic layer is dried over Na_2SO_4 and concentrated. Purification on silica gel eluting with toluene (**4j**: toluene/EtOAc 95:5) and/or by recrystallization afforded products **4**.

General Procedure According to *Route A* for the Synthesis of (R_BR_P)-1,2-Bis[(aryl)(phenyl)phosphino-*P*-borane]ethanes (5b, d–m)

To a cold (−30 °C) solution of (aryl)(methyl)-(phenyl)phosphine-*P*-borane (**4b, d–m**) in THF is added *s*-BuLi (1.0 mol equiv.). After stirring at −30 °C for 1 h, anhydrous $CuCl_2$ (1.05 equiv.) is added. The reaction is left at −30 °C for an additional hour then quenched with H_2O (20 mL). The mixture is extracted with EtOAc (3×10 mL), dried over Na_2SO_4, and concentrated. Purification on silica gel and/or by recrystallization afforded products **5**.

General Procedure for the Synthesis of 1,2-Bis-[(aryl)(phenyl)phosphino]ethane (6a–m)

The 1,2-bis[(aryl)(phenyl)phosphino-*P*-borane]ethane (**5a–m**) in Et_2NH is refluxed for 2 h under an inert atmosphere. After concentration, purification on silica gel and/or by recrystallization under an inert atmosphere afforded products **6**.

(R_BR_P)-1,2-Bis[(phenyl)(2,3,4,5-tetramethoxyphenyl)-phosphino]ethane (6j): Purification on silica gel eluting with CH_2Cl_2, then with toluene/EtOAc 8:2 (R_f = 0.6) afforded a white powder; yield: 99%; mp 78–81 °C; $[\alpha]_D^{25}$: −44.8 deg cm^3 g^{-1}dm^{-1} (*c* 1.0 g dcL^{-1} in $CHCl_3$); ^{1}H NMR: δ = 2.01 [m, 2H; (PCH_aH$_b$)$_2$], 2.20 [m, 2H; (PCH$_a$$H_b$)$_2$], 3.63 (s, 6H; 2 OMe), 3.67 (s, 6H; 2 OMe), 3.87 (s, 6H; 2 OMe), 3.88 (s, 6H; 2 OMe), 6.32 (m, 2H; Ar-H), 7.28–7.34 (m, 6H; Ar-H), 7.36–7.43 (m, 4H; Ar-H); ^{13}C NMR: δ = 22.9 (m), 56.1, 60.5, 60.8, 61.0, 109.1 (m), 125.9 (m), 128.3 (m), 128.7, 133.1 (m), 137.5 (m), 143.7, 146.6 (m), 149.3 (m), 149.6 (m); ^{31}P NMR: δ = −21.5 (s); MS (EI): *m/z* (%) = 638 (20) [M^+]; HR-MS (EI): *m/z* = 638.221, calcd. for $C_{34}H_{40}O_8P_2$ [M^+]: 638.220; anal. calcd. for $C_{34}H_{40}O_8P_2$, (638.62): C 63.94, H 6.31; found: C 64.03, H 6.40.

Preparation of the Solvated [Rh(6)(MeOH)$_2$]BF$_4$ Catalysts

To a solution of [Rh(nbd)$_2$]BF$_4$ (2.8 mg) in MeOH (0.5 mL), a solution of the ligand **6a–m** (0.8 equiv. to Rh atom) in MeOH (0.5 mL) or CH_2Cl_2 (0.5 mL) is added dropwise at room temperature. The resulting solution is hydrogenated under 1 bar of H_2 for *ca.* 15 min. Elimination of metallic rhodium by filtration through a No. 3 sintered-glass filter afforded a clear brown solution of [Rh(**6**)(MeOH)$_2$]BF$_4$.

Procedure for the Hydrogenation of the Substrates in Table 1

To a solution of the substrate (0.5 mmol) in MeOH (7 mL), three freeze-pump-thaw cycles are applied and the system is filled with Ar. Then to the substrate solution is added under argon a solution of the preformed [Rh(**6**)(MeOH)$_2$]BF$_4$ catalyst (substrate/catalyst molar ratio of 100 for MAC, *Z*-MAB, DMI, AA, and 200 for MAA) in MeOH (prepared as above). A vacuum is applied to this system then it is backfilled with H_2. The mixture is stirred at room temperature under 1 bar of H_2 (10 bar for AA). The progress of the hydrogenation is monitored by the diminution of the volume of the closed reaction system at 1 bar (until H_2 uptake ceased). In case of *Z*-MAB, the reaction mixture is analyzed after 16 h, and with AA analysis is carried out after 3 h. The reaction mixture is analyzed by chiral GC (H_2 as carrier gas). Absolute configurations were assigned by comparison of optical rotation of isolated products with the literature data.

Acknowledgements

This work was supported by the Ministry of Higher Education, Science, and Technology of the Republic of Slovenia through grants P1-242 and J1-9806, and by the Ministry of National Education, Research, and Technology of France through grant 00P141 to PhosPhoenix SARL. We thank Dr. Barbara Modec, University of Ljubljana, for X-ray crystal structure analyses.

References

[1] a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, **1994**; b) *Asymmetric Catalysis on Industrial Scale*, (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**.

[2] T. P. Dang, H. B. Kagan, *J. Chem. Soc. D* **1971**, 481.

[3] a) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, *J. Am. Chem. Soc.* **1975**, *97*, 2567–2568; b) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952; c) W. S. Knowles, W. C. Christopfel, K. E. Koenig, C. F. Hobbs, *Adv. Chem. Ser.*, American Chemical Society, Washington D.C. **1982**, Vol. 196, pp 325–336; d) W. S. Knowles, *Angew. Chem.* **2002**, *114*, 2096–2107; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998–2007.

[4] M. Stephan, B. Mohar, (PhosPhoenix SARL, Nat. Inst. of Chem. of Slovenia), FR2887253, **2005**; WO2006136695, **2006**.

[5] Knowles et al. have reported their results for the hydrogenation of (*Z*)-α-acetamidocinnamic acid (AAC)

with various Rh{(*R*,*R*)-1,2-bis[(Ar)(Ph)phosphino]-ethane} catalysts (conditions: S/C = 1000 under 3 atm of H_2 in *i*-PrOH (88%) at 50 °C for 0.8–1 h): 96% *ee* (*S*) with Ar = 2-MeO-C_6H_4 (DiPAMP), 85% *ee* with 2-MeO-4-$NaOSO_2$-C_6H_3, 79% *ee* with 2-MeO-4-Me_2NSO_2-C_6H_3, 84% *ee* with 2-HO-C_6H_4, 63% *ee* with 2-AcO-C_6H_4; noteworthy, 1,2-bis[(*o*-An)(Cy)phosphino]ethane (DiCAMP) led to 64% *ee*.[3c]

[6] a) T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, K. Sato, *J. Am. Chem. Soc.* **1990**, *112*, 5244–5252; b) S. Jugé, M. Stephan, J. A. Laffitte, J.-P. Genêt, *Tetrahedron Lett.* **1990**, *31*, 6357–6360; c) S. Jugé, J.-P. Genêt, (Société Nationale Elf Aquitaine), WO9100286, **1991**; d) J. A. Laffitte, S. Jugé, J.-P. Genêt, M. Stephan, (Société Nationale Elf Aquitaine), FR2672603, **1991**; WO9214739, **1992**; e) M. Stephan, *PhD thesis*, Université Pierre et Marie Curie, Paris VI (France), **1991**; f) A. R. Muci, K. R. Campos, D. A. Evans, *J. Am. Chem. Soc.* **1995**, *117*, 9075–9076.

[7] a) For DPPP/DiPAMP hybrid, see: C. R. Johnson, T. Imamoto, *J. Org. Chem.* **1987**, *52*, 2170–2174; b) for DPPB/DiPAMP hybrid, see ref.[6a]; c) for $Me_2Si(CH_2P$-(*o*-An)Ph)$_2$, see ref.[6e] and F. Maienza, F. Santoro, F. Spindler, C. Malan, A. Mezzetti, *Tetrahedron: Asymmetry* **2002**, *13*, 1817–1824; d) for PYRPHOS/DiPAMP hybrid, see: U. Nagel, T. Krink, *Chem. Ber.* **1995**, *128*, 309–316; e) for DIOP/DiPAMP hybrid, see: K. Burgess, M. J. Ohlmeyer, K. H. Whitmire, *Organometallics* **1992**, *11*, 3588–3600; f) X. Zhang, (The Penn State Research Foundation), WO9713763, **1997**; g) for DPPF/DiPAMP hybrid, see: U. Nettekoven, P. C. J. Kamer, P. W. N. M. van Leeuwen, M. Widhalm, A. L. Spek, M. Lutz, *J. Org. Chem.* **1999**, *64*, 3996–4004; F. Maienza, M. Wörle, P. Steffanut, A. Mezzetti, *Organometallics* **1999**, *18*, 1041–1049; h) for dissymmetric DPPE/DiPAMP hybrid, see: J. A. Ramsden, J. M. Brown, M. B. Hursthouse, A. I. Karalulov, *Tetrahedron: Asymmetry* **1994**, *5*, 2033–2044; i) for dissymmetric Me-BPE/DiPAMP and RoPHOS/DiPAMP hybrids, see: D. Carmichael, H. Doucet, J. M. Brown, *Chem. Commun.* **1999**, 261–262; j) for MOP/PAMP hybrid, see: L. J. Higham, E. F. Clarke, H. Müller-Bunz, D. G. Gilheany, *J. Organomet. Chem.* **2005**, *690*, 211–219; k) for a PAMP derivative with a β-sp^2 N donor group, see: H. Yang, N. Lugan, R. Mathieu, *An. Quim. Int. Ed.* **1997**, *93*, 28–38.

[8] a) Y. Wada, T. Imamoto, H. Tsuruta, K. Yamaguchi, I. D. Gridnev, *Adv. Synth. Catal.* **2004**, *346*, 777–788; therein the hydrogenation of MAC under 3 atm H_2 in *i*-PrOH at 50 °C with Rh{1,2-bis[(Ar)(Ph)phosphino]-ethane} where Ar = *o*-Tol, *o*-EtC_6H_4, and α-(5′,6′,7′,8′-tetrahydronaphthyl) (WadaPHOS), furnished 92, 97, and >99% *ee*, respectively, demonstrating that such groups can simulate the enantiodifferentiation of *o*-An groups of DiPAMP; b) M. Gómez, S. Jansat, G. Muller, D. Panyella, P. W. N. M. van Leeuwen, P. C. J. Kamer, K. Goubitz, J. Fraanje, *Organometallics* **1999**, *18*, 4970–4981; c) F. Maienza, F. Spindler, M. Thommen, B. Pugin, C. Malan, A. Mezzetti, *J. Org. Chem.* **2002**, *67*, 5239–5249; therein hydrogenation of MAC with (Rh{(*S*,*S*)-1,2-bis[(α-naphthyl)(phenyl)phosphino]ethane)-(cod)}BF_4) under 1.1 bar H_2 in MeOH at 25 °C furnished surprisingly the (*S*)-enantiomer in 98.6% *ee*.

[9] H.-J. Drexler, W. Baumann, T. Schmidt, S. Zhang, A. Sun, A. Spannenberg, C. Fischer, H. Buschmann, D. Heller, *Angew. Chem.* **2005**, *117*, 1208–1212; *Angew. Chem. Int. Ed.* **2005**, *44*, 1184–1188; X-ray of major diastereomers of {Rh(dipamp)[methyl (*Z*)-β-(*N*-acetamido)-β-aryl-acrylate]}BF_4 complexes controlling the stereochemistry of the final compound showed Rh···O ~2.3 Å.

[10] J. A. Ramsden, T. D. W. Claridge, J. M. Brown, *J. Chem. Soc. Chem. Commun.* **1995**, 2469–2471.

[11] For modification of the methyl of methoxy groups, see ref.[4]

[12] M. M. S. Stephan, D. Šterk, B. Modec, B. Mohar, *J. Org. Chem.* **2007**, *72*, 8010–8018; therein, related (R_P)-(aryl)[(1*S*,2*R*)-*N*-ephedrino](phenyl)phosphine-*P*-boranes, where aryl = 2,6-dimethoxyphenyl, 2,4,6-trimethoxyphenyl, and 2-methoxy-1-naphthyl, were prepared.

[13] According to ^{1}H NMR of the mixture of the inseparable products, we believe that the by-product is most likely (ethyl)(5-methoxy-2-anisyl)(phenyl)phosphine-*P*-borane.

[14] Our results using $[Rh(dipamp)]^+$ are in agreement with the literature data for MAA (see: J. W. Scott, D. D. Keith, G. Nix Jr. , D. R. Parrish, S. Remington, G. P. Roth, J. M. Townsend, D. Valentine Jr. , R. Yang, *J. Org. Chem.* **1981**, *46*, 5086–5093), MAC,[3b] *Z*-MAB,[18h] and DMI;[18j] with DiPAMP an increase in temperature leads to an increase in *ee*, and an increase in pressure leads to a decrease in *ee*.

[15] J. M. Brown, P. A. Chaloner, *J. Am. Chem. Soc.* **1980**, *102*, 3040–3048.

[16] Evolution of H_2 was monitored by the diminution of the volume of the closed reaction system under 1 bar (until uptake ceased). In the case of *Z*-MAB, the reaction mixture was analyzed only after 16 h, and with AA after 3 h. Reported results correspond to the average of duplicate independent runs.

[17] Under identical conditions, hydrogenation of itaconic acid with $[Rh(4Mebigfus)(MeOH)_2]BF_4$ led to 85% *ee* with total conversion in 35 minutes, while with DiPAMP, 11% *ee* was obtained and up to 40% conversion in 1 hour.

[18] a) B. Bosnich, N. K. Roberts, *Adv. Chem. Ser.* American Chemical Society, Washington D.C. **1982**, Vol. 196, pp 337–354; b) J. M. Brown, P. A. Chaloner, in: *Homogeneous Catalysis with Metal Phosphine Complexes*, (Ed.: L. H. Pignolet), Plenum Press, New York, **1983**, pp 137–165; c) J. Halpern, in: *Asymmetric Synthesis*, Vol. 5, (Ed.: J. D. Morrison), Academic Press, New York, **1985**, pp 41–69; d) C. R. Landis, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 1746–1754; e) B. McCulloch, J. Halpern, M. R. Thompson, C. R. Landis, *Organometallics* **1990**, *9*, 1392–1395; f) J. S. Giovannetti, C. M. Kelly, C. R. Landis, *J. Am. Chem. Soc.* **1993**, *115*, 4040–4057; g) M. Yasutake, I. D. Gridnev, N. Higashi, T. Imamoto, *Org. Lett.* **2001**, *3*, 1701–1704; h) D. Heller, H.-J. Drexler, J. You, W. Baumann, K. Drauz, H.-P. Krimmer, A. Börner, *Chem. Eur. J.* **2002**, *8*, 5196–5203; i) ref.[9]; j) W. C. Christopfel, B. D. Vine-

yard, *J. Am. Chem. Soc.* **1979**, *101*, 4406–4408; k) J. M. Brown, D. Parker, *J. Chem. Soc. Chem. Commun.* **1980**, 342–344; l) J. M. Brown, D. Parker, *J. Org. Chem.* **1982**, *47*, 2722–2730; m) H.-J. Drexler, S. Zhang, A. Sun, A. Spannenberg, A. Arrieta, A. Preetz, D. Heller, *Tetrahedron: Asymmetry* **2004**, *15*, 2139–2150.

[19] CCDC 694160 {Rh[(*R*,*R*)-**6e**](nbd)}$BF_4$and CCDC 694161 {Rh[(*R*,*R*)-4Mebigfus](nbd)}BF_4 contain the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: +44–1223–336–033; e-mail: deposit@ccdc.cam.ac.uk]. X-Ray crystal structure analysis of the few known Rh complexes of C_2-symmetrical tetraaryldiphosphines of the type $[Rh(P^*P^*)(diene)]^+$ like {Rh[(*S*,*S*)-dipamp](nbd)}BF_4,[18m] {Rh[(*R*,*R*)-dipamp](cod)}BF_4,[18m] and {Rh[(*S*,*S*)-wadaphos](cod)}BF_4,[8a] shows a rather symmetrical half-chair λ- or δ-conformation for the saturated 5-membered chelate ring of (R_R,R_P)-P*P* and (S_R,S_P)-P*P*, respectively. These complexes possess an alternating ''edge-face exposed'' disposition of the four P-aryls and the backbone CH_2 groups are situated out-of-plane, one above and one below the P–Rh–P coordination-plane. In this arrangement, the bulky P-(*o*-substituted)-phenyls are positioned face-on (occupying the pseudoequatorial sites), and the P-phenyls are positioned edge-on (occupying the pseudoaxial sites). Moreover, the P-(*o*-substituted)-phenyls could adopt an 'in' (as in {Rh[(*R*,*R*)-dipamp](cod)}BF_4) or an 'out' (as in {Rh[(*S*,*S*)-dipamp](nbd)}BF_4) orientation to the Rh.

[20] H. Tsuruta, T. Imamoto, K. Yamaguchi, I. D. Gridnev, *Tetrahedron Lett.* **2005**, *46*, 2879–2882; therein, an envelope λ-conformation for {Rh[(*R*,*R*)-(Ph(*o*-Tol)$PCH_2)_2$](cod)}SbF_6 was observed as well.

[21] For enantioselectivity and reaction rate versus conformation of 5-membered chelate rings of the type $[Rh(PP)(diene)]^+$ wherein PP is a stereogenic DPPE-derived ligand with chirality on the ethane-bridge, see: a) J. D. Oliver, D. P. Riley, *Organometallics* **1983**, *2*, 1032–1038; b) J. M. Brown, P. L. Evans, *Tetrahedron* **1988**, *44*, 4905–4916; c) H. Brunner, A. Winter, J. Breu, *J. Organomet. Chem.* **1998**, *553*, 285–306.

[22] The first proof of concept using chiral phosphines in catalysis to transfer chirality was applied in hydrogenation of α-ethylstyrene and atropic acid leading to 5–15% *ee* by the use of (Me)(Pr)PPh. For this, see: a) L. Horner, H. Siegel, H. Büthe, *Angew. Chem.* **1968**, *80*, 1034–1035; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942; b) W. S. Knowles, M. J. Sabacky, *Chem. Commun. (London)* **1968**, 1445–1446.

