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Combinations of Acidic and Basic Monodentate Binaphtholic Phosphites as Supramolecular Bidentate Ligands for Enantioselective Rh-Catalyzed Hydrogenations

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A small library of chiral BINOL-derived monodentate phosphites containing either a carboxylic acid (-COOH, **A1**–**A3**) or a tertiary amine (-NMe_2, **B1**–**B4**) was synthesized. The ligand combinations were screened in the enantioselective rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate. The heterocombinations of the amine-derived phosphite (*R*)-**B2** and of a carboxylic-phosphite [(*R*)-**A1**, (*R*)-**A2**, (*R*)-**A3**] displayed a slightly higher level of enantioselectivity compared to the corresponding homocombinations [up to 90 % *ee* using (*R*)-**A1**/(*R*)-**B2**]. The nature and extent of the interaction between the acidic and basic ligands in the rhodium complexes were studied by IR and ^{31}P-NMR spectroscopy. The formation of an intramolecular salt in the Rh-heterocomplex, between the carboxylic acid and the tertiary amine, was suggested by the IR spectra. The selective formation of the Rh-heterocomplex was quantitatively assessed by ^{31}P-NMR spectroscopy, using a modified acidic ligand (*R*)-**A1-Me**. In this way, a moderate (ca. 70:30) heterocomplex/homocomplexes ratio was determined.

Introduction

Enantioselective homogeneous rhodium-catalyzed hydrogenation of functionalized olefins constitutes a very appealing strategy for the synthesis of industrially relevant enantiopure compounds (e.g. pharmaceuticals, agrochemicals and flavors).[1] Chiral phosphorus ligands, either mono- or bidentate, are among the most widely used for enantioselective homogeneous catalysis, with the bidentate ligands being initially the most represented and successful. More recently, readily accessible, inexpensive and highly diverse chiral monodentate phosphorus-ligands such as phosphoramidites, phosphites and phosphonites have been applied advantageously.[2] In addition to their outstanding activity and selectivity, comparable or even superior to those of bidentate ligands, the convenient, fast and practical preparation from commercially available materials underlines their potential for industrial applications.[3] Furthermore, the modular nature of all these ligands allows the synthesis of a wide variety of representatives, thereby making a combinatorial approach possible.[4]

An important breakthrough in this area was made independently by the groups of Reetz[5] and Feringa,[6] who used a binary mixture of chiral monodentate P-ligands in several asymmetric rhodium catalyzed reactions (hydrogenations, conjugate additions).[7] By mixing two ligands (L^a and L^b) in the presence of Rh, three species can be formed: RhL^aL^a, RhL^bL^b (homocomplexes), and RhL^aL^b (heterocomplex). This methodology is relevant whenever at least two monodentate ligands L are coordinated to the metal in the transition state of a reaction. It has been observed that in several cases the combination of ligands performs better than the corresponding single ligands, i.e. the heterocomplex possesses a higher level of activity, and regio-, diastereo-, enantioselectivity than the homocomplexes. Quite interestingly, also mixtures of chiral and achiral ligands can lead to an enhancement of stereoselectivity.[7] Under thermodynamic control (fast and reversible ligand exchange) the heterocomplex: homocomplexes ratios usually exceed the statistical value (2:1:1).[6b,7] In these cases, the preferential formation of heteroleptic catalysts from two monodentate ligands is probably favored by weak interactions, such as van der Waals, π-stacking or dipole–dipole interactions. The equilibrium can also be influenced by adjusting the amounts of the ligands L^a and L^b relative to each other and relative to the metal, thus pushing the formation of the

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heterocomplex towards completion.[8] Ideally, if the equilibrium is shifted completely in favor of the heterocomplex RhL^aL^b, only a single well-defined catalyst exists in the reaction and the undesired competition of the less selective homocomplexes would be avoided.

An alternative way to selectively assemble two monodentate ligands around a transition metal is possible if the system contains supramolecular interactions in addition to the primary metal–ligand bonds.[7,9] The advantage of this approach is the expectation that degrees of freedom in the respective metal coordination complex are reduced, resulting in the simulation of a preorganised bidentate system with predictable geometric properties, as in conventional bidentate ligands. In these cases, the preferential formation of heteroleptic catalysts from two monodentate ligands is favored by stronger interactions, such as complementary hydrogen bonds or coordinative bonding of nitrogen to zinc (Breit, van Leeuwen, Reek, Takacs).[7,9] Because of this analogy, these are often referred to as "supramolecular bidentate ligands" (Figure 1). More recently, the non-covalent bonding between crown ethers and ammonium salts,[10] ionic interactions,[11] the formation of inclusion complexes,[12] and donor-acceptor interactions[13] have also been exploited to selectively form the heterocomplexes. This strategy has been applied so far in rhodium-catalyzed asymmetric hydrogenations[14,15] and regio- and enantioselective hydroformylations,[16] in palladium-catalyzed asymmetric allylic alkylations[17] and allylations of indoles and pyrroles with allylic alcohols.[18] Other recent original applications by Breit and co-workers include the ruthenium-catalyzed hydration of alkynes[19] and nitriles,[20] and the nickel-catalyzed hydrocyanation of alkenes.[21]

In this paper we report our efforts aimed at the development of novel self-assembled supramolecular bidentate P-ligands, exploiting the complementary interaction of acidic and basic groups, which is so far unprecedented. In particular, several binaphtholic phosphites containing either a carboxylic acid (-COOH) or a tertiary amine (-NMe_2) were prepared. The rhodium complexes derived from a single ligand or from a combination of two complementary ligands (acidic + basic) were then tested in the rhodium-catalyzed

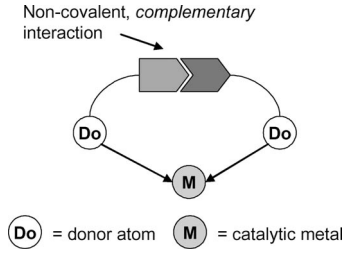


Figure 1. Supramolecular assembly of monodentate ligands through additional non-covalent complementary interactions.

enantioselective hydrogenation of methyl 2-acetamidoacrylate. The formation of the rhodium complexes was studied by IR- and ^{31}P-NMR spectroscopy using both the single ligands (homocombinations) and the combinations of a carboxylic-phosphite and a tertiary amine-derived phosphite (heterocombinations).[15] In this way, the role of the acid–base interactions in determining the heterocomplex/homocomplexes ratios was investigated.

Results and Discussion

Synthesis of the Ligands

A small collection of ligands (Figure 2) was prepared via a slight modification of the usual procedure for the synthesis of binaphtholic phosphites.[22] In particular, the phosphites **A1**–**A3** containing a carboxylic acid were obtained by reaction of (*R*)-binaphthyl-chlorophosphite[23] in dichloromethane (DCM) with the corresponding phenols bearing a carboxylic group, in the presence of 3 equiv. of triethylamine (Scheme 1). Under these conditions, partial deprotonation of the carboxylic acid occurred. In order to restore the carboxylic acid, the reaction mixture was rapidly washed with a dilute HCl solution (0.5 M) and then with water. This acid work-up, albeit rather unusual, does not seem to lower the yields, and the products were obtained pure after trituration with a small volume of DCM or DCM/Et_2O if the compound is too soluble in pure DCM.

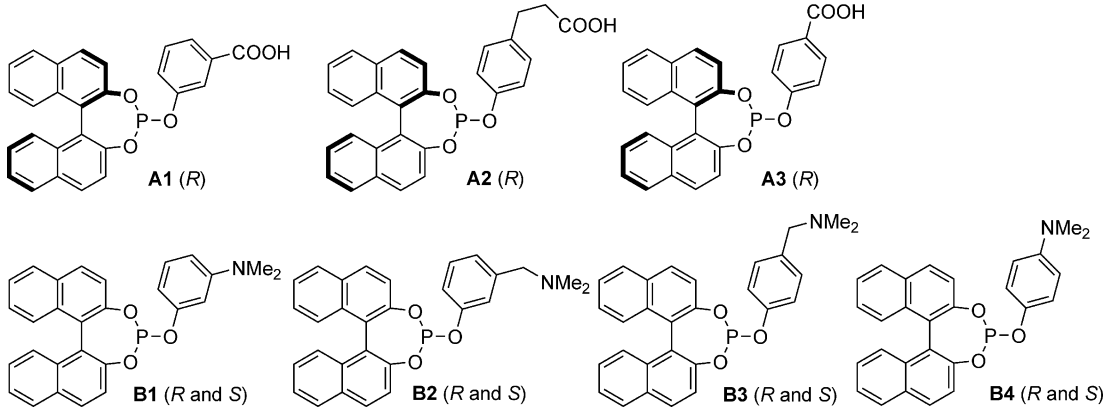
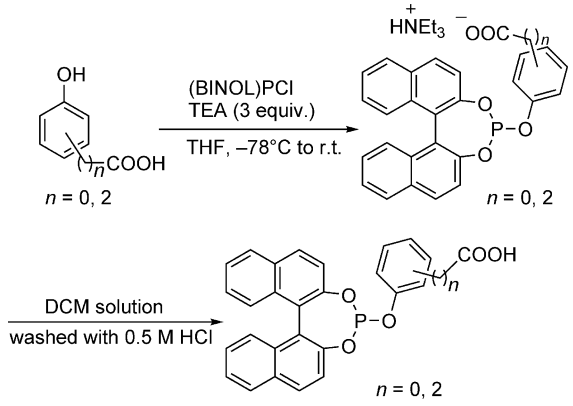
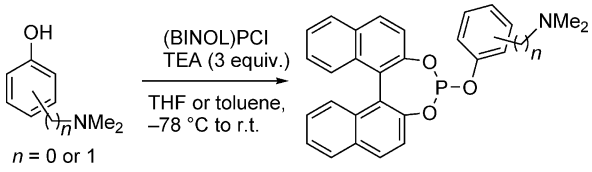


Figure 2. Library of acidic and basic binaphtholic phosphites.



Scheme 1. Synthesis of binaphtholic phosphites containing a carboxylic acid substituent.

The phosphites **B1**–**B4** bearing a tertiary amine were prepared by condensation of the corresponding chlorophosphites (either *R* or *S*) with aminophenol derivatives (either commercially available or prepared according to reported procedures, see the experimental section), in the presence of a base (Scheme 2).[24] The phosphites **B1** and **B4** bearing an aromatic amino group were purified by flash chromatography on a short pad of silica, although with quite reduced yields. On the contrary, the ligands **B2**, **B3** containing the more basic benzylic amino group decomposed over both silica and alumina. However, their purity after aqueous work-up was sufficient for further use, without the need of chromatography.

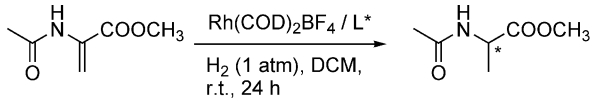


Scheme 2. Synthesis of binaphtholic phosphites containing a basic tertiary amine substituent.

Screening of the Ligands in Rh-Catalyzed Asymmetric Hydrogenation

The acidic and basic ligands were then screened in the rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate both as single ligands and as combinations of one acidic and one basic phosphite. The asymmetric hydrogenation of methyl 2-acetamidoacrylate was carried out in DCM at room temperature under an atmospheric pressure of hydrogen. $Rh(COD)_2BF_4$ was used as the rhodium source with a 1 mol-% loading. The single ligands (homocombinations) were used in a 2.2 mol-% amount, while for the heterocombinations (one acidic + one basic phosphites) 1.1 mol-% of each ligand was employed. The library screening includes 7 homocombinations and 24 heterocombinations [12 with the same absolute configuration ("homochiral") and 12 with the opposite absolute configuration ("heterochiral")]. Selected results of this screening are reported in Table 1.

Table 1. Screening of the library of acidic and basic binaphtholic phosphites (homo- and heterocombinations) in the rhodium-catalyzed asymmetric hydrogenation of methyl 2-acetamidoacrylate.[a]



Entry	Ligands	% Conversion	*ee*% (*R*,*S*)
Homocombinations			
1	(*R*)-**A1**	100	80 (*S*)
2	(*R*)-**A2**	100	80 (*S*)
3	(*R*)-**A3**	100	80 (*S*)
4	(*R*)-**B1**	100	84 (*S*)
5	(*R*)-**B2**	30	86 (*S*)
6	(*R*)-**B3**	89	89 (*S*)
7	(*R*)-**B4**	100	87 (*S*)
Heterocombinations			
8	(*R*)-**A1**/(*R*)-**B1**	100	83 (*S*)
9	(*R*)-**A1**/(*R*)-**B2**	**100**	**90 (*S*)**
10	(*R*)-**A1**/(*S*)-**B2**	84	30 (*R*)
11	(*R*)-**A1**/(*R*)-**B3**	89	79 (*S*)
12	(*R*)-**A1**/(*R*)-**B4**	100	82 (*S*)
13	(*R*)-**A2**/(*R*)-**B1**	100	81 (*S*)
14	(*R*)-**A2**/(*R*)-**B2**	**100**	**88 (*S*)**
15	(*R*)-**A2**/(*R*)-**B3**	100	86 (*S*)
16	(*R*)-**A2**/(*R*)-**B4**	100	83 (*S*)
17	(*R*)-**A3**/(*R*)-**B1**	100	86 (*S*)
18	(*R*)-**A3**/(*R*)-**B2**	**66**	**89 (*S*)**
19	(*R*)-**A3**/(*R*)-**B3**	100	85 (*S*)
20	(*R*)-**A3**/(*R*)-**B4**	100	85 (*S*)

[a] Reaction conditions: ligand or mixture of ligands (0.0154 mmol), $Rh(COD)_2BF_4$ (0.007 mmol), methyl 2-acetamidoacrylate (0.7 mmol), CH_2Cl_2 (1.0 mL), H_2 (1 bar), room temp., 24 h. Conversions and *ee* values were determined by GC equipped with a chiral capillary column (MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin, see the experimental section).

The homocombinations (Table 1, entries 1–7) gave reasonably good enantiomeric excesses (80–89%). However, in the case of the benzylic amines (*R*)-**B2** and (*R*)-**B3**, which probably act as poisons towards the catalyst due to their strongly basic amine character, the conversions were poor (30%, entry 5) or moderate (89%, entry 6). Mixing these ligands [(*R*)-**B2** and (*R*)-**B3**] with an acidic ligand, the basicity of the amine was strongly reduced by interaction with the carboxylic acid, and the catalytic activity of the rhodium complexes was restored (entries 9, 10, 11, 14, 15, 18, 19). In particular, the heterocombinations containing the benzylic amine-derived phosphite (*R*)-**B2** and an acidic ligand [(*R*)-**A1**, (*R*)-**A2**, (*R*)-**A3**] displayed a slightly higher level of enantioselectivity (entries 9, 14, 18, data printed in bold) compared to the corresponding homocombinations. Although the differences are tiny, they were measurable (multiple capillary GC analyses) and could be reproduced by repeating the key reactions. It is interesting to note how the "heterochiral" combination (*R*)-**A1**/(*S*)-**B2** (entry 10) is "mismatched" in terms of stereoselectivity (the enantio-

meric excess drops to 30%), and leads to the *R* enantiomer of the product [the enantiomer obtained using the homocombination of (*S*)-**B2**].

The effect of hydrogen pressure on the reaction outcome was also evaluated: the best-performing combination (*R*)-**A1**/(*R*)-**B2** was tested in experiments at 5 and 10 bar. In both cases a 10% decrease of the enantiomeric excess was observed. The negative effect of the increased hydrogen pressure on the enantioselectivity of hydrogenation reactions has been reported several times in the literature and is in agreement with the mechanism proposed by Halpern.[25] The effect of different solvents was also investigated: when THF was tested with several heterocombinations, lower reactivity and selectivity were observed [e.g. (*R*)-**A1**/(*R*)-**B1** 96% conv. and 56% *ee*; (*R*)-**A1**/(*R*)-**B2** 13% conv. and 68% *ee*]. Other solvents such as EtOAc or toluene were found unsuitable, due to the limited solubility of the Rh-source.

Characterization of the Acidic-Phosphite/Basic Phosphite Homo- and Heterocomplexes

The acidic and basic phosphites were investigated by ^{31}P-NMR spectroscopy: all the ligands gave a singlet at very similar chemical shift (δ = 145.6–147.1, see Table 2). The homocomplexes were then prepared by mixing the single ligands with Rh(acac)(C_2H_4)$_2$ in CD_2Cl_2 or [D_8]THF. Their ^{31}P-NMR spectra showed one or two doublets, depending on Rh/L ratio: the upfield doublet corresponds to the complex containing only one ligand Rh(L)(C_2H_4)(acac), while the downfield doublet belongs to the homocomplex Rh(L)$_2$-(acac). The value of the $^1J_{P,Rh}$ coupling constant was typically around 302–305 Hz (Table 2).

Table 2. ^{31}P-NMR spectroscopic data of the acidic and basic binaphtholic phosphites.

Ligand	^{31}P-NMR Solvent[a]	L (δ)	Rh(L)$_2$(acac) (δ)	$^1J_{P,Rh}$ (Hz)
(*R*)-**A1**	[D_8]THF	145.9	150.5	303
(*R*)-**A2**	CD_2Cl_2	146.1	148.3	302
(*R*)-**A3**	[D_8]THF	145.6	146.0	303
(*R*)-**B1**	CD_2Cl_2	146.2	149.4	305
(*R*)-**B2**	CD_2Cl_2	145.8	150.2	303
(*R*)-**B3**	CD_2Cl_2	146.0	148.8	303
(*R*)-**B4**	[D_8]THF	147.1	150.6	304

[a] Some spectra are recorded in [D_8]THF since the ligands or the corresponding Rh complexes are only sparingly soluble in CD_2Cl_2. However we did not notice any appreciable difference in the ^{31}P-chemical shift upon change of the solvent.

The heterocombinations were then studied by mixing one acidic ligand of type **A1**, **A2**, **A3** and one basic ligand of type **B1**, **B2**, **B3**, **B4** with Rh(acac)(C_2H_4)$_2$ and analyzing the mixture by ^{31}P-NMR spectroscopy. For each couple of ligands both the "homochiral" combination (with ligands having the same configuration at the BINOL stereogenic axes) and the "heterochiral" combination (with ligands having opposite BINOL configurations) were studied. In the ^{31}P-NMR spectra of the rhodium complexes resulting from the heterocombinations of P-ligands (L^a and L^b), it is usually possible to observe two doublets belonging to the two homocomplexes Rh(L^a)$_2$(acac) and Rh(L^b)$_2$(acac), and two dd signals belonging to the heterocomplex Rh(L^{a}L^b)(acac), due to the Rh-P coupling ($^1J_{P,Rh}$) and the coupling between the two different P-ligands bound to rhodium ($^2J_{P,P}$).

In the "heterochiral" combinations, two dd-type signals typical of the heterocomplexes (see above), together with the two doublets of the two homocomplexes, were observed. This behavior is well exemplified for the "heterochiral" (*R*)-**A1**/(*S*)-**B2** combination: two dd signals (♦ and *) centered at δ = 149.7 and 146.9 with $^2J_{P,P}$ = 113 Hz and $^1J_{P,Rh}$ = 303 Hz and 306 Hz, respectively, plus one doublet (●) for both the homocomplexes at δ = 150.5 with $^1J_{P,Rh}$ = 303 Hz were observed in an overall 57:43 heterocomplex/homocomplexes ratio (Figure 3, a).

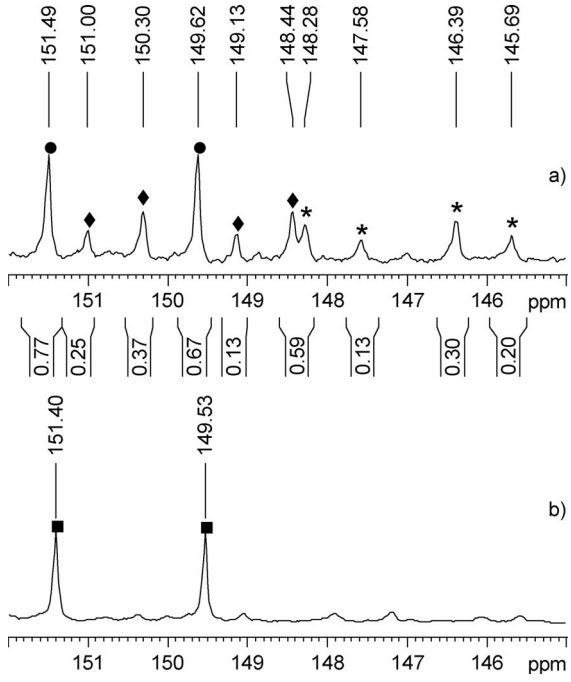


Figure 3. ^{31}P-NMR spectra of the rhodium complexes resulting from the combination of Rh(acac)(C_2H_4)$_2$ with: a) ligands (*R*)-**A1**/(*S*)-**B2** and b) (*R*)-**A1**/(*R*)-**B2**.

On the contrary, in the case of the "homochiral" combinations, the eight-signal pattern typical of the heterocomplexes (two dd signals) was not observed. These spectra are generally of difficult interpretation, featuring either a dominant doublet (with other minor signals) or a system of four doublets having the same intensity. In the case of the (*R*)-**A1**/(*R*)-**B2** combination (Figure 3, b), i.e. the best combination found in the enantioselective hydrogenation screening, a pattern featuring one major doublet (■) centered at δ = 150.5 ppm with a coupling constant of 303 Hz was observed. It should be noted that the respective homocomplexes show very similar doublets in their ^{31}P-NMR spectra [δ = 150.5, $^1J_{P,Rh}$ = 303 Hz and δ = 150.2, $^1J_{P,Rh}$ = 303 Hz for (*R*)-**A1** and (*R*)-**B2**, respectively, see Table 2]. These very close values can be rationalized considering that these ligands possess a very similar environment around the phos-

phorus atoms and differ for the presence of a remote functionalization, which apparently does not alter significantly their steric and electronic properties. It can also be assumed that in the case of the "homochiral" heterocombinations, the geometrical properties of the heterocomplex should not differ dramatically from those of the related homocomplexes. In such a scenario, it can be postulated that the two ligands of the "homochiral" heterocomplex become "quasi-homotopic" and thus almost magnetically equivalent. For this reason, a single doublet for the two ligands is observed, instead of the expected two dd patterns. Under these circumstances, it is not possible to determine the heterocomplex/homocomplex ratios.

In order to investigate the intramolecular interaction between the carboxylic group and the tertiary amine, we ran infrared spectra of diluted solutions (4 mM, in DCM) of the ligands (*R*)-**A1** and (*R*)-**B2**, of the 1:1 mixture of the two ligands and of the heterocombination in the presence of $Rh(acac)(C_2H_4)_2$. While no definitive conclusion could be drawn from the analysis of the O–H/N–H region of the spectra, the carbonyl region proved much more informative (Figure 4).

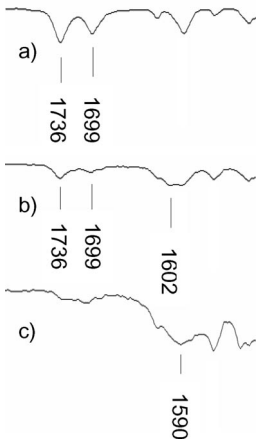
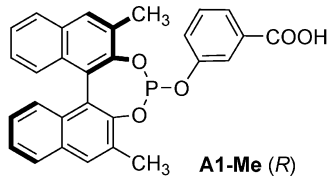


Figure 4. IR spectra (4 mM solutions in CH_2Cl_2) of the carbonyl region of: a) ligand (*R*)-**A1**; b) a 1:1 mixture of ligand (*R*)-**A1** and (*R*)-**B2**; c) a 1:1 mixture of ligand (*R*)-**A1** and (*R*)-**B2** after addition of 1 equiv. of $Rh(acac)(C_2H_4)_2$.

In fact, the spectrum of ligand (*R*)-**A1** showed two bands at 1736 and 1699 cm^{-1} (Figure 4, a), typical of the stretching of the carbonyl group in the monomeric and dimeric carboxylic acid, respectively. When ligand (*R*)-**B2** was added, an additional band at 1603 cm^{-1}, corresponding to the formation of the carboxylate group could be detected (Figure 4, b). Upon addition of $Rh(acac)(C_2H_4)_2$, this signal became the major band of the carbonyl region (Figure 4, c), thus suggesting that a strong interaction of the carboxylic group of (*R*)-**A1** with the amine group of (*R*)-**B2** had taken place. Furthermore, due to the high dilution of the sample, it can be assumed that the interaction of the carboxylate and the amine group occurred intramolecularly (albeit no quantitative conclusion can be drawn from these results).

As described above, no quantification of the heterocomplex/homocomplexes ratio could be obtained for the "homochiral" combination of ligands (*R*)-**A1** and (*R*)-**B2** from the analysis of the ^{31}P-NMR spectra, and this was attributed to the similarity of the ligands. We speculated that an increased difference in the ligand structures would cause a bigger NMR dispersion and restore the classical heterocomplex NMR pattern, thus allowing a quantitative determination of the complexes present in solution. For this reason, we synthesized phosphite (*R*)-**A1-Me**, derived from 3,3′-dimethyl-1,1′-bi-2-naphthol[26] and 3-hydroxybenzoic acid.



A1-Me (*R*)

The expected ^{31}P-NMR pattern (Figure 5), consisting of two doublets for the homocomplexes and two dd signals for the heterocomplex, was observed in the heterocombinations of (*R*)-**A1-Me** with the basic phopshites (*R*)-**B1**–(*R*)-**B4**. In particular, in the case of the combination (*R*)-**A1-Me**/(*R*)-**B2** two dd signals (♦ and *) centered at δ = 147.3 and 143.4 with $^2J_{P,P}$ = 112 Hz and $^1J_{P,Rh}$ = 305 Hz and 298 Hz respectively, plus one doublet (●) for the (*R*)-**B2** homocomplex at δ = 150.7 with $^1J_{P,Rh}$ = 303 Hz and one doublet (■) for the (*R*)-**A1-Me** homocomplex at a δ = 144.6 with $^1J_{P,Rh}$ = 302 Hz were observed in a 68:32 heterocomplex/homocomplexes ratio. The heterocomplex/homocomplexes ratio increased to 73:27 for the combination (*R*)-**A1-Me**/(*R*)-**B3**, thus reflecting a moderate selectivity for heterocomplex formation due to the interaction of the two complementary ligands. However, being ligand (*R*)-**A1-Me** bulkier than ligand (*R*)-**A1**, the heterocomplex/homocomplexes ratios determined with (*R*)-**A1-Me** might not reflect those we could not establish with (*R*)-**A1**.[27]

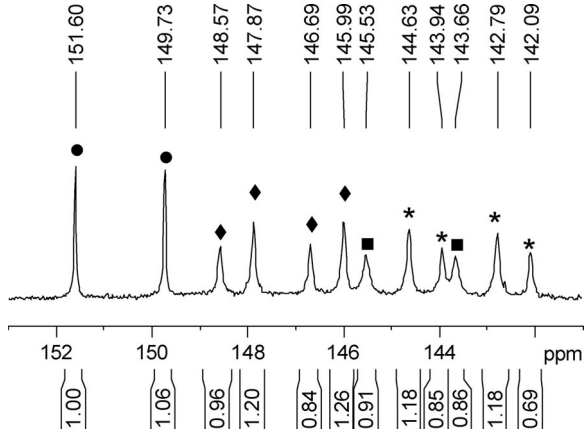


Figure 5. ^{31}P-NMR spectrum of the rhodium complexes resulting from the combination of ligands (*R*)-**A1-Me** and (*R*)-**B2** with $Rh(acac)(C_2H_4)_2$ as the rhodium source.

Conclusions

In this work we have investigated the possibility of exploiting acid–base interactions for achieving the selective formation of supramolecular bidentate ligands. For this purpose, a small library of chiral BINOL-derived monodentate phosphites containing either a carboxylic acid (-COOH) or a tertiary amine (-NR_2) was synthesized. The new ligands were screened in the rhodium-catalyzed hydrogenation of methyl 2-acetamidoacrylate. The heterocombinations of the amine-derived phosphite (*R*)-**B2** and of a carboxylic-phosphite [(*R*)-**A1**, (*R*)-**A2**, (*R*)-**A3**] displayed a slightly higher level of enantioselectivity compared to the corresponding homocombinations [up to 90% *ee* using (*R*)-**A1**/(*R*)-**B2**]. The formation of an intramolecular salt between the carboxylic acid and the tertiary amine in the heterocomplex was suggested by IR spectroscopy. A quantitative assessment of the selectivity for the Rh-heterocomplex formation was investigated by ^{31}P-NMR spectroscopy. Unfortunately, for the catalytically relevant "homochiral" (*R*)-**A1**/(*R*)-**B2** combination, the usual ^{31}P-NMR pattern of the heterocomplex could not be observed due to the similarity of the phosphorus atoms ("quasi-homotopic"). The introduction of a structural modification in the BINOL moiety of the acidic ligand [i.e. use of (*R*)-**A1-Me**, derived from 3,3′-dimethyl-1,1′-bi-2-naphthol and 3-hydroxybenzoic acid] restored the classical NMR pattern of the heterocomplexes. In this way, a moderate (ca. 70:30) heterocomplex/homocomplexes ratio was determined. In conclusion, this is an example of cheap and easy-to-prepare chiral self-assembling ligands of high potential for a number of interesting catalytic applications.

Experimental Section

General Remarks: All reactions were carried out in flame-dried glassware with magnetic stirring under nitrogen atmosphere, unless otherwise stated. The solvents for reactions were dried by distillation over the following drying agents and transferred under nitrogen: CH_2Cl_2 (CaH_2), MeOH (CaH_2), THF (Na), toluene (Na), hexane (Na), Et_3N (CaH_2). Dry Et_2O (over molecular sieves in bottles with crown cap) was purchased from Fluka and stored under nitrogen. The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 μm, following the procedure by Still and co-workers.[28] Proton NMR spectra were recorded on a spectrometer operating at 400.13 MHz. Proton chemical shifts are reported as δ values (ppm) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$: δ = 7.26 ppm; CD_2Cl_2: 5.32 ppm; [D_8]THF: δ = 3.58, 1.73 ppm; [D_6]DMSO: δ = 2.50 ppm). The following abbreviations are used to describe spin multiplicity: s for singlet, d for doublet, t for triplet, q for quartet, m for multiplet, br. for broad signal, dd for double doublet. ^{13}C-NMR spectra were recorded on a 400 MHz spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.23 ppm. CD_2Cl_2 = 54.00 ppm; [D_8]-THF: δ = 67.57, 25.37 ppm; [D_6]DMSO: δ = 39.51 ppm). ^{31}P-NMR spectra were recorded on a 400 MHz spectrometer operating at 162 MHz, with complete proton decoupling. ^{31}P-NMR chemical shifts are reported as δ values (ppm) relative to external 85% H_3PO_4 at 0 ppm (positive values downfield). Infrared spectra were recorded on a standard FT/IR spectrometer. Optical rotation values were measured on an automatic polarimeter with a 1-dm cell at the sodium-D line (λ = 589 nm). Gas chromatography was performed on a GC instrument equipped with a flame ionization detector, using a chiral capillary column. Mass spectra (MS) were performed on a Thermo-Finnigan LCQ Advantage mass spectrometer equipped with an ion trap detector and an ESI ion source. Elemental analyses were performed on a CHN Analyzer.

Materials: Commercially available reagents were used as received. All the hydroxy acids employed and 3-(dimethylamino)phenol are commercially available. 4-(dimethylamino)phenol,[29] 3- and 4-[(dimethylamino)methyl]phenol[24] were prepared according to literature procedures. While both enantiomers of 2,2′-dihydroxy-1,1′-binaphthalene (BINOL) are commercially available, (*R*)-3,3′-dimethyl-2,2′-dihydroxy-1,1′-binaphthalene (3,3′-Me-BINOL) was synthesized from BINOL according to known protocols.[30] The preparation of the corresponding chlorophosphites (BINOL-PCl and 3,3′-Me-BINOL-PCl) was carried out on gram scale according to a literature procedure.[23]

General Procedure for the Synthesis of the Basic Phosphites: A mixture of the aminophenol (1 equiv.) and triethylamine (2 equiv.) in THF or toluene (3 mL/mmol of aminophenol) was prepared and cooled to 0 °C while stirring. BINOL-PCl (1 equiv.; typical scale: 0.245 g) was dissolved in the same solvent (3 mL/mmol of chlorophosphite) and transferred into the reaction mixture, which was then warmed to room temperature and stirred overnight. After adding some hexane (the same volume as the reaction solvent) the mixture was filtered through a pad of celite. The solvent was then evaporated at reduced pressure, the crude product re-dissolved in DCM and the resulting solution washed three times with water. The organic solution was dried with Na_2SO_4 and filtered, and the solvent removed by rotary evaporation to give the crude product as a white solid. When indicated, the crude was purified by flash column chromatography.

(*R*)- and (*S*)-3-(Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)-*N*,*N*′-dimethylaniline (B1): The General Procedure was followed with THF as the solvent, starting from 0.245 g of BINOL-PCl (0.698 mmol), 0.096 g of 3-(dimethylamino)phenol (0.698 mmol) and 0.2 mL of triethylamine (1.40 mmol). The product was purified by column chromatography on silica gel (eluent: DCM). A white solid was obtained; yield 186 mg (59%); m.p. 89–93 °C. $[a]_D^{25}$ enantiomer *S* = +182.8 ($CHCl_3$, *c* = 1.00). FT-IR (film): $\tilde{\nu}$ = 1610.3, 1504.2, 1202.4, 1070.3, 952.7 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.8 Hz, 1 H), 8.02–7.98 (m, 3 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.57–7.48 (m, 5 H), 7.38–7.30 (m, 3 H), 6.73 (d, *J* = 7.2 Hz, 1 H), 6.62–6.60 (m, 2 H), 2.98 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 152.7, 148.4, 147.9, 133.6, 133.4, 132.4, 132.1, 131.2, 130.8, 130.6, 129.2, 129.1, 127.8, 127.7, 127.1, 127.9, 125.9, 125.8, 125.2, 123.7, 122.6, 122.5, 109.4, 108.7, 105.3, 41.2 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 146.0 ppm. MS (ESI +): calcd. for $C_{28}H_{22}NO_3P$: 451.1; found 452.5 [*M* + H]$^+$. $C_{28}H_{22}NO_3P$ (451.46): calcd. C 74.49, H 4.91, N 3.10; found C 74.52, H 4.89, N 3.13.

(*R*)- and (*S*)-1-[3-(Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)phenyl]-*N*,*N*′-dimethylmethanamine (B2): The General Procedure was followed with toluene as the solvent, starting from

0.245 g of BINOL-PCl (0.698 mmol), 0.106 g of 3-[(dimethylamino)methyl]phenol (0.698 mmol) and 0.2 mL of triethylamine (1.40 mmol). This phosphite could not be purified by chromatography (it underwent degradation), but its purity was sufficient for further use; yield 244 mg (75%); m.p. 100 °C. $[a]_D^{18}$ enantiomer *R* = –230.0 (CH_2Cl_2, *c* = 1.09). FT-IR (film): $\tilde{\nu}$ = 1587.1, 1224.6, 1070.3, 940.1 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2): δ = 8.09 (d, *J* = 8.8 Hz, 1 H), 8.04–7.99 (m, 3 H), 7.64 (d, *J* = 8.8 Hz, 1 H), 7.51–7.40 (m, 5 H), 7.36–7.26 (m, 4 H), 7.15 (m, 2 H), 3.43 (s, 2 H), 2.26 (s, 6 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 153.6, 152.3, 148.3, 147.7, 141.7, 133.5, 133.2, 132.4, 132.0, 131.3, 130.6, 130.2, 129.1, 127.5, 127.4, 127.1, 127.0, 126.0, 125.8, 123.5, 122.4, 122.3, 121.6, 121.5, 119.7, 119.6, 64.10, 45.5 ppm. ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 145.8 ppm. MS (ESI +): calcd. for $C_{29}H_{24}NO_3P$: 465.2; found 466.2 $[M + H]^+$. $C_{29}H_{24}NO_3P$ (465.49): calcd. C 74.83, H 5.20, N 3.01; found C 74.79, H 5.18, N 3.06.

(*R*)- and (*S*)-1-[4-(Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)phenyl]-*N*,*N*′-dimethylmethanamine (B3): The product was prepared following the General Procedure with toluene as the solvent, starting from 0.245 g of BINOL-PCl (0.698 mmol), 0.106 g of 4-[(dimethylamino)methyl]phenol (0.698 mmol) and 0.2 mL of triethylamine (1.40 mmol). **B3** could not be purified by chromatography because of degradation. Solvent was removed to yield the crude product as a white foamy solid; yield 202 mg (62%); m.p. 150 °C. $[a]_D^{19}$ enantiomer *R* = –114.5 (CH_2Cl_2, *c* = 1.04). FT-IR (film): $\tilde{\nu}$ = 1589.1, 1504.2, 1201.4, 1069.3, 954.6 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2): δ = 8.09 (d, *J* = 8.8 Hz, 1 H), 8.03–7.98 (m, 3 H), 7.63 (d, *J* = 8.8 Hz, 1 H), 7.55–7.37 (m, 5 H), 7.35–7.28 (m, 4 H), 7.20–7.15 (m, 2 H), 3.44 (s, 2 H), 2.24 (s, 6 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 154.0, 148.2, 147.7, 133.5, 133.2, 132.5, 132.0, 131.4, 131.3, 130.6, 129.1, 129.0, 127.5, 127.4, 127.0, 126.9, 126.0, 125.8, 122.4, 122.3, 120.9, 120.8, 116.5, 63.5, 45.0 ppm. ^{31}P NMR (162 MHz, CD_2Cl_2): δ = 145.6 ppm. MS (ESI +): calcd. for $C_{29}H_{24}NO_3P$: 465.2; found 466.2 $[M + H]^+$. $C_{29}H_{24}NO_3P$ (465.49): calcd. C 74.83, H 5.20, N 3.01; found C 74.86, H 5.19, N 2.97.

(*R*)- and (*S*)-4-(Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)-*N*,*N*′-dimethylaniline (B4): The product was prepared in THF according to the General Procedure, starting from 0.245 g of BINOL-PCl (0.698 mmol), 0.096 g of 4-(dimethylamino)phenol (0.698 mmol) and 0.2 mL of triethylamine (1.40 mmol). After column chromatography on a short pad of silica gel (eluent: DCM) the product was obtained as a white solid; yield 151 mg (48%); m.p. 179 °C. $[a]_D^{25}$ enantiomer *R* = –100.5 ($CHCl_3$, *c* = 1.07). FT-IR (film): $\tilde{\nu}$ = 1589.1, 1509.1, 1326.8, 1210.1, 1070.3 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.8 Hz, 1 H), 7.98–7.92 (m, 3 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.50–7.40 (m, 4 H), 7.33–7.27 (m, 3 H), 7.12 (d, *J* = 9.1 Hz, 2 H), 6.73 (d, *J* = 9.1 Hz, 2 H), 2.95 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 148.3, 147.8, 133.5, 133.2, 132.4, 131.9, 131.2, 130.5, 129.1, 129.0, 127.4, 127.3, 127.0, 126.9, 125.9, 125.7, 124.9, 123.6, 122.5, 122.4, 121.7, 121.6, 114.4, 41.6 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 146.9 ppm. MS (ESI +): calcd. for $C_{28}H_{22}NO_3P$: 451.1; found 452.1 $[M + H]^+$. $C_{28}H_{22}NO_3P$ (451.46): calcd. C 74.49, H 4.91, N 3.10; found C 74.47, H 4.97, N 3.09.

General Procedure for the Synthesis of the Acidic Phosphites: A solution of chlorophosphite (1 equiv; typical scale: 0.245 g) in THF (5.7 mL/mmol) was transferred into a solution (or suspension) of the chosen hydroxy acid (1 equiv., previously azeotropically dried with toluene) and triethylamine (3 equiv.) in THF (2.9 mL/mmol of hydroxy acid) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The solvent was removed, and the crude product dissolved in DCM (29 mL/mmol of substrate). The solution was rapidly washed with water (10 mL), 0.5 M HCl aqueous solution (2 × 10 mL), and finally with brine (10 mL). The organic phase was dried with Na_2SO_4, filtered, concentrated to give the product as a white or yellowish solid. Most of the products were only sparingly soluble in DCM (see below), so they could be washed with small amounts of this solvent as it follows: DCM (1 or 2 mL) was added to the crude solid, then the resulting yellowish solution (containing the impurities) was decanted away from the white residue. The residue was washed again in the same way once or twice.

(*R*)-3-(Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)benzoic Acid (A1): The product, a white solid, was prepared and purified according to the General Procedure, starting from 0.245 g of BINOL-PCl (0.698 mmol), 0.096 g of 3-hydroxybenzoic acid (0.698 mmol) and 0.3 mL of triethylamine (2.09 mmol); yield 262 (83%); m.p. 143 °C. $[a]_D^{26}$ = –170.6 (THF; *c* = 1.18). FT-IR (4 mM solution in DCM): $\tilde{\nu}$ = 3524.3, 1735.9, 1699.3, 1587.4, 1294.0 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.23 (d, *J* = 8.8 Hz, 1 H), 8.17–8.09 (m, 3 H), 7.85–7.72 (m, 3 H), 7.60–7.53 (m, 5 H), 7.42–7.38 (m, 2 H), 7.26–7.21 (m, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 167.5, 152.0, 148.0, 147.4, 133.1, 132.9, 132.6, 132.3, 132.1, 131.8, 131.6, 129.9, 129.8, 128.1, 128.0, 127.2, 127.0, 126.8, 126.6, 124.6, 123.1, 122.7, 122.6, 121.8, 121.7 ppm. ^{31}P NMR (162 MHz, [D$_6$]DMSO): δ = 145.0 ppm. MS (ESI–): calcd. for $C_{27}H_{17}O_5P$: 452.1; found 451.1 $[M - H]^-$. $C_{27}H_{17}O_5P$ (452.40): calcd. C 71.68, H 3.79; found C 71.74, H 3.82.

(*R*)-3-[4-(Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)-phenyl]propanoic Acid (A2): The product was prepared according to the General Procedure, starting from 0.245 g of BINOL-PCl (0.698 mmol), 0.116 g of 3-(4-hydroxyphenyl)propanoic acid (0.698 mmol) and 0.3 mL of triethylamine (2.09 mmol). This product could not be purified by the DCM washing, due to its high solubility. By careful column chromatography on silica gel (eluent: 8:2 DCM/Et_2O), a fraction of pure product could be isolated as a white solid; yield 67 mg (20%); m.p. 170 °C. $[a]_D^{30}$ = –56.7 (THF; *c* = 1.15). FT-IR (film): $\tilde{\nu}$ = 1707.7, 1204.3 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.8 Hz), 7.98–7.93 (m, 3 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.50–7.40 (m, 5 H), 7.34–7.27 (m, 2 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 7.14 (d, *J* = 8.5 Hz, 2 H), 2.98 (t, *J* = 7.6 Hz, 2 H), 2.71 (t, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 155.0, 148.2, 147.7, 137.0, 133.6, 133.3, 132.7, 132.4, 131.2, 130.6, 130.3, 130.0, 129.1, 129.0, 127.8, 127.6, 127.1, 127.0, 126.0, 125.8, 123.6, 122.4, 121.2, 121.1, 116.1, 36.3, 30.5 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 145.9 ppm. MS (ESI –): calcd. for $C_{29}H_{21}O_5P$: 480.1; found 479.1 $[M - H]^-$. $C_{29}H_{21}O_5P$ (480.46): calcd. C 72.50, H 4.41; found C 72.52, H 4.39.

(*R*)-4-(Dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-yloxy)benzoic Acid (A3): The product was obtained as a white solid following the General Procedure, starting from 0.245 g of BINOL-PCl (0.698 mmol), 0.096 g of 4-hydroxybenzoic acid (0.698 mmol) and 0.3 mL of triethylamine (2.09 mmol); yield 215 mg (68%); m.p. 183 °C. $[a]_D^{30}$ = –124.0 (THF; *c* = 1.08). FT-IR (nujol): $\tilde{\nu}$ = 2723.9, 1677.7, 1216.9 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.25 (d, *J* = 8.8 Hz, 1 H), 8.18–8.10 (m, 3 H), 8.01 (d, *J* = 8.6 Hz, 2 H), 7.77 (d, *J* = 8.8 Hz, 1 H), 7.59–7.52 (m, 3 H), 7.41–7.35 (m, 4 H), 7.26–7.23 (m, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 167.0, 155.0, 154.9, 147.3, 146.7, 132.5, 132.2, 131.9, 131.7, 131.4, 131.0, 129.2, 129.1, 127.7, 127.4, 127.3, 126.5, 126.4, 126.1, 125.9, 123.9, 122.5, 122.0, 120.7, 120.6 ppm. ^{31}P NMR (162 MHz, [D$_6$]-DMSO): δ = 144.9 ppm. MS (ESI –): calcd. for $C_{27}H_{17}O_5P$: 452.1; found 451.1 $[M - H]^-$. $C_{27}H_{17}O_5P$ (452.40): calcd. C 71.68, H 3.79; found C 71.69, H 3.77.

(*R*)- and (*S*)-3-[(2,6-Dimethyldinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yl)oxy]benzoic Acid (A1-Me): This product was prepared according to the General Procedure, starting from 0.360 g of 3,3′-Me-BINOL-PCl (0.950 mmol), 0.131 g of 3-hydroxybenzoic acid (0.950 mmol) and 0.4 mL of triethylamine (2.85 mmol); yield 301 mg (66%); m.p. 120 °C. $[\alpha]_D^{19}$ enantiomer *R* = –108.0 ($CHCl_3$, *c* = 1.00). FT-IR (film): $\tilde{\nu}$ = 3364.2, 2724.0, 1696.1, 1584.2, 1205.3, 1099.2 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 8.05 (s, 1 H), 7.99–7.94 (m, 3 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 7.73 (s, 1 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.48–7.43 (m, 3 H), 7.28–7.22 (m, 2 H), 7.15–7.12 (m, 2 H), 2.61 (s, 3 H), 2.51 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 166.8, 151.8, 147.3, 145.8, 133.4, 131.7, 131.4, 131.2, 131.1, 130.9, 130.4, 130.0, 128.4, 128.3, 126.4, 126.2, 126.1, 125.9, 125.8, 124.6, 124.3, 122.6, 120.3, 120.2, 17.8, 17.4 ppm. ^{31}P NMR (162 MHz, [D_6]DMSO): δ = 142.9 ppm. MS (ESI –): calcd. for $C_{29}H_{21}O_5P$: 480.1; found 479.1 [*M* – H]$^-$. $C_{29}H_{21}O_5P$ (452.40): calcd. C 72.50, H 4.41; found C 72.51, H 4.43.

General Procedure for Complexation Experiments: The complexation experiments were run in NMR tubes under nitrogen atmosphere and monitored by ^1H and ^{31}P-NMR spectroscopy. The typical scale of the complexation experiments was about 0.02 mmol of Rh(acac)(C_2H_4)$_2$ in 0.75 mL of deuterated solvent (0.027 M concentration) and up to 0.04 mmol of ligand or ligands (0.02 mmol each). CD_2Cl_2 was the most frequently used solvent, except in the case of DCM-insoluble ligands (such as **A1**, **A3** or **A1-Me**). In such cases, [D_8]THF was used instead. No significant discrepancies were found when the same experiment was performed both in CD_2Cl_2 and in [D_8]THF.

Experiments with One Ligand: Rh(acac)(C_2H_4)$_2$ (0.5 equiv.) was added to a solution of the ligand (1 equiv.) and then ^1H and ^{31}P-NMR spectra were recorded. More rhodium source was then added portionwise (always monitoring the experiment by NMR) until the [Rh]/ligand ratio was reversed. At low [Rh]/ligand ratios the doublet signal of the homocomplex Rh(L)$_2$(acac) was dominant, while at high [Rh]/ligand ratios the signal of the mono complex Rh(L)(C_2H_4)(acac) became bigger.

Ligand Combinations: The two ligands (1 equiv. each) were weighed and dissolved in the chosen deuterated solvent into the NMR tube and Rh(acac)(C_2H_4)$_2$ (1 equiv.) was added; ^1H NMR and ^{31}P-NMR spectra were recorded.

General Procedure for Asymmetric Hydrogenation Catalysis Tests: The hydrogenations were carried out on methyl 2-acetamidoacrylate at room temperature in DCM using Rh(COD)$_2BF_4$ as the Rh source. A standard laboratory hydrogenation apparatus was used. The ligand (0.0154 mmol) or the mixture of ligands (0.0077 mmol each) was weighed in the reaction vessel, then a 0.007 M stock solution of Rh(COD)$_2BF_4$ in DCM (1 mL) was added. A 0.7 M solution of methyl 2-acetamidoacrylate (1 mL) was finally added to the vessel. The vessel was subjected to three vacuum/hydrogen cycles and then stirred for 24 h under hydrogen atmosphere; yields and enantiomeric excesses were determined by GC using a chiral column (aliquots were taken directly from the reaction vessels and injected in the GC). GC conditions: capillary column: MEGADEX DACTBSβ, diacetyl-*tert*-butylsilyl-β-cyclodextrin, 0.25 μm; diameter: 0.25 mm; length: 25 m; carrier gas: H_2; flow: 1 mL/min; oven temperature: 80 °C for 10 min, then a 0.5 °C/min gradient is applied: $t_{substrate}$ = 23.8 min; t_S = 26.1 min; t_R = 33.2 min.[8]

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[1] a) J. G. de Vries, C. J. Elsevier, *The Handbook of Homogeneous Hydrogenation*, Wiley-VCH, Weinheim, **2007**; b) N. B. Johnson, I. C. Lennon, P. H. Moran, J. A. Ramsden, *Acc. Chem. Res.* **2007**, *40*, 1291–1299.
[2] T. Jerphagnon, J.-L. Renaud, C. Bruneau, *Tetrahedron: Asymmetry* **2004**, *15*, 2101–2111, and references therein.
[3] a) J. G. de Vries, L. Lefort, *Chem. Eur. J.* **2006**, *12*, 4722–4734, and references cited therein; b) C. Jäkel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912–2942.
[4] a) R. den Heeten, B. H. G. Swennenhuis, P. W. N. M. van Leeuwen, J. G. de Vries, P. C. J. Kamer, *Angew. Chem. Int. Ed.* **2008**, *47*, 6602–6605; b) O. Pamies, M. Dieguez, *Chem. Eur. J.* **2008**, *14*, 944–960; c) 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.
[5] a) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, patent application DE20021047633, application date October 11, **2002**; b) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem. Int. Ed.* **2003**, *42*, 790–793; c) M. T. Reetz, G. Mehler, *Tetrahedron Lett.* **2003**, *44*, 4593–4596.
[6] a) D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Biomol. Chem.* **2003**, *1*, 1087–1089; b) A. Duursma, R. Hoen, J. Schuppan, R. Hulst, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 3111–3113.
[7] For a recent review on the use of combinations of monodentate ligands to control enantio-, diastereo-, and regioselectivity in transition-metal catalysis, see: M. T. Reetz, *Angew. Chem. Int. Ed.* **2008**, *47*, 2556–2588.
[8] C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries, L. Lefort, *Chem. Eur. J.* **2005**, *11*, 6701–6717.
[9] a) P. E. Goudriaan, P. van Leeuwen, M. N. Birkholz, J. N. H. Reek, *Eur. J. Inorg. Chem.* **2008**, 2939–2958; b) B. Breit, *Pure Appl. Chem.* **2008**, *80*, 855–860; c) A. J. Sandee, J. N. H. Reek, *Dalton Trans.* **2006**, 3385–3391; d) B. Breit, *Angew. Chem. Int. Ed.* **2005**, *44*, 6816–6825.
[10] G. Hattori, T. Hori, Y. Miyake, Y. Nishibayashi, *J. Am. Chem. Soc.* **2007**, *129*, 12930–12931.
[11] H. Gulyas, J. Benet-Buchholz, E. C. Escudero-Adan, Z. Freixa, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2007**, *13*, 3424–3430.
[12] C. Machut, J. Patrigeon, S. Tilloy, H. Bricout, F. Hapiot, E. Monflier, *Angew. Chem. Int. Ed.* **2007**, *46*, 3040–3042.
[13] a) O. Chuzel, C. Magnier-Bouvier, E. Schulz, *Tetrahedron: Asymmetry* **2008**, *19*, 1010–1019; b) B. Lynikaite, J. Cvengroš, U. Piarulli, C. Gennari, *Tetrahedron Lett.* **2008**, *49*, 755–759.
[14] a) F. W. Patureau, M. Kuil, A. J. Sandee, J. N. H. Reek, *Angew. Chem. Int. Ed.* **2008**, *47*, 3180–3183; b) A. C. Laungani, B. Breit, *Chem. Commun.* **2008**, 844–846; c) A. J. Sandee, A. M. van der Burg, J. N. H. Reek, *Chem. Commun.* **2007**, 864–866; d) M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188–4189; e) J. M. Takacs, K. Chaiseeda, S. A. Moteki, D. S. Reddy, D. Wu, K. Chandra, *Pure Appl. Chem.* **2006**, *78*, 501–509; f) X. B. Jiang, L. Lefort, P. E. Goudriaan, A. H. M. de Vries, P. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Angew. Chem. Int. Ed.* **2006**, *45*, 1223–1227.
[15] For structure elucidation of chiral hydrogenation catalysts self-assembling via hydrogen bonding and the role of the solvent used, see: a) I. A. Shuklov, N. V. Dubrovina, E. Barsch, R. Ludwig, D. Michalik, A. Börner, *Chem. Commun.* **2009**, 1535–1537; b) 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; c) N. V. Dubrovina, I. A. Shuklov, M.-N. Birkholz, D. Michalik, R. Paciello, A. Börner, *Adv. Synth. Catal.* **2007**, *349*, 2183–2187.
[16] a) P. E. Goudriaan, X. B. Jang, M. Kuil, R. Lemmens, P. Van Leeuwen, J. N. H. Reek, *Eur. J. Org. Chem.* **2008**, 6079–6092; b) T. Smejkal, B. Breit, *Angew. Chem. Int. Ed.* **2008**, *47*,

3946–3949; c) T. Smejkal, B. Breit, *Angew. Chem. Int. Ed.* **2008**, *47*, 311–315; d) V. F. Slagt, P. van Leeuwen, J. N. H. Reek, *Dalton Trans.* **2007**, 2302–2310; e) M. Kuil, P. E. Goudriaan, P. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2006**, 4679–4681; f) W. Seiche, A. Schuschkowski, B. Breit, *Adv. Synth. Catal.* **2005**, *347*, 1488–1494; g) V. F. Slagt, P. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2003**, 2474–2475; h) B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608–6609.

[17] a) X. B. Jiang, P. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2007**, 2287–2289; b) J. N. H. Reek, M. Roder, P. E. Goudriaan, P. C. J. Kamer, P. van Leeuwen, V. F. Slagt, *J. Organomet. Chem.* **2005**, *690*, 4505–4516; c) V. F. Slagt, M. Roder, P. C. J. Kamer, P. van Leeuwen, J. N. H. Reek, *J. Am. Chem. Soc.* **2004**, *126*, 4056–4057.

[18] L. Usui, S. Schmidt, M. Keller, B. Breit, *Org. Lett.* **2008**, *10*, 1207–1210.

[19] F. Chevallier, B. Breit, *Angew. Chem. Int. Ed.* **2006**, *45*, 1599–1602.

[20] T. Smejkal, B. Breit, *Organometallics* **2007**, *26*, 2461–2464.

[21] M. de Greef, B. Breit, *Angew. Chem. Int. Ed.* **2009**, *48*, 551–554.

[22] M. T. Reetz, G. Mehler, *Angew. Chem. Int. Ed.* **2000**, *39*, 3889–3890, and references therein.

[23] A. Duursma, J.-G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2004**, *69*, 8045–8052.

[24] C. Vallée, Y. Chauvin, J.-M. Basset, C. C. Santini, J.-C. Galland, *Adv. Synth. Catal.* **2005**, *347*, 1835–1847.

[25] M. Alame, N. Pestre, C. de Bellefon, *Adv. Synth. Catal.* **2008**, *350*, 898–908, and references therein.

[26] Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155–3211.

[27] In the rhodium-catalyzed asymmetric hydrogenation of methyl 2-acetamidoacrylate with ligand (*R*)-**A1-Me**, a poor enantiomeric excess (47%) was obtained, much lower than with ligand (*R*)-**A1** (80%). The combination (*R*)-**A1-Me**/(*R*)-**B2** gave 76% *ee*, to be compared with 90% *ee* obtained with (*R*)-**A1**/(*R*)-**B2**.

[28] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

[29] J. A. Hodges, R. T. Raines, *Org. Lett.* **2006**, *8*, 4695–4697.

[30] a) T. R. Wu, L. Shen, J. M. Chong, *Org. Lett.* **2004**, *6*, 2701–2704; b) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86.

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