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A Highly Tunable Family of Chiral Bisphospholanes for Rh-Catalyzed Enantioselective Hydrogenation Reactions

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Abstract: A set of 16 new and closely related bisphospholane ligands have been prepared by using a highly flexible and convergent approach. Each synthesis can be performed on an industrially relevant scale. The bisphosphines differ in the nature of the bridge connecting both phospholane units. Bridges are formed by three-, four-, five- and six-membered heterocyclic or alicyclic rings. Bisphospholanes and their Rh-precatalysts have been investigated by using results of theoretical calculations (DFT) and analytic measurements (^{31}P and ^{103}Rh NMR spectroscopy, X-ray structure analysis). The studies showed that catalysts based on ligands with maleic anhydride or maleimide bridges give constantly superior enantioselectivities in methanol as the solvent. This may account for optimised steric and electronic effects. However, by changing the solvent catalysts with other backbones can give rise to excellent results. This gives proof that simple correlations between steric and electronic properties and results in the enantioselective hydrogenation frequently claimed in literature are not general.

Keywords: asymmetric catalysis · density functional calculations · hydrogenation · phosphane ligands · rhodium

Introduction

Transition-metal-catalyzed enantioselective hydrogenation has been established as one of the most popular reactions for the synthesis of optically active compounds in both academic and industrial environments.[1] In particular chiral ligands bearing a trivalent phosphorus ligating atom for "soft" metals like rhodium(I), ruthenium(II), or iridium(I) play a pivotal role in this area.[2] Over the last 35 years a tremendous number of phosphorus ligands have been described for this purpose. While significant progress has been made in finding new ligand motifs, there remains a lack of a fundamental understanding of how the enantioselectivity can be controlled.

Enantioselectivity is the result of several factors. Besides reaction conditions, geometric or/and electronic parameters of ligands and catalysts play a pivotal role. A literature survey revealed that different aspects have been addressed in the last years. Achiwa was one of the first who suggested that electron-rich phosphines could be an important requisite for achieving high enantioselectivity (respective control concept).[3] In agreement with this assumption, RajanBabu and co-workers observed enhanced enantioselectivities in the Rh-catalyzed hydrogenation of α-acetamido acrylates with sugar-derived diarylphosphinites as ligands bearing electron-donating groups in *meta* or *para* position.[4] However, in strong contrast, Bakos et al.[5a] and some of us[5b] found with rhodium complexes derived from C_2-symmetric 1,3-bisphosphine ligands that the hydrogenation of itaconic acid and its dimethyl ester takes benefit from catalysts bearing P ligands with electron-withdrawing groups.

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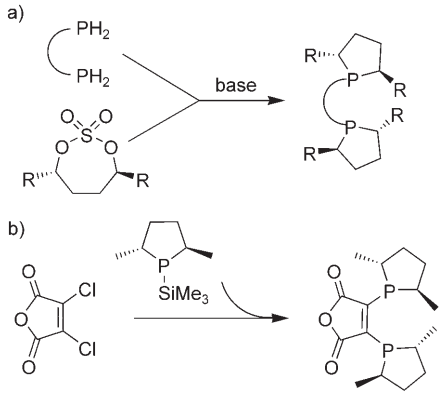
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It contains the full experimental details and all hydrogenation results.

Several efforts were also made to find correlations between geometric features in the catalysts and enantioselectivity. From the stereochemical point of view the quadrant diagram model is one of the best known concepts.[6] In this model, occupied and vacant quadrants indicate areas of maximum and miminum repulsive interactions between parts of the catalysts and the prochiral substrate. Provided that the mechanism of the hydrogenation reaction is known,[6c] this model may help to predict the dominant configuration in the product. Derived from the theory of metal-catalyzed regioselective C–C coupling reactions, van Leeuwen and co-workers stressed the importance of a natural bite angle P-Rh-P of 85–95° for efficient enantiodiscrimination in hydrogenation reactions.[7] A practical example of geometric fine-tuning of the catalyst was provided by Zhang et al. with the discovery of the tunephos (tunephos = (*R*)-(6,6′-*O*-(1,3-alkylene)oxylbiphenyl-2,2′-diyl)bis(diphenyl)-phosphine) family.[8] This allowed the selection among six electronically similar ligands, but with different dihedral angles for the efficient hydrogenation of β-keto esters.[8a] Later on Genêt et al. gave proof that this transformation may be also run by electronic effects.[9] Thus, a binap-type (binap = (1,1′-binaphthalene)-2,2′-diylbis(diphenylphosphine)) ligand with enhanced π-acidic character on the phosphorus atom, but constant dihedral angle (e.g., 4,4′-bis(2,2-difluoro-1,3-benzodioxol)-5,5′-diyl]bis(diphenylphosphine) = difluorphos) was found to be superior. Recently, in extending the quadrant diagram model Saito et al. developed a mathematical approach, in which atoms or groups that can impact enantioselectivity were localized in a three-dimensional space.[10] The idea was advocated that broad mapping of catalysts and identification of so-called "sweet spots" could be helpful to find most effective catalysts for the hydrogenation of a particular substrate.

Currently, the realization of this demand is hampered by some serious problems: thus, up to now the synthesis of chiral P ligands is mainly governed by synthetic limitations. Therefore, a vast number of strongly varying ligand motifs has been described in the literature,[2] but families covering a large set of closely related ligands are very scarce (exceptions are for example, permutations of binap[11] and 1-[2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (josiphos).[12] Only a few such related ligands required for broad testing are commercially available. In addition, only a small number of P ligands and their metal complexes have been comprehensively characterized in terms of steric and electronic properties.

One of the most prominent bisphosphine ligands for enantioselective hydrogenation is the bisphospholane duphos (duphos = 1,2-bis(phospholano)benzene), which was developed by Burk based on Achiwa's idea to create an electron-rich bisphosphine.[13] This ligand and the related bisphospholane BPE (BPE = 1,2-bis(phospholano)ethane) were successfully applied for the reduction of a broad range of prochiral olefins and ketones.[13,14] Now, duphos is used on an industrial scale.[15] Moreover, the ligand could also be advantageously employed in other enantioselective catalytic reactions.[16] These unique features have stimulated several groups to construct other chiral phospholanes[17,18] or related saturated P heterocycles with varying ring sizes, such as phosphetanes,[19] and phosphinanes.[20]

From industrial as well from academic points of view there are some serious problems connected with the employment of this ligand type. The main drawback is the traditional and commonly used synthesis first suggested by Burk based on the double nucleophilic substitution of a chiral cyclic sulfate by two primary phosphine groups (Scheme 1a).[13] This methodology is restricted to accessible



Scheme 1. Different pathways for the construction of chiral bisphospholanes.

primary phosphines as starting material. Unfortunately, most primary phosphines are quite expensive. In addition, strong bases are required for the generation of the nucleophilic phosphide anion[21] that may interfere with other functional groups in the molecule. Due to these reasons the number of synthetically feasible permutations is rather limited.

Due to the restricted selection of required bisphosphines a stepwise variation of the steric and electronic properties of the bridge connecting both phospholane units is difficult to achieve. In addition, structural modifications, for example, in the bridge, typically 1,2-phenylene,[22] may break the C_2 symmetry of the ligand, commonly considered as a precondition for high stereodiscriminating ability of bisphospholanes catalysts. The amount of structural modifications published up to now has lead to dramatic differences in the physical properties of these ligands (geometry, polarity). Moreover, only a few of them are commercially available.[23] Therefore, until now comprehensive testing and reliable comparisons of catalytic properties were not possible.

Recently, we discovered an alternative process to access a chiral bisphospholane ligand based on the reaction of 2,3-dichloromaleic anhydride with a trimethylsilylphospholane (TMS-phospholane; Scheme 1b).[24] The new ligand, now already commercialized, gives enhanced selectivities over Me-duphos (Me-duphos = 1,2-bis(2,5-dimethylphospholano)benzene) in several Rh-catalyzed enantioselective hydrogenation applications.[25,26] Herein, we show that through certain

modifications this synthetic approach can be easily scaled up. Moreover, it establishs one of the most comprehensive sets of closely related P ligands.[27]

For the design of ligands we were inspired by the idea of creating a selection of bisphospholanes with different C=C–P angles (γ; type **1**) and varying alkyl groups on the phospholane ring (type **2**), respectively (Figure 1).

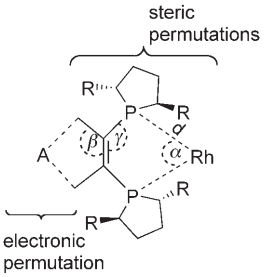


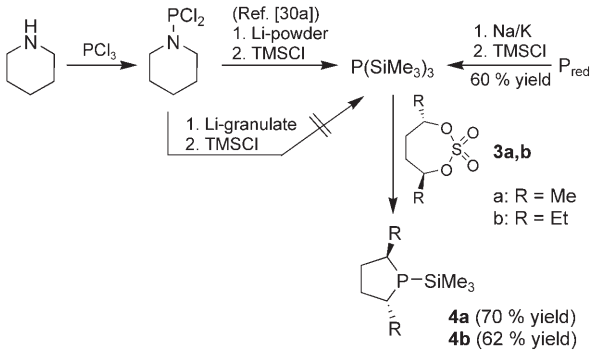
Figure 1. Tunable properties of Rh catalysts with bisphospholane ligands of type **1** (variation of the bite angle α) and **2** (variation of R); (d = distance P–Rh).

Different C=C–P angles γ can be easily adjusted by the variation of the angle β. The size of the latter should be directly proportional to the size of the ring. These parameters determine the magnitude of the bite angle α at the rhodium center as well as the length of the Rh–P bond (d). The latter should be also dependent on the basicity of the ligating phosphorus atom. It is reasonable to assume that an increase of the bite angle and a shortening of the Rh–P bond corresponds to a decrease of the distance between the catalytic center and ligand backbone. This should therefore affect the strength of the repulsive interactions between catalyst and prochiral substrate. Further and more subtle permutations of geometric and electronic parameters can be achieved by replacement of single atoms in bridges of the same ring size.

Results and Discussion

Synthesis of ligands: An important reaction in our convergent approach is the coupling of 2,5-dialkyl-1-trimethylsilylphospholanes with activated 1,2-dichlorides. We had to modify several steps of our originally reported route[24,28] for broader applicability, safety issues, and commercial scale-up.

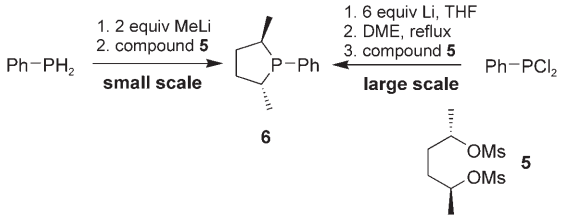
*Laboratory-scale synthesis of TMS-phospholanes **4a,b***: Our recently reported approach was based on the synthesis of trimethylsilylphospholane **4a** starting from tris(trimethylsilyl)phosphine (Scheme 2).[24] The latter was synthesized by the condensation of piperidine with PCl_3[29] and a subsequent reaction of the product with chlorotrimethylsilane in the presence of lithium as a strong base.[30a] The major drawback of this procedure is the availability of appropriate lithium powder on a commercial scale. Unfortunately, we did not succeed in an alternative approach by using granulated lithium. However, $P(SiMe_3)_3$ could be successfully synthesized from a procedure noted in literature by using red phosphorus and sodium/potassium alloy for the formation of sodium/potassium phosphide followed by the addition of chlorotrimethylsilane.[30b] The product was obtained in 60% yield. This step could be scaled up to 1 mol.



Scheme 2. Small-scale synthesis of TMS-phospholanes **4a**,**b**.

An amount of 150 g of $P(SiMe_3)_3$ was used for the further trials. This reacts easily with chiral sulfates **3a**,**b** to afford TMS-phospholanes **4a**,**b** in good yields. Both compounds proved to be remarkably stable reagents. The pyrophoric phospholanes could be distilled and stored under argon for several months without any tendency to decompose or epimerize. For safety issues the compounds were diluted with THF to 50% and 20%.

Scale-up synthesis of TMS-phospholane 4a and preparation of bisphospholanes: To provide the material on a commercial scale we developed an alternative synthesis for **4a**, avoiding the hazardous sodium/potassium alloy and the use of the chiral cyclic sulfate **3a**, which is part of a patent claim.[28] First we tried the synthesis of phenylphospholane **6** by the reaction of (*S*,*S*)-2,5-hexanediolbismesylate (**5**) and phenylphosphine in the presence of a strong base as reported by Burk[13a,b] and Wilson,[31] respectively (Scheme 3). This

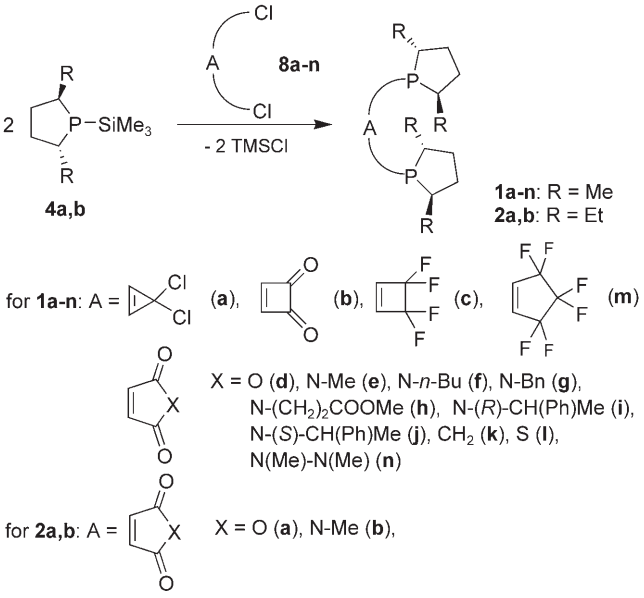


Scheme 3. Alternative syntheses of 2,5-dimethyl-1-phenylphospholane **6**.

procedure gave fast access to chiral 2,5-dimethyl-1-phenylphospholane (**6**) in 76% yield and could also be used for laboratory-scale experiments. However, due to the high raw-material costs and the handling of flammable and highly volatile phenylphosphine, the step was difficult to scale up. We found dichlorophenylphosphine as a more suitable starting material; however, the required halogen–lithium exchange in $PhPCl_2$ is a potential safety risk during scale up. The enthalpy (ΔH) of the strongly exothermic reaction was determined to be $-195\ kcal\,mol^{-1}$. Therefore, the temperature

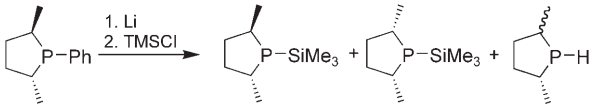
during the addition of lithium should be carefully controlled (<20 °C). Best results were obtained by exchanging the solvent from THF to DME 1 h after the addition. Then the mixture was refluxed for 5 h. The excess lithium was removed by filtration. Subsequently, bismesylate **5** was added to the solution at low temperature ($\Delta H = -160$ kcal mol^{-1}!). Pure (*R*,*R*)-2,5-dimethyl-1-phenylphospholane (**6**) was isolated with 51 % overall yield after distillation.

The next synthetic step relied on the ability to cleave the P–Ph bond, while avoiding epimerization of the chiral centers. Burk et al. found that the quality of lithium and the epimerization rate were related.[13a,b] They observed the formation of up to 40–50 % of the *meso* compound. In our preliminary experiments we could obtain the TMS-phospholane **4a** in a 4:1 chiral/*meso* ratio.[24] However, this mixture is not suitable for an industrial approach. After careful modification of reaction conditions, we were able to reduce the formation of compound *meso*-**4a** to below 13 % as well as the formation of the undesired secondary phospholane **7** (Table 1). Stirring of lithium in THF for 1 h before starting



Scheme 4. Convergent approach to the synthesis of chiral bisphospholanes.

Table 1. Cleavage of P–Ph bond in **6** with lithium.



	Li [equiv]	*T* [°C]	*t* [h]	**6** [%][a]	**4a** [%][a]	*meso*-**4a** [%][a]	**7** [%][a]	Other products[b] [%][a]
1	4	23	4	54	25	3	9	9
2	8	23	2	12	52	12	9	15
3[c]	4	23	4	0	65	6	9	18
4[c]	8	50	2	0	65	6	19	10
5[c]	3	50	4	0	72	8	2	18
6[c]	3	50	3	0	71	11	7	11
7[c,d]	4	23	4	73	5	1	6	15
8[c,e]	4	50	3	0	78	8	0	14
9[c,f]	4	50	3	21	51	5	10	13

[a] Determined by ^{31}P NMR spectroscopy in [D$_8$]THF. [b] Phosphine oxides, P–P coupling products etc. [c] Li was stirred for 1 h in THF before the reaction was initiated. [d] With two equivalents of DMPU. [e] With two equivalents of TMEDA. [f] With two equivalents of NMP.

the cleavage gave the best results. Under optimized conditions **4a** was obtained in 51 % yield and >95 % purity after distillation on a multigram scale.

Subsequent reaction of 2,5-dimethyl- or 2,5-diethyl-TMS-phospholanes **4a**,**b** with a series of dichlorides **8a–n** yielded the desired bisphospholanes **1a–n** and **2a**,**b** bearing three-, four-, five-, and six-membered hetero- or carbocycles as bridges (Scheme 4). Most of the required dichlorides are commercially available or could be synthesized in a few steps by means of known procedures. Based on this approach, one of the most comprehensive library of chiral bisphosphine ligands covering 16 closely related compounds could be prepared.

Synthesis of Rh complexes and characterization of ligands and precatalysts: Cationic Rh complexes of the type [Rh(cod)(bisphospholane)]BF$_4$ (cod = cyclooctadiene) were prepared by reaction of the bisphosphines with [Rh(cod)$_2$]BF$_4$. Remarkably, ligand **1a** did not give a uniform complex. In the NMR spectra various species were observed. Due to our unique construction principle, with the exception of ligands of type **2**, all variations are dependent on the nature of the backbone bridge. To quantify these differences, the bisphospholanes and corresponding Rh(cod) complexes were optimized at the B3LYP level of density functional theory with the LANL2DZ basis set as implemented in the Gaussian 98 program.[32] As clearly shown in Figure 2, which details data of most typical complexes based on ligands of type **1**, a decrease of the ring size (following the order six-, five-, four-, and three-membered rings) corresponds to a larger C=C–P

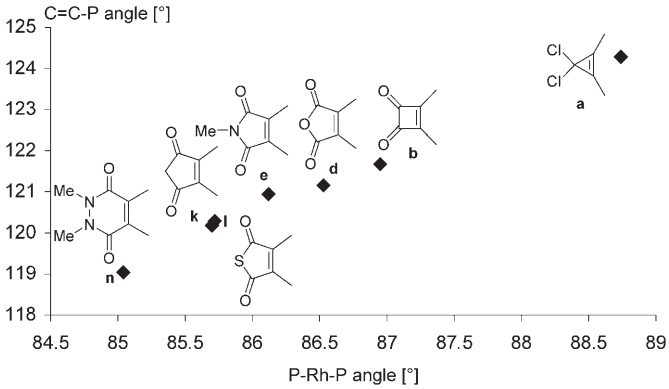


Figure 2. Calculated correlation between C=C–P angle (γ) and natural bite angle (α) of selected bisphospholanes of type **1** and their cationic [Rh(cod)(bisphospholane)]$^+$ complexes with different backbones.

angle. Simultaneously, the natural bite angle P–Rh–P angle increases. The largest difference is 3.8° (complexes derived from **1a** and **1n**). Apparently, due to the extremely large C=C–P angle of the bisphospholane with the three-membered backbone ring in **1a**, this ligand tends more to form bridged dinuclear or polymeric Rh species instead of the desired mononuclear complex (vide supra). Within the five-membered ring series, replacing the oxygen atom with nitrogen and carbon decreases the bite angle. This is clearly due to an increase in the radii of the concerned atom. The complex derived from ligand **1l** is unique and can be explained by the large atomic radius of sulfur (element of the second row of the periodic table).

Crystals suitable for X-ray analysis were obtained by slow diffusion of diethyl ether into a concentrated solution of the rhodium complexes in CH_2Cl_2.[33] X-ray single-crystal structural analyses established the structures of the cations as shown in Figure 3; selected bond lengths and intramolecular angles are given in the legend. Experimentally determined angles correlate well with the calculated values.

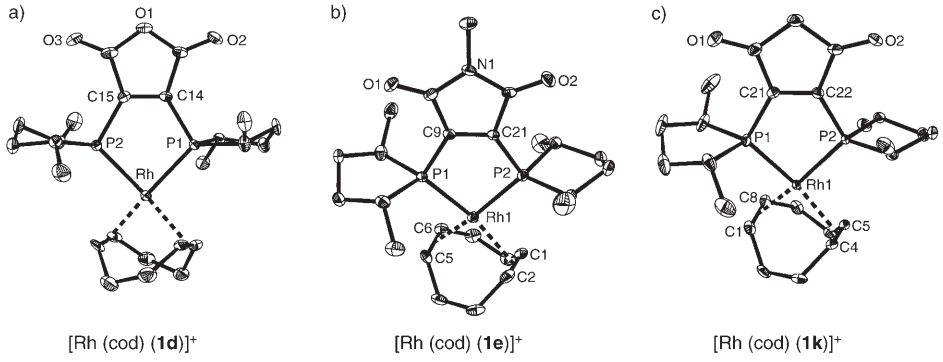


Figure 3. a)–c) Crystal structures of cationic complexes of the type [Rh(cod)(bisphospholane)]BF_4 based on ligands **1d**, **1e**, and **1k**, respectively. Hydrogen atoms as well as BF_4 anions have been omitted for clarity. The thermal ellipsoids correspond to 30% probability. The bite angles (α) are 87.04(5)° for **1d**, 86.30(5)° for **1e**, and 85.98(5)° for **1k**. Other interatomic distances (Å) and selected intramolecular angles (°) for a) [Rh(cod)(**1d**)]$^+$: Rh1–P1 = 2.275(1), Rh1–P2 = 2.284(1), C=C–P1 = 119.2(4), C=C–P2 = 119.8(4); dihedral angle P–C=C–P = 8.2. b) [Rh(cod)(**1e**)]$^+$: Rh1–P1 = 2.276(2), Rh1–P2 = 2.292(2), C=C–P1 = 118.5(6), C=C–P2 = 121.2(6); dihedral angle P–C=C–P = 4.0. c) [Rh(cod)(**1k**)]$^+$: Rh1–P1 = 2.258(2), Rh1–P2 = 2.260(2), C=C–P1 = 117.9(3), C=C–P2 = 119.0(3); dihedral angle P–C=C–P = 2.3.

Recently a discussion on which substituents on 2,5-dimethyl-phospholane rings are responsible for the high stereodiscriminating ability of the corresponding Rh catalysts has been debated in the literature. In Rh–duphos complexes this feature was attributed to the bulky alkyl groups.[13d,34,35] In contrast, Orpen and Pringle found that with a related Pt complex, bearing a ligand in which both phospholane units were connected by a 1,2-*trans*-cyclopentane bridge, the axially placed hydrogen atom in α′-position to the phosphorus atom rather than the equatorial α-methyl group dominates the critical diastereofacial repulsive interaction with the prochiral substrate.[36,37]

We have investigated this aspect in our Rh precatalysts. Inspection of the X-ray structure analyses of Rh complexes bearing ligands with planar five-membered-ring backbone bridges (Figure 3) show that the phospholane units adopt a half-chair conformation. All methyl groups are fixed in equatorial positions. Density functional theory (DFT) calculations were performed to identify atomic groups or single atoms that could be attributed to maximal repulsive interactions with a metal-coordinated substrate. In particular, the distance between the highest located hydrogen atom of the methyl group and the plane hosting both P atoms (Figure 4, distance *a*) and the distance of a relevant axially situated hydrogen atom connected with the phospholane ring (distance *b*) were compared. In all instances one of the hydrogen atoms of the (free-rotating) methyl groups projects more strongly out of the plane than the relevant ring hydrogen atom (Table 2). Therefore, the quadrant model attributing vacant and occupied diagonal quadrants can be depicted as shown in Figure 4c.

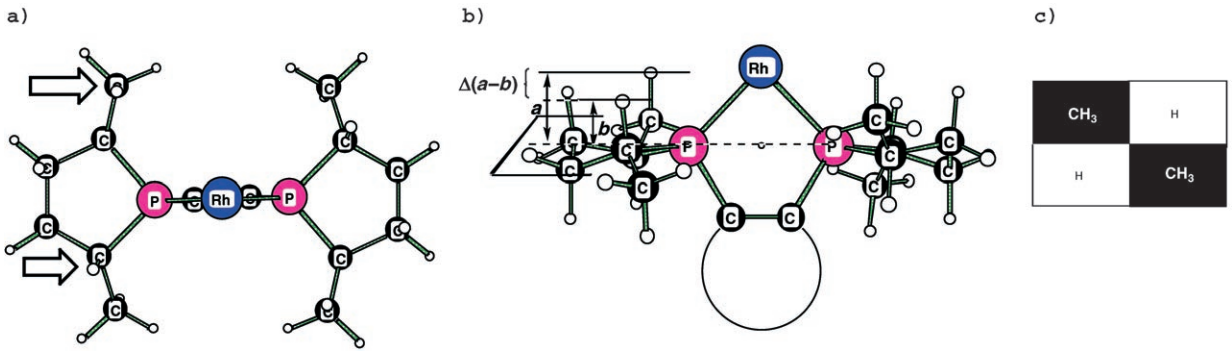


Figure 4. Methyl groups versus hydrogen atoms as stereodiscriminators a) top view (arrows indicate relevant H atoms); b) side view; c) quadrant model for the C_2-symmetric Rh complex.

Table 2. Computed structural parameters at the B3LYP/LANL2DZ(d) level.

Ligand	*a* [Å]	*b* [Å]	*a*–*b*	Rh–C[a] [Å]	Rh–P (*d*)[b] [Å]
1a	1.645	0.845	0.800	3.9703	2.4283
1b	1.650	0.835	0.815	3.9397	2.4013
1c	1.653	0.902	0.751	3.9445	2.3969
1d	1.645	0.925	0.720	3.8945	2.3821
1e	1.652	0.945	0.707	3.8843	2.3813
1l	1.667	0.976	0.691	3.8551	2.3708
1k	1.654	0.964	0.690	3.8679	2.3762
1m	1.688	1.106	0.582	3.7835	2.3567
	1.759	0.965	0.794	3.8743	2.3643
1n	1.720	1.036	0.684	3.7592	2.3541

[a] Distance between Rh and CH_3 group. [b] See Figure 1.

It is interesting to note, that the difference in length between *a* and *b* becomes smaller (in total by ca. 15%) in the order of three-, four-, five-, and six-membered-ring backbones. In other words, based on purely steric reasons it is justified to assume that the intrinsic stereodiscriminating power of Rh complexes with small backbone rings should be superior in comparison to catalysts with a larger backbone ring. The Rh complex derived from ligand (**1m**) bearing the hexafluorocyclopentene bridge also fits in the quadrant model depicted in Figure 4c, albeit the partially saturated ring adopts an envelope confirmation. Evidently, all Rh–bisphospholane complexes in which an ethylene bridge connects both phospholane units owe their intrinsic stereodiscriminating ability to the α-methyl groups. Only a *trans*-substitution pattern (e.g., caused by a fully saturated cyclopentane backbone as investigated by Orpen and Pringle[36a]) may give rise to a reversed steric arrangement. As a result, relevant axial α′-H atoms can become dominant in this respect.

Our calculations also reveal that the distance between the rhodium center and the C atoms of the methyl groups is largest with complexes based on ligands bearing small backbone rings. This can be easily explained by a widening of the bite angle. In terms of the quadrant model, our results can be summarized in the following way: catalysts discussed herein with a small bite angle offer the prochiral substrate rather "narrow" repulsive interactions caused by both methyl groups (Figure 5a). Their stereodifferentiating potential may be low due to less pronounced differences in the geometric position of competing atoms and atomic groups (methyl groups vs. H atoms). In contrast, catalysts with a large bite angle should have a larger stereodifferentiating potential. The decisive stereodifferenting methyl groups are remote, hence a maximal stereodifferentiating interaction with a prochiral substrate should be expected (Figure 5b).

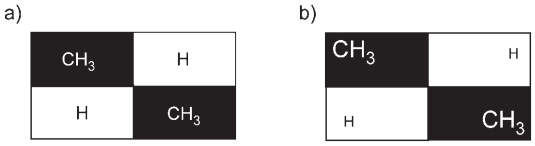
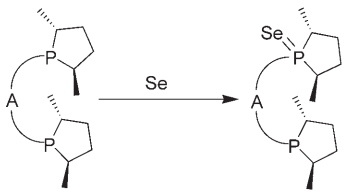


Figure 5. Quadrant models of small a) and large b) bite angle catalysts.

For the characterization of the σ-donor properties of phosphines, the comparison of phosphorus–selenium coupling constants $J(^{77}Se,^{31}P)$ has been suggested.[38] In general, the higher the magnitude of the coupling constant the higher the s character of the phosphorus lone-pair orbital and therefore the lower the basicity. A high basicity of the phosphine causes high electron density on the rhodium. This effect will strengthen the interactions between the occupied d orbital of the rhodium and the σ* orbital of the hydrogen molecule, which is important in the overall reaction steps.[3] Moreover, it supports the complexation of the prochiral olefinic substrate due to enhanced transfer of electron density from the metal d orbitals to the π* orbital of the olefin (π-back-bonding). More tightly bound π substrates should lead to shorter metal–substrate bond lengths and thus result in a greater stereochemical communication between the chiral ligand and the substrate.

Selected monoselenides were prepared by treating the bisphospholanes with one equivalent of elemental selenium in refluxing chloroform according to Equation (1).



(1)

Unfortunately, attempts to prepare the phosphorselenides of bisphospholane **1l** under standard conditions led to the decomposition of the phosphine.

In Table 3, the values are in order of decreasing *J*(P,Se) magnitudes. The largest difference measured for all the bisphospholane selenides is 68 Hz.[39] Apparently, the *J*(P,Se) coupling is significantly affected by the size of the C=C–P angle. Bisphospholane **1a** is the poorest and **1n** is the strongest σ donor. As the calculations of Table 2 show, strong basic phosphines coordinate with a shorter distance *d* (Figure 1) to the rhodium center than their electron-poor analogues. As expected incorporation of fluorine atoms (**1c**,**n**) increases the value of the coupling constants (ca. 10 Hz) in comparison to the parent dicarbonyl compounds (**1b**,**d**). Replacement of the electron pushing NMe group by oxygen in the five-membered ring enhances the *J*(P,Se) coupling (**1e** vs. **1d**).

Table 3. *J*(P,Se) coupling constants of selected bisphospholanes.

	1a	**1c**	**1b**	**1m**	**1d**	**1e**	**1n**
$\lvert J(P,Se)\rvert$ [Hz][a]	780	771	763	760	750	741	726

[a] Measured in [D]chloroform.

Summarizing the trends of electronic and steric effects on the stereodiscriminating coordination of a prochiral substrate, it can be concluded that these oppose each other. Thus, Rh complexes bearing ligands with a large stereodif-

ferentiating potential bind the prochiral substrate less effectively than Rh complexes with bisphosphine ligands that have a smaller C=C–P angle, but higher basicity.

For further characterization of the precatalysts, ^{103}Rh NMR spectra were recorded. It is known that the $\delta(^{103}Rh)$ values for a given array of coordinating atoms are governed primarily by the coordination geometry, bond angles, and bond lengths to the rhodium center.[40,41] Thus, all NMR shifts of $[Rh(cod)(PP)]^+$ complex ions, in which PP is a bidentate ligand forming a five-membered metal chelate, fall in a narrow range that is characterized by compounds such as $[Rh(cod)(dppe)]ClO_4$ (dppe = 1,2-bis(diphenylphosphino)ethane), $\delta = -505$ ppm[41c] or $[Rh(cod)(dipamp)]BF_4$ (dipamp = 1,2-ethanediylbis[(2-methoxyphenyl)phenylphosphine]), $\delta = -439$ ppm.[42] Calculations for the model compound $[Rh(acac)(PH_3)_2]$ (acac = acetyl acetonate) revealed a minimum for the ^{103}Rh shift at an P-Rh-P angle of approximately 85° that evidently permits an optimal orbital overlap.[41a,b] Any variation of this angle α, in either direction, immediately leads to an increase (i.e. shift toward higher frequency) in the $\delta(^{103}Rh)$ value. Taking into account α_{calcd} of 85.04° (see Figures 1 and 2) it can be concluded that [Rh(cod)(**1n**)]BF_4 with a ^{103}Rh shift of $\delta = -467$ ppm represents an energetic minimum among all investigated precatalysts. In a series of geometrically closely related complexes the one with the metal resonance at lowest frequency (lowest δ value) is usually the thermodynamically most stable.[41d]

The Rh–P distance (d) was found to have an even more pronounced effect on the metal NMR shift. A linear correlation with a coefficient larger than 10000 ppm Å^{-1} emerged from Bühl's investigations.[41a,b] In metal chelates, α and d are strongly dependent on each other (from the calculated structural data of the complexes presented in Table 2 follows $\alpha = 46.909\,d - 25.35$ with $r^2 = 0.9194$). In such terms, the observed shifts (Table 4) are caused by the increasing ring strain in the ligand backbone (Figure 2). Consequently, ligand **1b** (based on squaric acid), which forms the complex with the highest $\delta(^{103}Rh)$ value, is also the least stable[41d] chelate (vide infra).

Table 4. ^{103}Rh NMR spectra (δ) of precatalysts derived from **1**.

	Rh-**1a**	Rh-**1b**	Rh-**1l**	Rh-**1d**	Rh-**1k**	Rh-**1e**	Rh-**1n**
^{103}Rh [ppm][a]	–	−246	−355	−376	−377	−386	−467

[a] Measured in [D_6]acetone.

Remarkably enough, the already discussed J(P,Se) coupling constants are also predictive for the steric effects of the rhodium complexes. The trend is clear-cut: an increasing $|J(P,Se)|$ is directly related to increasing P–Rh distance d and also bite angle α. Only the fluorinated system **m** behaves somewhat differently. In this case the electronegativity of six fluorine atoms might override the otherwise dominant steric influence.

DFT calculations considering the relative thermodynamic stability of the interaction between chiral phospholane ligand and the Rh center support this conclusion. The relative stability of the complexes has been estimated on the basis of the ligand exchange reaction, such as Rh(**1n**) + **1d** → Rh(**1d**) + **1n** and Rh(**1d**) + **1b** → Rh(**1b**) + **1d**. A positive reaction energy (endothermic) means a disfavored thermodynamic trend for ligand exchange, while a negative reaction energy (exothermic) means a favored thermodynamic trend for ligand exchange. At the B3LYP/LANL2DZ(D) level of theory (see Supporting Information for details), the cationic Rh(**1n**) complex is computed to be 15.9 kcal mol^{-1} more stable than the complex with the maleic anhydride backbone (**1d**). The latter is 5.9 kcal mol^{-1} more stable than the Rh complex derived from the squaric acid ligand **1b** (Figure 6).

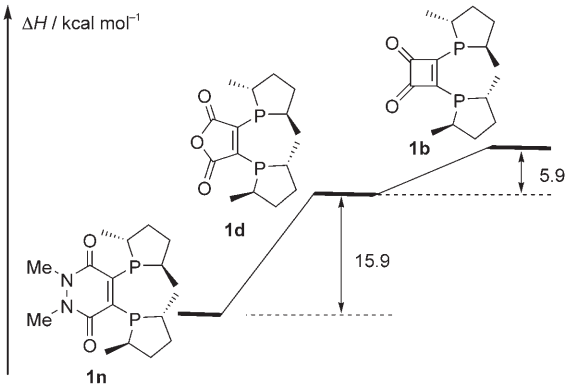
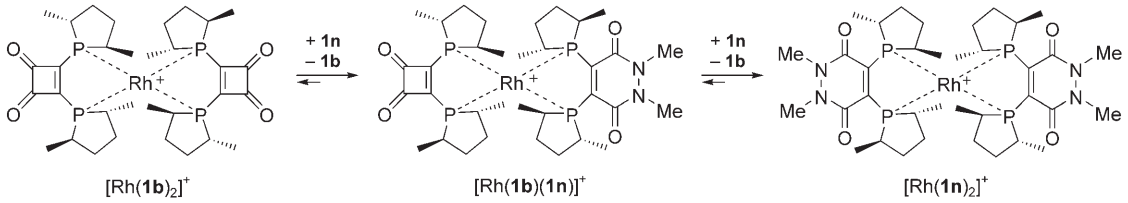


Figure 6. Calculated stabilities of [Rh(cod)(bisphospholane)]$^+$ complexes based on ligands **1b**, **1d**, and **1n**.

The differences in stability could be confirmed by a ligand-exchange experiment (Scheme 5). Thus treatment of [Rh(**1b**)$_2$]BF_4 (^{31}P NMR: $\delta = 60.7$, $J_{Rh\text{-}P} = 130$ Hz), which had been prepared by reaction of $[Rh(cod)_2]BF_4$ with two equivalents of **1b** in CH_2Cl_2, with one or two equimolar amounts of bisphospholane **1n** afforded a stepwise exchange of the coordinated ligand. The addition of the first equivalent of **1n** liberated one diphospholane **1b** and gave rise to a mixture consisting of the mixed ligand complex and the homo-(**1n**)$_2$ complex. The mixed ligand complex was characterized in the ^{31}P NMR spectrum in CD_2Cl_2 by two double doublets at $\delta = 56.0$ ($J_{Rh\text{-}P} = 129$ Hz, $J_{P\text{-}P} = 22.9$ Hz) and 98.0 ppm ($J_{Rh\text{-}P}$=132 Hz). By the addition of a second equivalent of **1n**, the bis-homoligand complex [Rh(**1n**)$_2$]BF_4 was formed which gave a doublet at $\delta = 94.7$ ppm ($J_{Rh\text{-}P} = 130$ Hz) in the ^{31}P NMR spectrum.

Results of the enantioselective hydrogenation reactions: The new precatalysts were tested in the hydrogenation of benchmark substrates such as, methyl (*Z*)-*N*-acetamido cinnamate[43] and dimethyl itaconate, but also β-dehydroamino acid precursors,[44] in order to assess its stereodiscriminating ability for a broad range of chiral substituted olefins. Hydro-



Scheme 5. Ligand exchange reaction due to different complex stabilities.

genations were performed with a molar precatalyst/substrate ratio of 1:100 at 1 bar hydrogen pressure at 25 °C in CH_2Cl_2, THF, and MeOH as solvent.

In Figures 7–12 selected results are listed in order of increasing σ-donor capacity of the phospholanes and decreasing bite angle in the precatalyst.[45] In several attempts the sulfur-containing ligand **1l** blocked the hydrogenation. The results obtained with ligand **1a** varied over a broad range. Therefore, results were only reported when constant values were observed within two runs.

In general, differences in the enantioselectivities by up to $\Delta ee = 90\,\%$ were noted. With the same substrate all catalysts induced the same configuration in the product. Deviations of the enantioselectivity in the hydrogenation of methyl (*Z*)-*N*-acetamido cinnamate are less pronounced than with dimethyl itaconate as substrate (Figure 7). Apparently for the assessment of the intrinsic stereodiscriminating ability of this type of catalyst dimethyl itaconate as benchmark substrate is better suited than the former. In MeOH or THF as solvent for most substrates investigated herein, catalysts with a maleic anhydride or maleimide backbone gave the best results. Replacement of these ligands by more electron-deficient or electron-rich phosphines may negatively affect the enantioselectivity. In CH_2Cl_2 as solvent these sometimes dramatic differences are leveled and in general superior enantioselectivities result. The differences in the level of enantioselectivity observed when (*E*)- or (*Z*)-β-dehydroamino acid esters were subjected to the hydrogenation have been already described (Figures 8 and 9).[24,44]

In his pioneering work, Burk found that in some cases the replacement of methyl groups in 2,5-position of the phospholane unit by ethyl groups (Et-duphos = 1,2-bis(2,5-diethylphospholano)benzene) can increase the enantioselectivity of the hydrogenation.[13d] As shown in Figure 10 this effect may hold sometimes also for hydrogenations with ligands considered herein. However, a general tendency can not be deduced.

As cited in the introduction, electronic fine tuning of ligands has been proposed several times as a powerful tool for the increase of the enantioselectivity of chiral hydrogenation catalysts.[4,5,46] Our results observed with nonfluorinated and fluorinated ligands show that the reaction can indeed be significantly influenced by electronic changes in the backbone of the ligand. However, in general, no clear correlation such as that found by RajanBabu,[4] Bakos,[5a] and us[5b] exist in the series of ligands investigated herein (Figures 11 and 12).

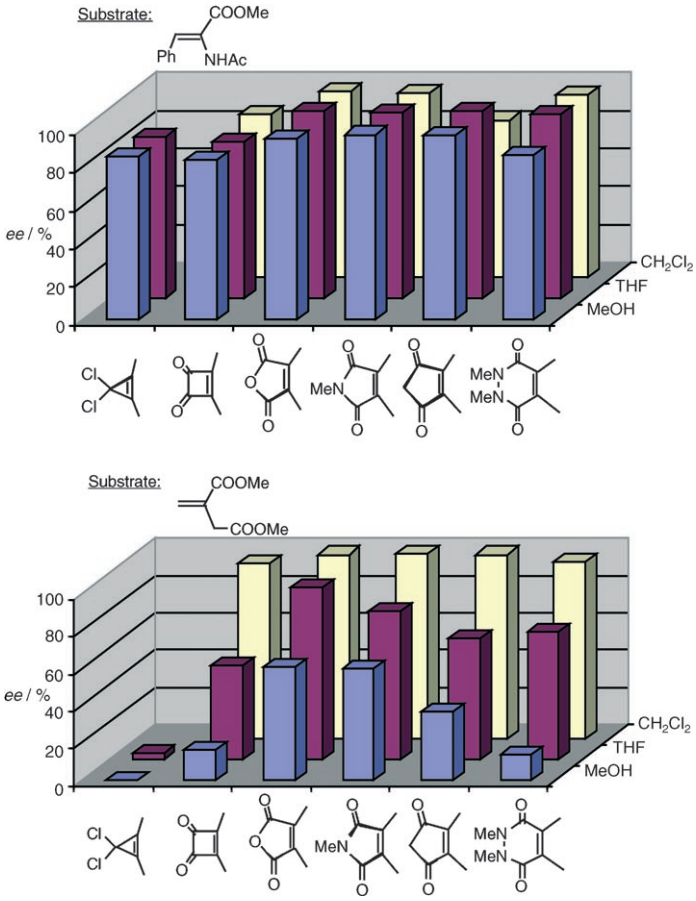


Figure 7. Results of the enantioselective hydrogenation of methyl (*Z*)-*N*-acetamido cinnamate (top) and dimethyl itaconate (bottom) with ligands of type **1**. Values are listed in order of decreasing bite angle in the precatalysts.

Table 5 summarizes the best results of all 360 hydrogenation runs. The data clearly show that our set of 16 ligands allows each substrate to find the best conditions. In those instances in which a ligand bearing a maleimide backbone was identified as the most effective catalysts further fine-tuning was possible by variation of the *N*-alkyl group. Further improvements could be achieved by variation of the chiral *N*-phenylethyl unit (**1i,j**) taking benefit from the application of the matched versus mismatched diastereomeric catalysts. In general, our results fulfill the recent assertion of Saito et al. who proposed that each substrate needs its own catalyst.[10] However, it should be noted that in this model purely steric reasons have been attributed to play a pivotal role. Our re-

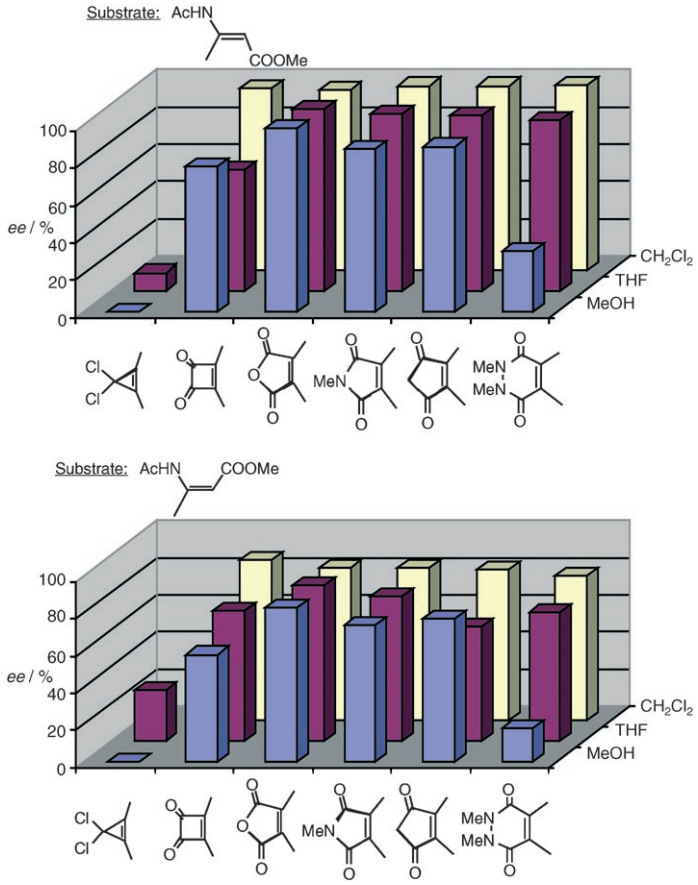


Figure 8. Results of the enantioselective hydrogenation of methyl (*E*)-β-acetamido acrylate (top) and methyl (*Z*)-β-acetamido acrylate (bottom) with ligands of type **1**. Values are listed in order of decreasing bite angle in the precatalysts.

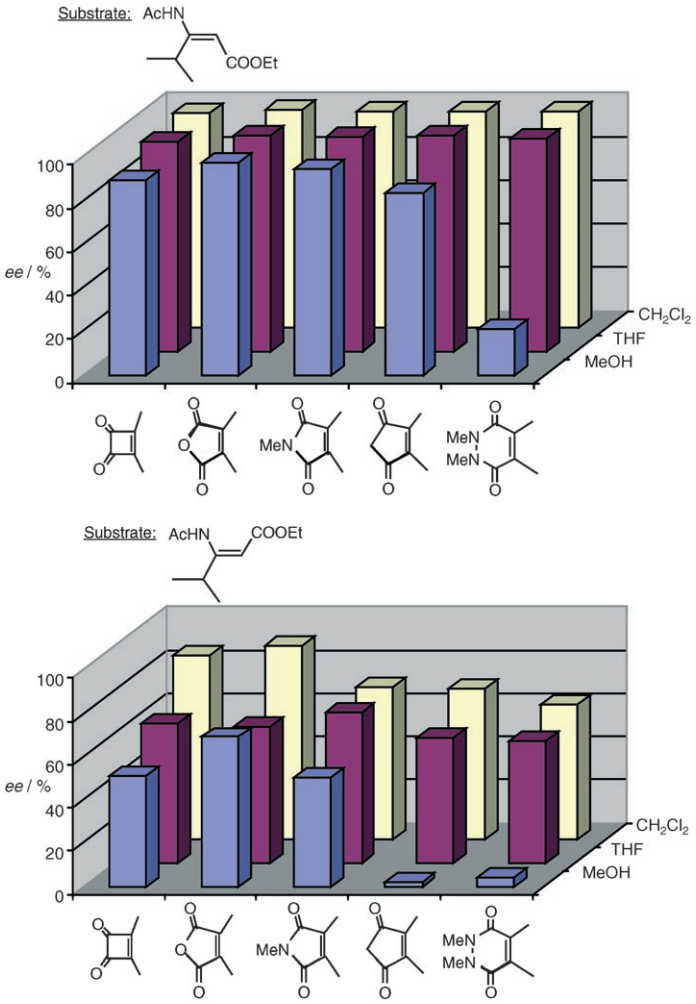


Figure 9. Results of the enantioselective hydrogenation of ethyl (*E*)-2-acetamido-3-methylbutenoate (top) and ethyl (*Z*)-2-acetamido-3-methylbutenoate (bottom) with ligands of type **1**. Values are listed in order of decreasing bite angle in the precatalysts.

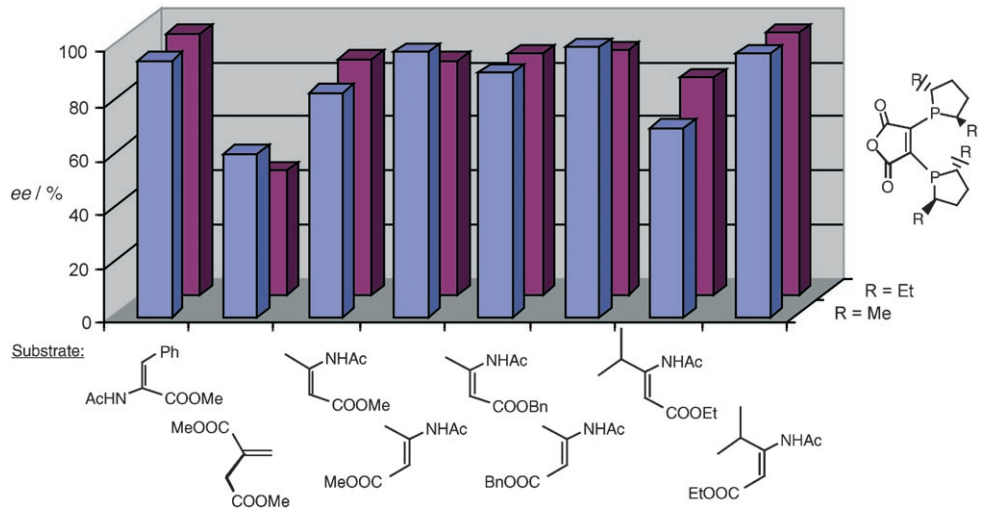


Figure 10. 2,5-Methyl- versus ethyl-substituted phospholanes as ligands (**1d** vs. **2a**)

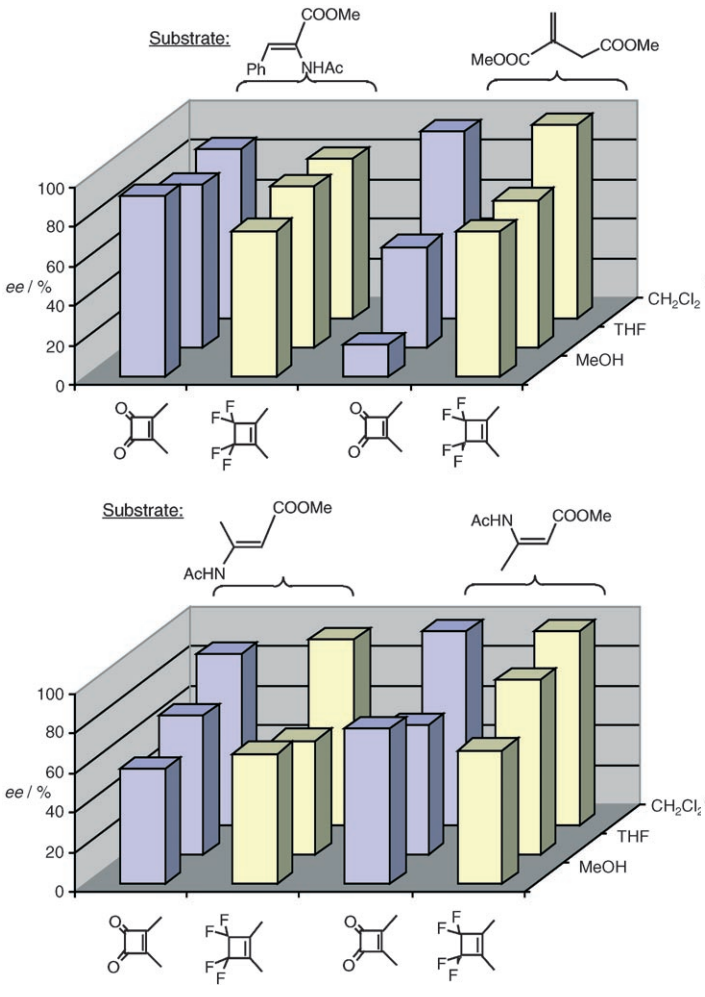


Figure 11. Influence of electronic effects on the enantioselective hydrogenations with bisphospholanes of type **1** bearing a four-membered backbone bridge.

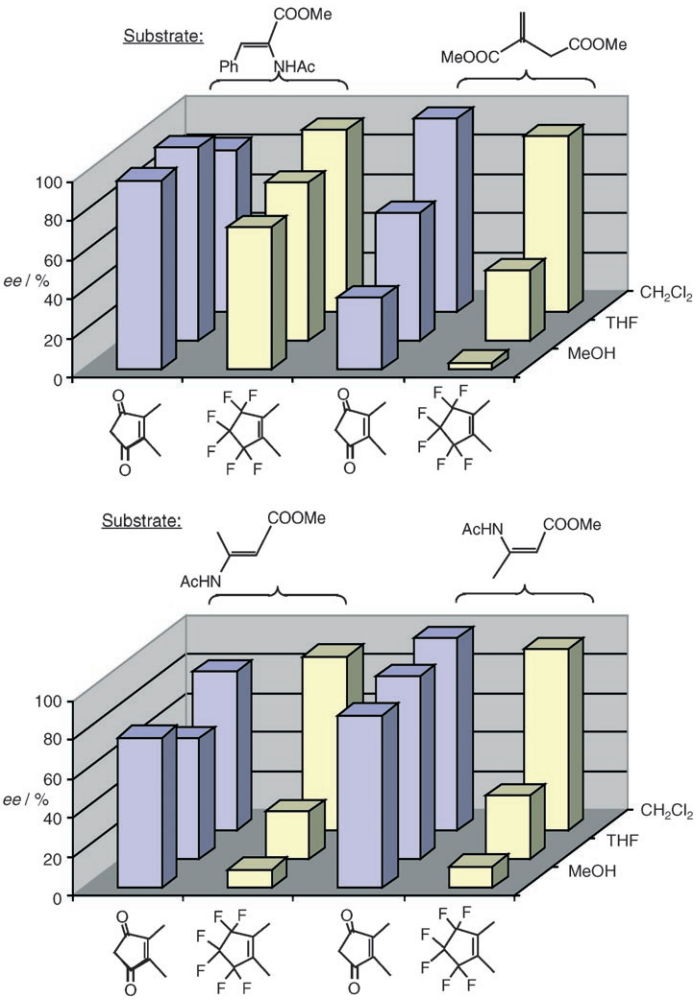


Figure 12. Influence of electronic effects in enantioselective hydrogenations with bisphospholanes of type **1** with a five-membered backbone bridge.

Table 5. Best results of all hydrogenations.

Substrate						
R^1	R^2	R^3	R^4	Ligand	Solvent	*ee* [%]
COOMe	NHAc	H	Ph	**2b**	THF	99.0
CH_2COOMe	COOMe	H	H	**1e**	CH_2Cl_2	99.1
COOMe	H	Me	NHAc	**1e**	CH_2Cl_2	98.6
H	COOMe	Me	NHAc	**1b**	CH_2Cl_2	93.6
COOBn	H	Me	NHAc	**1b**	CH_2Cl_2	99.5
H	COOBn	Me	NHAc	**1d**	MeOH	89.9
COOEt	H	*i*Pr	NHAc	**1d**	CH_2Cl_2	99.7
H	COOEt	*i*Pr	NHAc	**1j**	CH_2Cl_2	89.6

sults reveal, however, that also electronic effects may be of significant importance. Sometimes dramatic differences were noted only by a slight change of the bite angle and/or the basicity of the ligand. Moreover, by a change of the solvent other catalysts could give rise to superior results.

Conclusion

In conclusion, by a simple and signficantly improved convergent strategy, one of the most comprehensive family of chiral bisphosphine ligands have been synthesized. This methodology, which can be easily scaled up for industrial requirements, was used for the construction of closely related bisphospholanes, differing in the size of the natural bite angles and σ-donor properties of the phosphine. These features are caused by three-, four-, five-, and six-membered heterocyclic or alicyclic rings connecting both phospholane units. Replacement of methyl groups by ethyl groups in the phospholane opened up avenues to further modifications. Bisphospholanes and their Rh precatalysts have been investigated by means of density functional theory (DFT) calculations and analytic measurements (^{31}P, ^{103}Rh NMR spectroscopy, X-ray structure analysis). The catalytic studies showed that ligands with maleic anhydride or maleimide bridges give consistently superior enantioselectivities in polar solvents. It is reasonable to assume that these Rh com-

plexes represent unique structures among the whole family of catalysts tested for which opposite trends of beneficial geometric and electronic effects are optimum. Interestingly, these precatalysts are not thermodynamically the most stable ones. By changing the solvent, other catalysts could provide superior results. It seems that simple steric or electronic models are limited in the prediction of enantioselectivities. They are not able to describe the complexity of enantioselective hydrogenation reactions. Evidently, correlations between geometric or electronic parameters in ligands and precatalysts, respectively, and hydrogenation results, frequently quoted in the literature and derived from small sets of ligands and reactions conditions, are not general. They can be easily overridden by other effects (e.g. solvent effects). At the current level of investigations a combination of a large family of related and scalable ligands with the facility of high through-put screening[47] seems to be the best guarantee for the fast identification of most effective hydrogenation conditions. This precondition is fulfilled by the new and large family of tuneable bisphospholanes described herein. Further work will address the functionalization of appropriate ligands for reactions under multiphase conditions and the ongoing search for relationships between the structure of catalysts or catalytic intermediates and the results in enantioselective hydrogenation.

Experimental Section

Solvents were dried and freshly distilled under argon before use. All reactions were performed under an argon atmosphere by using standard Schlenk techniques.

NMR spectra were recorded at a Bruker ARX 400 spectrometer at the following frequencies: 400.13 MHz (^{1}H), 100.63 MHz (^{13}C), 161.98 MHz (^{31}P), 282 MHz (^{19}F). Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm downfield from TMS as internal standard. Chemical shifts of ^{31}P NMR spectra are referred to H_3PO_4 as external standard. Signals are quoted as s (singlet), d (doublet), br (broad) and m (multiplet). ^{103}Rh NMR spectroscopy was performed with the same spectrometer (B_0= 9.4 T), equipped with a commercial triple-resonance probe (doubly-tuned ^{1}H/^{31}P coil with a surrounding broadband coil) with $\pi/2$ pulse width for ^{103}Rh of 29.5 μs. Chemical shifts $\delta(^{103}\text{Rh})$ are given in ppm relative to Ξ= 3.16 MHz,[40a] positive signs indicating low-field shifts, and were determined by inverse detected (four-pulse HMQC) triple-resonance experiments ^{31}P,^{103}Rh{^{1}H};[40b,c] each determination was carried out at least twice with variation of the ^{103}Rh frequency and the t_1 increment to ensure that the signals in the F_1 dimension were not folded. The temperature was about 297 to 298 K.

Large-scale synthesis of tris(trimethylsilyl)phosphine: Na/K alloy was prepared by carefully melting of potassium (51.0 g, 1.3 mol) and sodium (39.0 g, 1.7 mol) in a 4 L three-necked round-bottomed flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser. Dry DME (2 L) was added and the mixture was then heated under reflux for 1 h. The slightly purple mixture was cooled to 23 °C and red phosphorus (31.0 g, 1 mol) was added. The mixture was heated to reflux for 18 h in total (for safety reasons the mixture was cooled down to 23 °C). Chlorotrimethylsilane (420 mL, 3.3 mol) in DME (500 mL) was added dropwise to the black solution and the temperature was allowed to rise to gentle reflux. The mixture was refluxed for an additional hour and cooled to 23 °C. The resulting gray suspension was filtered through dried Celite under Ar. The residue was washed with pentane (2×100 mL). The solvent was removed at ambient pressure. The crude product was purified by distillation (b.p.$_1$ 80–85 °C) to give a colorless liquid of **1** (150.3 g, 60 %). ^{1}H NMR [D$_6$]benzene: δ = 0.06 ppm (d, 27 H); ^{31}P NMR [D$_6$]benzene: δ = −251.6 ppm (caution: pyrophoric and moisture sensitive).

Large-scale synthesis of (*S*,*S*)-2,5-hexanediolbismethanesulfonate (5): In a 2 L flask (*S*,*S*)-2,5-hexanediol (120 g, 1.015 mol) was suspended in toluene (450 mL), and triethylamine (353.5 mL, 2.54 mol) was added. The suspension was cooled to 0 °C and a solution of methanesulfonylchloride (255.9 g, 2.23 mol) in toluene (50 mL) was slowly added. During the addition the temperature was kept below 25 °C. The suspension changed its color to yellow/brownish. The solution was stirred for 1 h. The reaction mixture was hydrolyzed by addition of water (250 mL). The organic layer was separated and the aqueous layer extracted with toluene (200 mL). The organic layers were washed with brine and dried with magnesium sulfate. Toluene was removed until the solution contained about 30 % of **5**. This solution was used for subsequent reactions. ^{1}H NMR [D]chloroform: δ = 4.85 (m, 2 H; CHO), 3.02 (s, 6 H; CH_3), 1.80 (m, 4 H; CH_2), 1.44 (d, J = 6.3 Hz, 6 H; CH_3). Data were in accordance with those reported in reference [13b].

(*R*,*R*)-2,5-Dimethyl-1-phenylphospholane (6): A suspension of lithium (44.4 g, 6.4 mol) and THF (400 mL) was stirred at 5 °C. A solution of dichlorophenylphosphine (143.2 g, 0.8 mol) in THF (220 mL) was added dropwise over a period of 90 min, while maintaining the temperature between 5–17 °C. The resulting orange suspension was warmed up to 23 °C and stirred for 1 h. The solvent was removed under reduced pressure, and DME (600 mL) was added to the semisolid residue. The suspension was refluxed for 5 h and cooled to 23 °C. The excess lithium was removed by transferring the suspension into another flask. Lithium was washed with DME (50 mL). The suspension was cooled to −15 °C and the solution of **5** (182.2 g, 0.66 mol) in toluene (200 mL) was added over a period of 1 h. During the addition the temperature was kept between −15 and −2 °C. The solution was allowed to warm up to 23 °C and stored for 16 h. The solvent was removed under reduced pressure and heptane (500 mL) was added. The suspension was filtered and the solid washed with heptane (2×300 mL). The solvent was removed under reduced pressure and the crude product was purified by distillation (b.p. = 125–130 °C/30 mbar) to give **6** as a colorless liquid (65.2 g, 0.34 mol, 51 %). NMR data were in accordance with those reported in reference [13b].

Large-scale synthesis of (*R*,*R*)-2,5-dimethyl-1-trimethylsilylphospholane (4a): A suspension of lithium (76.0 g, 11.0 mol) was stirred in THF (2 L) for 1 h. The suspension was cooled to −5 °C and a solution of **6** (531.0 g, 2.76 mol) in THF (400 mL) was added over a period of 1 h, while maintaining the temperature between −5 and 10 °C. The reaction mixture was warmed to 23 °C and stirred for additional 4 h. The remaining lithium was removed by filtration and washed with THF (100 mL). The filtrate was cooled to −10 °C and trimethylchlorosilane (764 mL, 6.07 mol) in THF (300 mL) was added over a period of 1 h. The temperature was held between −5 and 25 °C. After the complete addition the solution was stirred for 1 h at 23 °C. About 60 % of the solvent was removed under reduced pressure and the remaining salts were removed by filtration. Solvents were removed and the crude product was purified by distillation. It was important to remove the byproduct trimethylphenylsilane completely from **4a** (b.p. = 93 °C/20 mbar). Compound **4a** was obtained as a colorless liquid in 51 % yield (265.2 g).

Large-scale synthesis of 3,4-bis-[(*R*,*R*)-(2,5-dimethylphospholan-1-yl]maleic anhydride (1d): A solution of TMS-phospholane **4a** (51.1 g, 0.270 mol, 2 equiv) in absolute Et_2O (50 mL) was added drop-wise to a stirred solution of dichloromaleic anhydride (22.5 g, 0.135 mmol) in Et_2O (200 mL) over a period of 30 min at 0 °C under Ar (a dark-red color appeared immediately after first few drops). After stirring for 15 min at 0 °C and an additional 30 min at room temperature, the reaction mixture was cooled to −78 °C and left for 48 h to crystallize. The mother liquor was removed and the first fraction of dark-brownish crystals of **1d** were isolated and dried under vacuum (25.0 g, 57 %). The mother liquor was evaporated again to dryness and a second fraction of **1d** could be isolated (16.4 g, 37 %).

Acknowledgements

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