Supramolecular Ligands

DOI: 10.1002/ange.201002958

PhthalaPhos: Chiral Supramolecular Ligands for Enantioselective Rhodium-Catalyzed Hydrogenation Reactions**

Luca Pignataro, Stefano Carboni, Monica Civera, Raffaele Colombo, Umberto Piarulli, and Cesare Gennari**

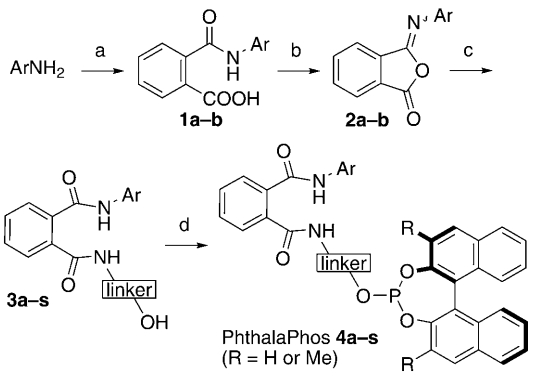
Chemists have largely taken inspiration from Nature in the development of new approaches to synthetic challenges. Combinatorial chemistry stems from the concept of evolution, whereby random mutation of a chemical structure gives rise to libraries of compounds, from which an optimal lead can be found with high probability. On the other hand, Nature makes wide use of noncovalent interactions to build its complex supramolecular architectures and to achieve efficient and selective transformations. In recent years, combinatorial and supramolecular approaches to the development of new ligands for asymmetric catalysis has gained momentum.[1,2d] The term "supramolecular ligand" encompasses all ligands possessing, besides the atom(s) coordinating to the catalytic metal atom, an additional functionality capable of noncovalent interactions (mainly hydrogen[3] or coordinative bonds[4]) which can play the following roles: 1) self-assembly of two monodentate ligands to form a so-called supramolecular bidentate ligand;[5] 2) binding the substrate(s) in proximity to the catalytic metal center[2] in analogy to metalloenzymes.[6] Among the different kinds of noncovalent interactions that have been used so far for developing supramolecular ligands,[5] hydrogen bonds are arguably the most practical and efficient[2,3] for several reasons: 1) functional groups capable of hydrogen bonding (e.g., amides, ureas, guanidines) are stable and relatively easy to introduce; 2) hydrogen bonds are created dynamically and reversibly in the reaction medium (where catalysis is to take place), are capable of self-repair when broken, and often coexist with other interactions in a "noninvasive" manner.

[*] Dr. L. Pignataro, Dr. M. Civera, R. Colombo, Prof. C. Gennari
Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, Centro Interdipartimentale CISI, Istituto di Scienze e Tecnologie Molecolari (ISTM) del CNR
Via G. Venezian, 21, 20133 Milano (Italy)
Fax: (+39) 02-5031-4072
E-mail: cesare.gennari@unimi.it
S. Carboni, Prof. U. Piarulli
Università degli Studi dell'Insubria, Dipartimento di Scienze Chimiche e Ambientali
Via Valleggio, 11, 22100 Como (Italy)
Fax: (+39) 031-238-6449
E-mail: umberto.piarulli@uninsubria.it

[**] We thank the European Commission [RTN Network (R) Evolutionary Catalysis MRTN-CT-2006-035866] for financial support. L. Pignataro thanks Milan University for a postdoctoral fellowship ("Assegno di ricerca"). HRMS spectra were performed at CIGA (Milan University). We are grateful to Dr. Laura Belvisi of Milan University for the helpful discussions on the computational studies.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002958.

As a result of our continued interest in developing supramolecular ligands,[7] we report herein the design and synthesis of a novel class of chiral monodentate phosphite ligands, named PhthalaPhos, which contain a phthalic acid primary diamide moiety (Scheme 1). The phthalamidic group



Scheme 1. a) Phthalic anhydride, $CHCl_3$, reflux, 94–98%; b) $(CF_3CO)_2O$, TEA, dioxane or THF, 0°C to RT, 97–99%; c) amino alcohol, THF, RT, 66–90%; d) (*S*)-binol-PCl, TEA, THF, RT, 62–78%. TEA = triethylamine.

displays both donor and acceptor hydrogen-bonding properties that, in principle, can give rise to supramolecular interactions both between the ligands and with the reaction substrate. The modular nature of the PhthalaPhos ligands allows their properties to be tuned by simply varying structural elements such as the linker, the binol moiety, and the ancillary amide group (i.e., the amide not connected to the phosphite group), and thus parallel-combinatorial ligand optimization is possible.[1a,c]

The PhthalaPhos ligands were easily prepared in four steps as outlined in Scheme 1: phthalic anhydride was treated with a primary amine to give phthalic acid mono amides **1** in 94–98% yield.[8] Dehydration of the latter in the presence of trifluoroacetic anhydride gave phthalisoimides **2** in high yields, whose reaction with a chosen amino alcohol led to phthalic acid diamides **3**.[9] Diamide mono-alcohols **3** were treated with binol-derived chlorophosphites[10] to give PhthalaPhos ligands **4**.

Although we synthesized and screened a relatively large library of nineteen members (**4a**–**s**, see the Supporting Information for the complete layout of the library and the complete set of results), here we present the results obtained with a selected subset of the most successful nine ligands (**4a**–

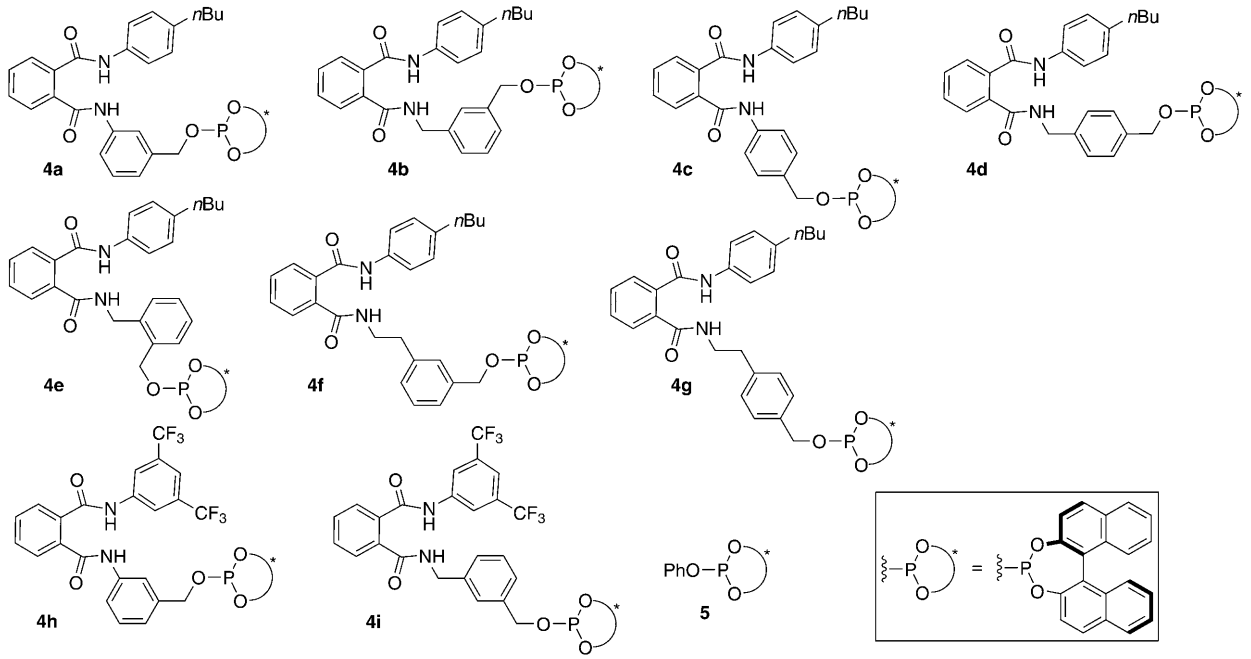
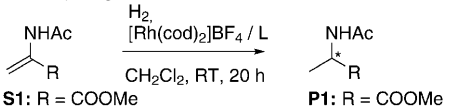


Figure 1. Selected ligands **4a–i** from the PhthalaPhos library and reference phosphite **5**.

i, Figure 1) in the rhodium-catalyzed enantioselective hydrogenation of olefins.

We assessed the catalytic properties of the new ligands in the hydrogenation of two classical benchmark substrates, namely, methyl 2-acetamidoacrylate (**S1**) and *N*-(1-phenylvinyl)acetamide (**S2**; Table 1), taking the known phosphite **5** as touchstone.[11]

Table 1: Selected screening results of the PhthalaPhos library in enantioselective hydrogenation of substrates **S1** and **S2**.[a]



S1: R = COOMe
S2: R = Ph

P1: R = COOMe
P2: R = Ph

Entry	Substrate	Ligand	*ee* [%],[d] abs. config.[e]
1	**S1**[b]	**4b**	98, *R*
2	**S1**[b]	**4e**	>99, *R*
3	**S1**[b]	**4f**	98, *R*
4	**S1**[b]	**4i**	98, *R*
5	**S1**[b]	**5**	84, *R*
6	**S2**[c]	**4a**	98, *R*
7	**S2**[c]	**4b**	98, *R*
8	**S2**[c]	**4e**	97, *R*
9	**S2**[c]	**4f**	98, *R*
10	**S2**[c]	**4g**	99, *R*
11	**S2**[c]	**4h**	97, *R*
12	**S2**[c]	**5**	90, *R*

[a] Reaction conditions: substrate/ligand/$[Rh(cod)_2]BF_4$ = 100:2.2:1, solvent = CH_2Cl_2, c_0(**S1**) = 0.048 M, c_0(**S2**) = 0.024 M, T = 25 °C. All reactions proceeded with 100 % conversion. See the Supporting Information for the complete set of results. [b] p = 1 bar. [c] p = 5 bar. [d] Determined by GC equipped on a chiral capillary column (MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin). [e] Assignment based on the GC retention times, by comparison with the results obtained with **5**, whose stereochemical preference is known.[11]

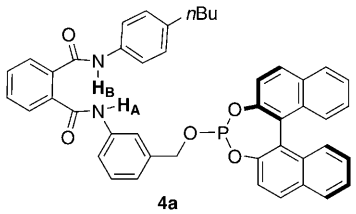
The results of this preliminary screening turned out to be very encouraging: four ligands gave *ee* values higher than 97 % with substrate **S1** (Table 1, entries 1–4), and six reached the same level of performance with **S2** (Table 1, entries 6–11). Remarkably, the reference ligand **5**, featuring the same binol phosphite moiety as **4a–i**, gave only 84 % *ee* with **S1** and 90 % *ee* with **S2** (entries 5, 12), which suggests that the phthalamide residue significantly influences the catalytic properties of these ligands. Further support to this conclusion came from the effect on the enantioselectivity displayed by the linker, particularly evident in the case of ligands **4h** and **4i**, for which a subtle variation of the linker length resulted in remarkably different *ee* values (**S1**, **4h**: 89 % *ee*, **4i**: 98 % *ee*; **S2**, **4h**: 97 % *ee*, **4i**: 83 % *ee*; see the complete set of results in the Supporting Information). Indeed, if the phthalamide residue were a simple bystander and **4a–i** behaved as "normal" monodentate phosphites, only negligible differences in enantioselectivity should be expected for the ligands. Another interesting observation is that not always the best *ee* values with **S1** and **S2** were obtained with the same ligands, which underlines the advantage of the combinatorial approach followed in the ligand design.

Encouraged by these preliminary results, we decided to investigate the role of hydrogen bonding in the catalytic properties of the PhthalaPhos ligands. The precatalyst obtained by treating a representative ligand (**4a**, 2 equiv) with $[Rh(cod)_2]BF_4$ (cod = 1,5-cyclooctadiene, 1 equiv) in CH_2Cl_2 or CD_2Cl_2 was studied by spectroscopic methods. The ^{31}P NMR spectrum of the Rh complex displayed a clean doublet at 122.0 ppm with $J_{Rh,P}$ = 257.7 Hz which, matched with the ^1H NMR spectrum and the result of HRMS analysis (m/z 1643.49193), indicates formation of the cationic species $[Rh(\mathbf{4a})_2(cod)]^+$, where the phosphite groups occupy two adjacent *cis* positions. Only one set of signals could be

detected in the NMR spectra of the Rh complex, and the two coordinated molecules of **4a** could not be distinguished. The hydrogen bonding state of the NH protons for both the free ligand and the Rh complex was then investigated by ^{1}H NMR spectroscopy, and in particular the following data were collected: 1) temperature coefficient ($\Delta\delta/\Delta T$) of each NH proton; 2) kinetics of H/D exchange of the amide protons upon addition of excess CD_3OD; 3) downfield shift of the NH protons in the presence of excess CD_3OD. These experiments, which are commonly used to differentiate between random-coil peptides and peptides in hydrogen-bonded conformations,[12,13] were conducted in dilute (1.2 mM) solutions in CD_2Cl_2. This concentration was chosen since aggregation, at least of the Rh complex, is not significant at 1.2 mM, as determined by studying the dependence of the NH chemical shifts on the concentration in the 20.0–0.3 mM range.

From the experimental results, which are outlined in Table 2 and reported in detail in the Supporting Information, the following conclusions can be drawn: on the one hand, no evidence of intramolecular hydrogen bonding could be found for the free ligand **4a**, which, moreover, shows a strong tendency to intermolecular aggregation even at high dilution. On the other hand, proton NH_A in the Rh complex is definitely involved in an intramolecular hydrogen bond, as confirmed by its downfield chemical shift ($\delta = 9.6$ ppm), its reduced rate of exchange with CD_3OD ($t_{1/2} = 47$ min), and limited shift when CD_3OD is added ($\Delta\delta = 0.27$ ppm). Proton NH_B, conversely, appears to be in a nonbonded state. Consistent with these observations, two distinct NH stretching bands ($\tilde{\nu} = 3409.5$ and $3268.8\ cm^{-1}$) were detected in the IR spectrum of the Rh complex (1.2 mM solution in CH_2Cl_2), while only one band could be found for the free ligand ($\tilde{\nu} = 3408.6\ cm^{-1}$). Also, detection of the C=O stretching band of the Rh complex at a lower wavenumber than that of the free ligand ($\tilde{\nu} = 1661.4$ vs. $1676.8\ cm^{-1}$) confirmed the presence of an intramolecular hydrogen bond.

Table 2: Results of ^{1}H NMR studies on NH protons of ligand **4a** and its Rh complex.[a]



4a

	Free ligand **4a**		$[Rh(\mathbf{4a})_2(cod)]BF_4$	
	NH_A[b]	NH_B[b]	NH_A[b]	NH_B[b]
δ [ppm]	8.692	8.342	9.604	8.506
$\Delta\delta/\Delta T$ [ppb K^{-1}]	n.d.[c]	n.d.[c]	−12.94	1.73
H/D exchange: $t_{1/2}$ [min]	12.2	14.9	47.1	28.5
$\Delta\delta$ in presence of excess CD_3OD [ppm]	0.654	0.742	0.274	0.558

[a] $c = 1.2$ mM in CD_2Cl_2. [b] Assignment of H_A and H_B was based on the NOESY and COSY spectra. [c] Not determined: no linear dependence observed.

We ran a Monte Carlo conformational search[14,15] of the precatalyst $[Rh(\mathbf{4a})_2(cod)]^+$ using AMBER* force field[16] for the phthalamide region and a frozen core for the Rh(cod) phosphite complex, which was previously optimized with DFT calculations at the B3LYP/LACVP level of theory.[17] A number of low-energy conformers were identified which, in agreement with the spectroscopic data, are characterized by interligand hydrogen bonding involving proton NH_A. These low-energy conformers were used as starting geometries for DFT optimization[17] of the entire precatalyst $[Rh(\mathbf{4a})_2(cod)]^+$, which showed that the double hydrogen-bond array displayed in Figure 2 is highly favored over other arrangements involving a single hydrogen-bonding interaction (see the Supporting Information for details). In the DFT calculated structure shown in Figure 2, the ligands are held together by two hydrogen bonds between proton NH_A of each ligand and the carbonyl group of the ancillary amide, bearing NH_B, of the other ligand. Therefore, the two molecules of **4a** behave as a supramolecular bidentate ligand with a reduced degree of conformational freedom compared to two simple monodentate phosphites coordinated to a rhodium center.[18] This may explain the superior stereoselectivity displayed by PhthalaPhos ligands compared to simple monodentate phosphites, although substrate orientation in the catalytic cycle through hydrogen bonding with the ligand could also play a crucial role.[3o]

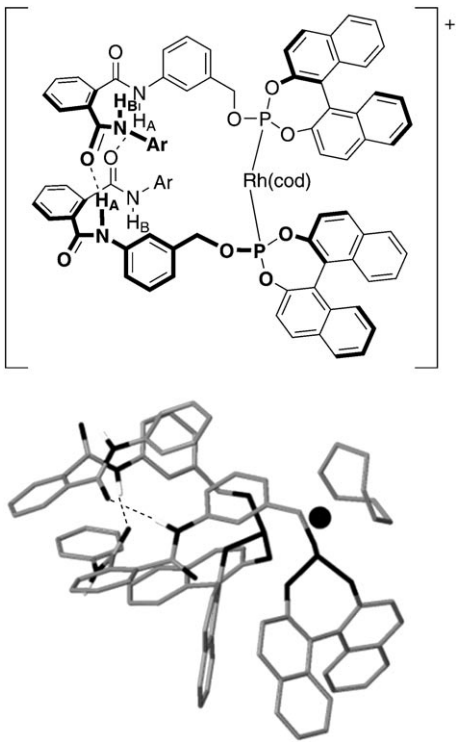
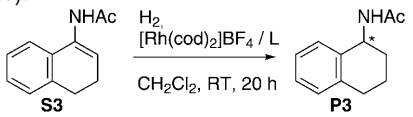


Figure 2. Supramolecular bidentate precatalyst $[Rh(\mathbf{4a})_2(cod)]^+$ and DFT calculated structure. Heteroatoms (N, O, P, Rh) are shown in black, carbon atoms in gray, and amide hydrogen atoms in light gray. For clarity, all hydrogen atoms bound to carbon are omitted.

To explore the scope of the PhthalaPhos ligands, we decided to investigate the Rh-catalyzed hydrogenation of more challenging substrates such as cyclic enamide **S3** [*N*-(3,4-dihydronaphthalen-1-yl)acetamide] and β^2-dehydro amino ester **S4** [(*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate], both of which are industrially relevant compounds.[3p] The hydrogenation of **S3** was carried out under 12 bar hydrogen pressure and gave the results reported in Table 3.[19]

Table 3: Selected results of the screening of the PhthalaPhos library in the enantioselective hydrogenation of *N*-(3,4-dihydronaphthalen-1-yl)-acetamide (**S3**).[a]



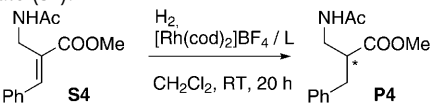
Entry	Ligand	Conv. [%][b]	*ee* [%],[b] abs. config.[c]
1	**4a**	99	96, *R*
2[d]	**4a**	70	57, *R*
3[e]	**4a**	77	21, *R*
4	**4b**	90	93, *R*
6	**4d**	98	92, *R*
7	**5**	30	53, *R*

[a] Reaction conditions: **S3**/ligand/$[Rh(cod)_2]BF_4$ = 100:2.2:1, solvent = CH_2Cl_2, c_0(**S3**) = 0.024 M, T = 25 °C, p = 12 bar. See the Supporting Information for the complete set of results. [b] Determined by GC on a chiral capillary column (MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin). [c] Assigned by comparison of the sign of optical rotation with literature data.[19] [d] THF/CH_2Cl_2 (7:1) used as solvent. [e] *i*PrOH/CH_2Cl_2 (7:1) used as solvent.

The results of this screening were quite variegated both in terms of activity and enantioselectivity, and excellent conversion and *ee* value were attained with ligand **4a** (Table 3, entry 1). The conversions followed more or less the same trend as the *ee* values, the most stereoselective ligands being also the most active. Poor results were obtained with reference ligand **5** (Table 3, entry 7). Additionally, the fact that the enantioselectivity strongly decreased with increasing polarity of the solvent (Table 3, entries 2 and 3; see the Supporting Information for the complete solvent screening) confirms that hydrogen-bonding interactions between the phthalamide groups play a crucial role in the activity and selectivity of the catalyst. To the best of our knowledge, the 96% *ee* obtained with ligand **4a** is the highest ever obtained for this substrate with phosphite ligands, and rivals the best literature precedents, obtained with a monodentate phosphoramidite (84% *ee* at RT, 98% *ee* at −20 °C)[20] and a bisphosphine (98% *ee* at RT).[21]

The screening of the ligand library on **S4** required a hydrogen pressure of 50 bar due to the lower reactivity of this substrate (Table 4). Also in this screening the enantioselectivity varied quite widely and appeared to be linked to the catalytic activity. Ligands **4c** and **4i** (Table 4, entries 1 and 2) gave very high *ee* values and good conversions, while the other ligands displayed moderate to fair enantioselectivity. Again, the reference phosphite **5** gave only very low conversion and *ee* with this substrate (Table 4, entry 3).

Table 4: Selected results of the screening of the PhthalaPhos library in the enantioselective hydrogenation of (*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate (**S4**).[a]



Entry	Ligand	Conv. [%][b]	*ee* [%],[b] $[\alpha]_D$ sign[c]
1	**4c**	75	91, +
2	**4i**	87	98, +
3	**5**	6	32, +

[a] Reaction conditions: **S4**/ligand/$[Rh(cod)_2]BF_4$ = 100:2.2:1, solvent = CH_2Cl_2, c_0(**S4**) = 0.024 M, T = 25 °C, p = 50 bar. See the Supporting Information for the complete set of results. [b] Determined by GC on a chiral capillary column (MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin). [c] Correlation of $[\alpha]_D$ sign with absolute configuration still not established.

Most importantly, 98% is the highest *ee* ever obtained with substrate **S4**, and only one highly stereoselective ligand was reported so far.[3p]

In conclusion, a library of novel chiral supramolecular ligands containing a phthalamide moiety capable of hydrogen-bonding interactions has been prepared. The new ligands, named PhthalaPhos, are easily prepared from inexpensive starting materials and show excellent enantioselectivity in the hydrogenation of both benchmark olefins and challenging substrates of potential industrial interest. The precatalytic Rh complex of one of these ligands was fully characterized and studied by NMR, IR, and mass spectroscopy, which confirmed the presence of hydrogen bonds between the coordinated ligands, and thus formation of a supramolecular bidentate ligand. Further work is underway to expand the scope of PhthalaPhos ligands to other substrates and different transition metal catalyzed processes.

Received: May 17, 2010
Published online: July 27, 2010

Keywords: asymmetric catalysis · combinatorial chemistry · hydrogen bonds · ligand design · supramolecular chemistry

[1] For relevant reviews, see: a) C. Gennari, U. Piarulli, *Chem. Rev.* **2003**, *103*, 3071–3100; b) M. J. Wilkinson, P. W. N. M. van Leeuwen, J. N. H. Reek, *Org. Biomol. Chem.* **2005**, *3*, 2371–2383; c) M. T. Reetz, *Angew. Chem.* **2008**, *120*, 2592–2626; *Angew. Chem. Int. Ed.* **2008**, *47*, 2556–2588.

[2] a) T. Šmejkal, B. Breit, *Angew. Chem.* **2008**, *120*, 317–321; *Angew. Chem. Int. Ed.* **2008**, *47*, 311–315, and references therein; b) T. Šmejkal, B. Breit, *Angew. Chem.* **2008**, *120*, 4010–4013; *Angew. Chem. Int. Ed.* **2008**, *47*, 3946–3949; c) L. Diab, T. Šmejkal, J. Geier, B. Breit, *Angew. Chem.* **2009**, *121*, 8166–8170; *Angew. Chem. Int. Ed.* **2009**, *48*, 8022–8026; d) T. Šmejkal, D. Gribkov, J. Geier, M. Keller, B. Breit, *Chem. Eur. J.* **2010**, *16*, 2470–2478.

[3] For examples of supramolecular ligands exploiting hydrogen bonding, see: a) B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608–6609; b) B. Breit, W. Seiche, *Angew. Chem.* **2005**, *117*, 1666–1669; *Angew. Chem. Int. Ed.* **2005**, *44*, 1640–1643; c) F. Chevallier, B. Breit, *Angew. Chem.* **2006**, *118*, 1629–1632;

Angew. Chem. Int. Ed. **2006**, *45*, 1599 – 1602; d) M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188 – 4189; e) Y. Liu, C. A. Sandoval, Y. Yamaguchi, X. Zhang, Z. Wang, K. Kato, K. Ding, *J. Am. Chem. Soc.* **2006**, *128*, 14212 – 14213; f) A. J. Sandee, A. M. van der Burg, J. N. H. Reek, *Chem. Commun.* **2007**, 864 – 866; g) M.-N. Birkholz, N. V. Dubrovina, I. A. Shuklov, J. Holz, R. Paciello, C. Waloch, B. Breit, A. Börner, *Tetrahedron: Asymmetry* **2007**, *18*, 2055 – 2060; h) M.-N. Birkholz, N. V. Dubrovina, H. Jiao, D. Michalik, J. Holz, R. Paciello, B. Breit, A. Börner, *Chem. Eur. J.* **2007**, *13*, 5896 – 5907; i) C. Waloch, J. Wieland, M. Keller, B. Breit, *Angew. Chem.* **2007**, *119*, 3097 – 3099; *Angew. Chem. Int. Ed.* **2007**, *46*, 3037 – 3039; j) A. C. Laungani, B. Breit, *Chem. Commun.* **2008**, 844 – 846; k) A. C. Laungani, J. M. Slattery, I. Krossing, B. Breit, *Chem. Eur. J.* **2008**, *14*, 4488 – 4502; l) B. Breit, *Pure Appl. Chem.* **2008**, *80*, 855 – 860; m) F. W. Patureau, M. Kuil, A. J. Sandee, J. N. H. Reek, *Angew. Chem.* **2008**, *120*, 3224 – 3227; *Angew. Chem. Int. Ed.* **2008**, *47*, 3180 – 3183; n) M. de Greef, B. Breit, *Angew. Chem.* **2009**, *121*, 559 – 562; *Angew. Chem. Int. Ed.* **2009**, *48*, 551 – 554; o) P.-A. R. Breuil, F. W. Patureau, J. N. H. Reek, *Angew. Chem.* **2009**, *121*, 2196 – 2199; *Angew. Chem. Int. Ed.* **2009**, *48*, 2162 – 2165; p) J. Meeuwissen, M. Kuil, A. M. van der Burg, A. J. Sandee, J. N. H. Reek, *Chem. Eur. J.* **2009**, *15*, 10272 – 10279.

[4] For examples of supramolecular ligands exploiting coordinative bonding, see: a) V. Slagt, P. W. N. M. van Leeuwen, J. Reek, *Angew. Chem.* **2003**, *115*, 5777 – 5781; *Angew. Chem. Int. Ed.* **2003**, *42*, 5619 – 5623; b) V. F. Slagt, M. Röder, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *J. Am. Chem. Soc.* **2004**, *126*, 4056 – 4057; c) J. M. Takacs, D. S. Reddy, S. A. Moteki, D. Wu, H. Palencia, *J. Am. Chem. Soc.* **2004**, *126*, 4494 – 4495; d) X.-B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1245 – 1249; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223 – 1227; e) V. F. Slagt, P. W. N. M. van Leeuwen, J. N. H. Reek, *Dalton Trans.* **2007**, 2302 – 2310; f) M. Kuil, P. E. Goudriaan, A. W. Kleij, D. M. Tooke, A. L. Spek, P. W. N. M. van Leeuwen, J. N. H. Reek, *Dalton Trans.* **2007**, 2311 – 2320; g) S. A. Moteki, J. M. Takacs, *Angew. Chem.* **2008**, *120*, 908 – 911; *Angew. Chem. Int. Ed.* **2008**, *47*, 894 – 897; h) P. E. Goudriaan, M. Kuil, X.-B. Jiang, P. W. N. M. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Dalton Trans.* **2009**, 1801 – 1805.

[5] For relevant reviews, see: a) B. Breit, *Angew. Chem.* **2005**, *117*, 6976 – 6986; *Angew. Chem. Int. Ed.* **2005**, *44*, 6816 – 6825; b) A. J. Sandee, J. N. H. Reek, *Dalton Trans.* **2006**, 3385 – 3391; c) G. Gasparini, M. Dal Molin, L. J. Prins, *Eur. J. Org. Chem.* **2010**, 2429 – 2440.

[6] A. J. Kirby, *Angew. Chem.* **1996**, *108*, 770 – 790; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 706 – 724.

[7] L. Pignataro, B. Lynikaite, J. Cvengroš, M. Marchini, U. Piarulli, C. Gennari, *Eur. J. Org. Chem.* **2009**, 2539 – 2547.

[8] G. V. Boyd, R. L. Monteil, *J. Chem. Soc. Perkin Trans. 1* **1978**, 1338 – 1350.

[9] E. G. Díaz de Toranzo, J. A. Brieux, *J. Med. Chem.* **1967**, *10*, 982 – 983.

[10] L. Pignataro, B. Lynikaite, R. Colombo, S. Carboni, M. Krupička, U. Piarulli, C. Gennari, *Chem. Commun.* **2009**, 3539 – 3541, and references therein.

[11] For **S1**, see: a) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem.* **2003**, *115*, 814 – 817; *Angew. Chem. Int. Ed.* **2003**, *42*, 790 – 793. For **S2**, see: b) M. T. Reetz, G. Mehler, A. Meiswinkel, T. Sell, *Tetrahedron: Asymmetry* **2004**, *15*, 2165 – 2167; c) ref. [10] of this paper.

[12] a) C. Gennari, M. Gude, D. Potenza, U. Piarulli, *Chem. Eur. J.* **1998**, *4*, 1924 – 1931; b) L. Belvisi, C. Gennari, A. Mielgo, D. Potenza, C. Scolastico, *Eur. J. Org. Chem.* **1999**, 389 – 400; c) L. Belvisi, C. Gennari, A. Madder, A. Mielgo, D. Potenza, C. Scolastico, *Eur. J. Org. Chem.* **2000**, 695 – 699.

[13] L. R. Steffel, T. J. Cashman, M. H. Reutershan, B. R. Linton, *J. Am. Chem. Soc.* **2007**, *129*, 12956 – 12957.

[14] All calculations were run with the Schrödinger suite of programs (http://www.schrodinger.com) through the Maestro graphical interface. Monte Carlo/energy minimization (MC/EM) conformational search[15] was performed within the framework of MacroModel version 9.5 (Schrödinger, LLC, New York, NY) using the MacroModel implementation of the Amber all-atom force field[16] (denoted AMBER*).

[15] G. Chang, W. C. Guida, W. C. Still, *J. Am. Chem. Soc.* **1989**, *111*, 4379 – 4386.

[16] S. J. Weiner, P. A. Kollman, D. T. Nguyem, D. A. Case, *J. Comput. Chem.* **1986**, *7*, 230 – 252.

[17] All DFT calculations were performed with Jaguar version 7.0 (Schrödinger, LLC, New York, NY). For DFT calculations on supramolecular bidentate Rh complexes, see ref. [3o].

[18] Chiral diphosphites were previously thought to be ligands leading to low or mediocre enantioselectivities in Rh-catalyzed olefin hydrogenation. However, Reetz and co-workers showed that binol-derived diphosphites with a properly shaped achiral backbone and optimal degree of flexibility can be highly efficient and stereoselective: M. T. Reetz, G. Mehler, O. Bondarev, *Chem. Commun.* **2006**, 2292 – 2294.

[19] Absolute configuration assigned by comparison of the sign of optical rotation with literature data: M.-J. Kim, W.-H. Kim, K. Han, Y. K. Choi, J. Park, *Org. Lett.* **2007**, *9*, 1157 – 1159.

[20] H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, B. L. Feringa, *J. Org. Chem.* **2005**, *70*, 943 – 951.

[21] a) Z. Zhang, G. Zhu, Q. Jiang, D. Xiao, X. Zhang, *J. Org. Chem.* **1999**, *64*, 1774 – 1775. For the use of highly efficient biaryl-type bis-phosphine ligands with a stereogenic axis in the Rh-catalyzed hydrogenation reaction, see: b) W. Tang, Y. Chi, X. Zhang, *Org. Lett.* **2002**, *4*, 1695 – 1698; c) Y. Zou, H. Geng, W. Zhang, S. Yu, X. Zhang, *Tetrahedron Lett.* **2009**, *50*, 5777 – 5779, and references therein.

