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"Backdoor Induction" of Chirality in Asymmetric Hydrogenation with Rhodium(I) Complexes of Amino Acid Substituted Triphenylphosphane Ligands

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This paper describes the synthesis and characterization of 5-(diphenylphosphanyl)isophthalic acid bioconjugates (Lig-$[R]_2$). In addition to symmetrically disubstituted conjugates with amino acids, peptides or amines, a convenient one-pot, two-step procedure for the synthesis of conjugates bearing two different substituents is reported. The 28 prepared phosphanes were used as monodentate ligands in the rhodium(I)-catalyzed hydrogenation of 2-acetamidoacrylate and (*Z*)-α-acetamidocinnamate. The ligand with the smallest side-chain substituents Lig-$[Ala\text{-}OMe]_2$ (**1a**) revealed the highest selectivity, with up to 84 % *ee*. The catalysts presented herein are models of artificial metalloenzymes in which the outer-coordination sphere controls the selectivity in catalysis. The chirality of distant hydrogen-bonded amino acids is transmitted by "backdoor induction" to the prochiral Rh^I center.

Introduction

The catalysis of chemical reactions has an enormous impact in industry, because the production of many important chemicals involves at least one catalytic step.[1] Catalysis is particularly important in the synthesis of chiral compounds.[2] Among chiral industrial products, small-molecule drugs hold a prominent place. In recent years, 80% of small-molecule drugs approved by the US American Federal Drug Agency (FDA) are chiral, and 75% are single enantiomers.[3]

Nowadays, bioinspired catalysts composed of amino acid or nucleotide building blocks are gaining growing importance.[4–7] Asymmetric hydrogenation is a particularly interesting catalytic reaction, with emphasis on industrial applications.[8] Following the discovery of Wilkinson's catalyst $[RhCl(PPh_3)_3]$, the use of chiral phosphane ligands in asymmetric hydrogenation is well established.[9] Chelating bis-(phosphane) ligands generally show higher selectivity when compared with monodentate ligands, but moderate to excellent selectivity in catalytic hydrogenation can also be achieved with monodentate phosphane ligands.[10–15] The advantages of monodentate ligands are easier synthesis and more straightforward structural variations (ligand libraries) for fine-tuning of catalytic properties.

Chiral metal complexes are very frequently used as homogeneous asymmetric catalysts. The importance of the incorporation of the chiral information as close as possible to the coordination sphere of the catalytic metal center is widely accepted. Within our work, we challenge this fundamental principle and use a catalytically active metal center that is only prochiral.[16] The chiral information is transmitted by "backdoor induction" through hydrogen bonding between distant pendant amino acids. An artificial C_2-symmetrical peptide turn is formed that controls the chirality of the catalytic metal coordination sphere. These catalysts could be models of artificial enzymes with a functional outer-coordination sphere. We and others have used "backdoor induction" in Rh^I complexes of amino acid triphenylphosphane ligands **I** or **II** (Figure 1), and obtained up to 68% *ee* in asymmetric hydrogenation.[16–18] In a similar approach, instead of using chiral substituents -CO-$(Aa)_n$-OMe in **II**, van Leeuwen et al. attached achiral Schiff bases; high selectivity in asymmetric hydrogenation was obtained by the addition of a remote chiral diol through the use of an assembly metal (Ti).[19] In this work, we present a comprehensive study using amino acid substituted triphenylphosphane bioconjugates **III** based on 5-(diphenylphosphanyl)isophthalic acid as monodentate ligands in rhodium(I)-catalyzed asymmetric hydrogenation. When com-

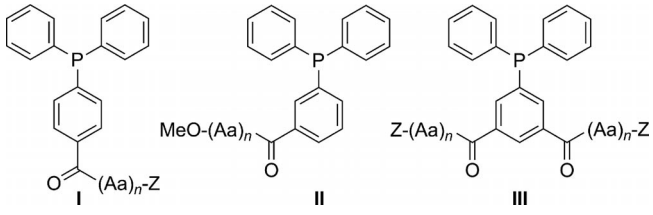

Figure 1. Amino acid substituted monodentate triphenylphosphane ligands **I** and **II** reported previously,[16–18] and ligands **III** studied in this paper; Aa = amino acid, Z = OMe or NH_2, n = 1, 2 or 3.

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pared with **I** or **II**, ligands **III** contain one additional amino acid substituent, allowing more supramolecular interactions that could stabilize the catalytic $[Rh(\mathbf{III})_2]^+$ complex and display higher selectivity in catalysis.

Results and Discussion

Ligands

Amino acid substituted monodentate triphenylphosphane ligands Lig-[Aa_1-Z]$_2$ (**1a**–**f**) (Z = OMe or NH_2), Lig-[Aa_1–Aa_2–OMe]$_2$ (**2a**–**f**), and Lig-[Aa_1–Aa_2–Aa_3–OMe]$_2$ (**3a**–**b**) were synthesized in good yields[16] by treating 5-(diphenylphosphanyl)isophthalic acid[20] with *N*-unprotected amino acids, dipeptides or tripeptides by using standard peptide coupling conditions in solution (Scheme 1).

Unsymmetrically substituted ligands Lig-[NH-R][Ala-OMe] (**5a**–**e**) and Lig-[Aa_1-OMe][Ala-OMe] (**5f**–**g**) were prepared by starting from 5-(diphenylphosphanyl)isophthalic acid using a one-pot, two-step approach (Scheme 2).[21–23] First, 5-(diphenylphosphanyl)isophthalic acid was activated with 1 equiv. of coupling reagent and treated with a mixture of 0.5 equiv. of an *N*-unprotected amino acid or amine and 0.5 equiv. of H-Ala-OMe. In the next step, this procedure was repeated. Activation with 1 equiv. of coupling reagent was followed by reaction with a mixture of 0.5 equiv. of the same *N*-unprotected amino acid or amine and 0.5 equiv. of H-Ala-OMe. This one-pot procedure gave a mixture of three products, two symmetrically substituted (**4a**–**g** and **1a**) as well as one unsymmetrically substituted (**5a**–**g**) (Scheme 2) with a 1:2:1 statistical distribution in favor of the latter (**5a**–**g**).[21] The three products could be separated by column chromatography when the employed amino acids or amines differed sufficiently in polarity and hydrophobicity.[24] Seven one-pot reactions were performed. As expected, during chromatographic purification the unsymmetrical products **5a**–**g** eluted between the two corresponding symmetrical products **4a**–**g** and **1a**. Ligands **5a**–**g** were isolated in up to 29% yield, which is consistent with the results of previous work.[21]

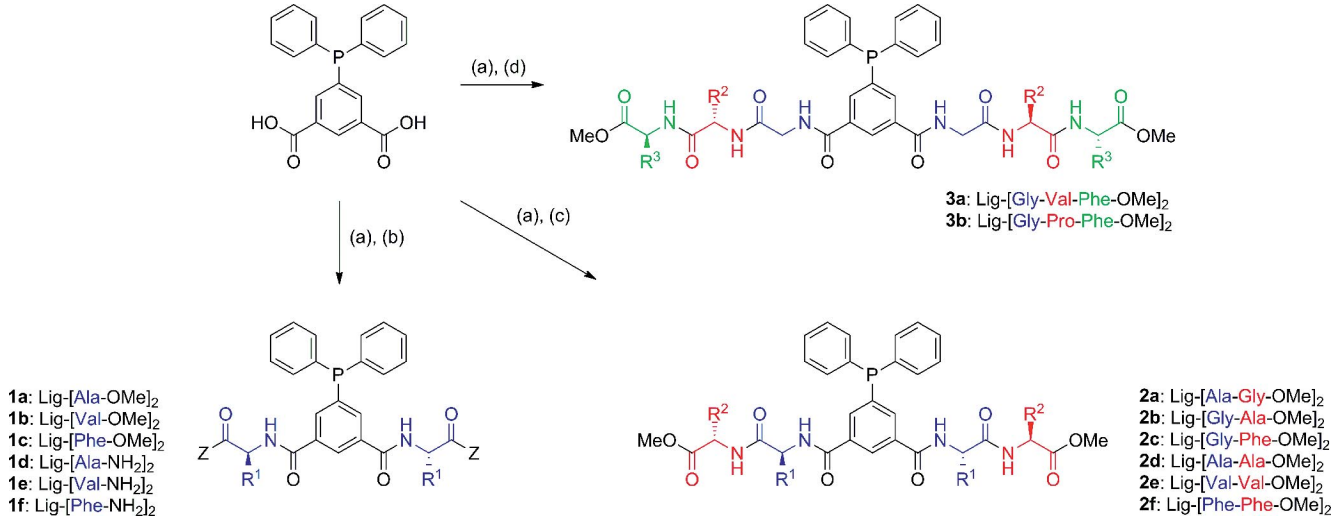
Ligands **1**–**5** were characterized by ^1H, ^{13}C and ^{31}P NMR spectroscopy, and by ESI and MALDI mass spectrometry. It is interesting to note that proline-containing peptides often show *cis* and *trans* isomers at the *tert*-amide bond, which has some double-bond character and is planar.[16,25] ^{13}C NMR spectra ($CDCl_3$) revealed traces of the *cis* isomer for Lig-[Pro-OMe]$_2$ (**4g**) and Lig-[Pro-OMe]-[Ala-OMe] (**5g**), along with the dominant *trans* isomer. In contrast, only the *trans* isomer was detected for Lig-[Gly-Pro-Phe-OMe]$_2$ (**3b**).

Precatalyst Rh^I Complexes

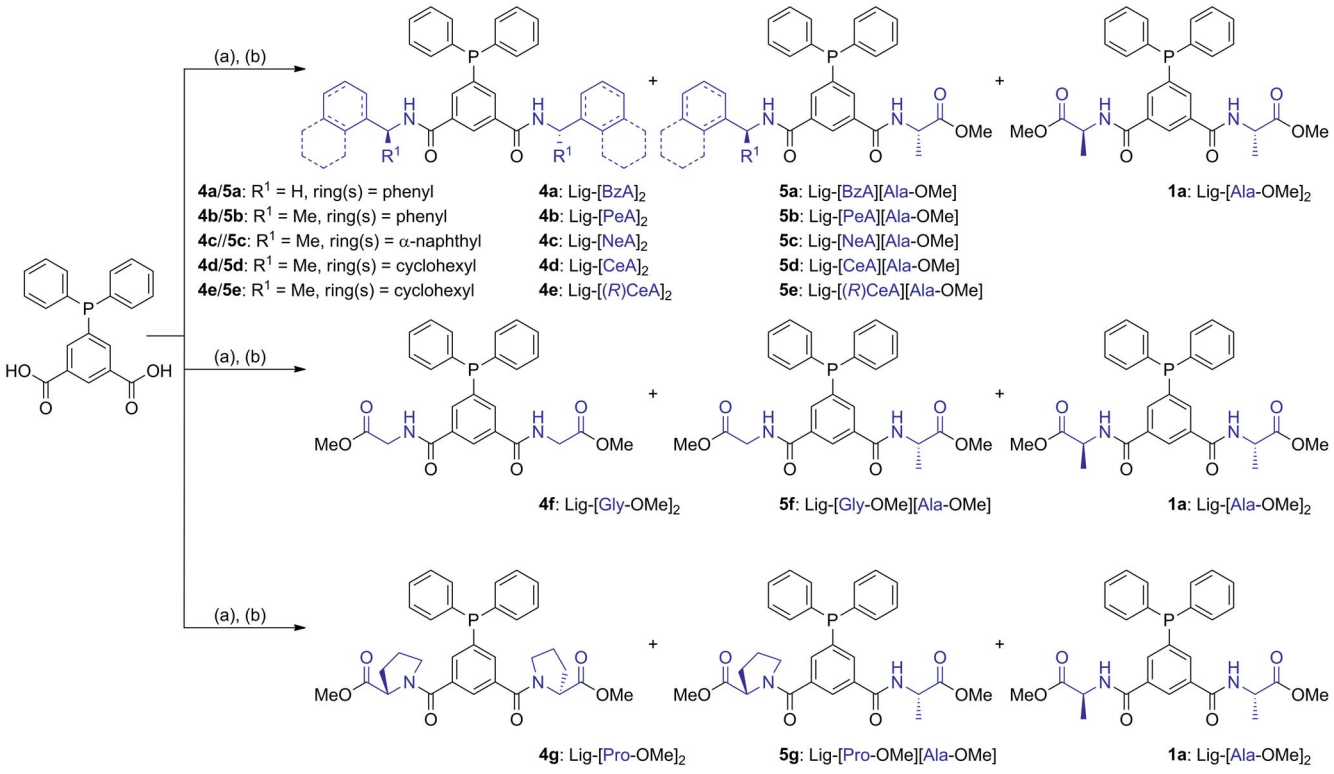
Complexation of ligands **1**–**5** with $[Rh(COD)(CH_3CN)_2]BF_4$ was performed in situ; the obtained precatalyst complexes were studied by ESI mass spectrometry, NMR and CD spectroscopy.

The 2:1 ligand/metal stoichiometry was supported by strong $[Rh(COD)(Lig\text{-}R)_2]^+$ signals found in the ESI mass spectra. ^{31}P NMR spectra featured, in some instances, one doublet indicating the presence of one compound with chemically equivalent phosphorus atoms, but in most cases a mixture of isomers was found (see the Supporting Information).[13a,19,26]

^1H NMR spectra reveal the absence of amide resonances in $[Rh(COD)(Lig\text{-}R)_2]BF_4$ at $\delta < 7$ ppm in a nonhydrogen-bonding solvent ($CDCl_3$), strongly indicating the presence of intramolecular hydrogen bonding. Such H-bonding is an indication of a folded conformation of the studied square-planar Rh^I complexes. In addition, a folded conformation of the complexes is directed by the *cis*-bonded COD ligand.[16,17] Further evidence for a folded conformation in solution is provided by CD spectroscopy of the rhodium chromophore.[21,26] CD signals in the visible region strongly



Scheme 1. Synthesis of ligands Lig-[Aa_1-Z]$_2$ (**1**), Lig-[Aa_1–Aa_2–OMe]$_2$ (**2**), and Lig-[Aa_1–Aa_2–Aa_3–OMe]$_2$ (**3**), Z = OMe or NH_2. *Reagents and conditions*: (a) TBTU/HOBt/DIPEA, CH_2Cl_2, r.t., 15 h; (b) H-Aa_1-Z; (c) H-Aa_1–Aa_2–OMe, (d) H-Aa_1–Aa_2–Aa_3–OMe.



Scheme 2. One-pot synthesis of ligands Lig-[NH-R or Aa_1]$_2$ (**4**), Lig-[NH-R or Aa_1][Ala-OMe]$_2$ (**5**) and Lig-[Ala-OMe]$_2$ (**1a**). *Reagents and conditions*: (a) HBTU (1 equiv.), HOBt (1 equiv.), DIPEA (4 equiv.), NH_2-R or H-Aa_1-OMe (0.5 equiv.) and H-Ala-OMe (0.5 equiv.), CH_2Cl_2, r.t., 15 h; (b) HBTU (1 equiv.), HOBt (1 equiv.), DIPEA (4 equiv.), NH_2-R or H-Aa_1-OMe (0.5 equiv.) and H-Ala-OMe (0.5 equiv.), CH_2Cl_2, r.t., 15 h. For an explanation of the non-standard three letter labels see the Experimental Section.

indicate an asymmetric coordination sphere of the Rh^I metal ion and support the proposed "backdoor induction" of chirality from the chiral amino acid substituents to the prochiral metal center. The sign and amplitude of the CD signals could not, however, be correlated with enantioselectivity obtained in catalysis.[9c,16,27]

Stereochemical Analysis

As shown previously,[16] the nomenclature initially developed for 1,*n*′-disubstituted ferrocene peptides[28,29] can be used as a possible interpretation to explain the stereochemical outcome in asymmetric hydrogenation of methyl 2-acetamidoacrylate (**S1**) by using [(COD)Rh(Ph_2P-C_6H_4-Aa_n)$_2$]BF_4 complexes with *meta* or *para* substitution of the central aromatic ring (Figure 2). The main secondary structures are (i) a β-turn involving two hydrogen-bonded ten-membered rings, Herrick conformation [β^2], and (ii) a γ-turn involving one hydrogen-bonded seven-membered ring, van Staveren conformation [γ^1].

Based on this interpretation, several folded conformations for Rh^I complexes derived from ligands **1**–**5** can be proposed (see second row in Figure 2). The first conformation [β^2]$_2$ is based on two β-turns containing a total of four intramolecular hydrogen bonds, whereas the second conformation [γ^1]$_3$ is based on three γ-turns and contains altogether three hydrogen bonds. The third conformation [β^2] contains one β-turn involving two hydrogen bonds. Although the two Aa strands adjacent to the phosphane groups of [β^2] are too far away for strong intramolecular H-bonding to the neighboring Aa strands, weak H-bonding interactions are possible, as found in closely related amino acids based on 1,3,5-trisubsituted benzenes (see the Supporting Information).[30,31] Interestingly, in all reported cases so far, including ferrocene peptides, metallated phosphane peptides and 1,3,5-trisubstituted benzene peptides, L-amino acids always induce (*P*)-helical chirality of the central aromatic rings.

It is important to note that in asymmetric hydrogenation, according to the stereochemical analysis proposed in Figure 2, an excess of the (*R*) product is expected when conformations [β^2]$_2$ or [γ^1]$_3$ are dominant, whereas an excess of the (*S*) product is expected when conformation [β^2] is preferred. In addition, an excess of (*R*) product is expected when the commercially available (*R*)-PhanePhos[32] is used as hydrogenation catalyst (Figure 2).

Asymmetric Catalysis

Supramolecular rhodium(I) complexes of monodentate phosphane ligands **1**–**3** prepared in situ were tested as catalysts in the asymmetric hydrogenation of methyl 2-acetamidoacrylate (**S1**) in dichloromethane at three different temperatures (room temp., –5 °C, and –20 °C; Table 1).

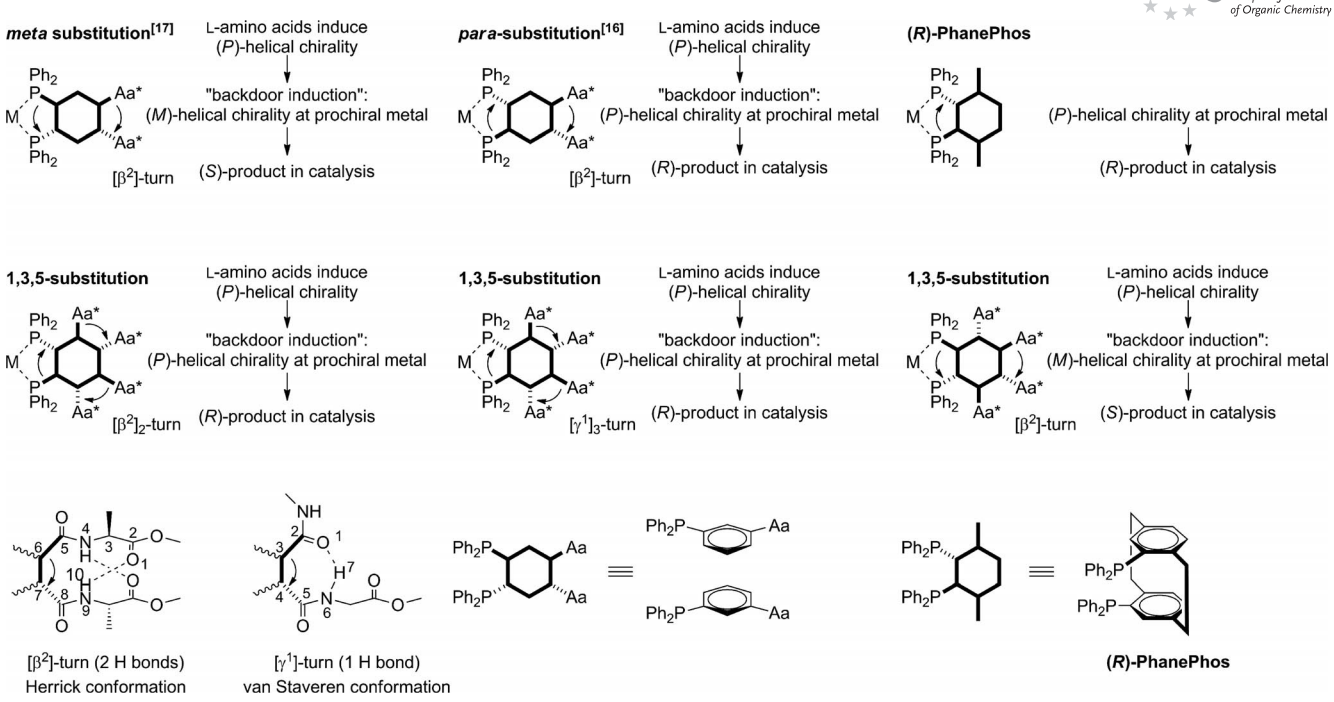


Figure 2. Proposed sterochemical analysis. Schematic representation (top view) of conformations in $[Rh(Lig\text{-}R)_2]^+$ complexes containing ligands with various substitution patterns; (*R*)-PhanePhos is included for comparison. The upper central aromatic rings are indicated in bold; the arrows indicate the sign of helical chirality between interacting interligand strands.

For Lig-[Aa_1-Z]$_2$ (**1**), the best results (up to 84% *ee*) were obtained by using the ligand with the smallest side-chain substituent (Ala ester **1a**) (Table 1, Entry 3). Introduction of steric bulk by side-chain substitutions at the γ-position (Phe derivatives **1c** or **1f**) and especially at the β-position (Val derivatives **1b** or **1e**) significantly lowered the selectivity in catalysis.

As expected, the selectivity was higher at lower temperature when compared to room temperature; the Δ*ee* was, however, less than 10%. Decreasing the concentration in CH_2Cl_2 by one order of magnitude revealed a small change in selectivity, Δ*ee* ≤ 5% (Table 1, Entries 1 and 21), indicating the significance of intramolecular over intermolecular hydrogen bonds in the studied catalysts. In addition, the catalysis was studied in methanol, a protic solvent. In this case, generally, the selectivity in MeOH decreased, with the decrease being significant for **1a**, **1c**, **2b** and **3b** (about half of the original value), but only small for **2a** and **2d** (Δ*ee* 10% or less). The relatively good selectivity in MeOH indicates stable secondary structures, particularly for **2a** and **2d**, comparable to peptides that can preserve their conformation even in a highly hydrogen-bond-competitive solvent such as water.

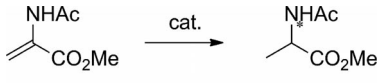
Similar results were obtained for the corresponding ester or amide derivatives, with amides giving slightly higher selectivities. However, triphenylphosphane ligands with a terminal amide group have the tendency to form gels[16] and are more difficult to purify by chromatography on silica due to their increased polarity. Therefore, only esters were studied for ligands **2** and **3** with longer side chains (that are already more polar due an increased number of amino acids) as well as for ligands **4** and **5** (where the separation of the three-component mixture strongly relies on favorable chromatographic properties).

Longer amino acid chains in Lig-[Aa_1–Aa_2–OMe]$_2$ (**2a**–**f**) and Lig-[Aa_1–Aa_2–Aa_3–OMe]$_2$ (**3a**–**b**) could induce more hydrogen bonding between neighboring monodentate ligands, resulting in a more stable supramolecular complex $[Rh(COD)(Lig\text{-}R)_2]BF_4$ and higher selectivity in catalysis.[16,33] However, results obtained in catalysis with the crowded Rh^I complexes derived from ligands **2** or **3** do not support this reasoning (Table 1); smaller ligand **1a** remains the most selective in the studied asymmetric hydrogenation.

Other selectivity trends obtained with ligands **1** could be confirmed with ligands **2** or **3**. A rather small improvement of selectivity was found at lower temperature. In addition, small amino acids Gly or Ala at the Aa_1 position gave the best results (ligands **2a**, **2b** and **2d**), whereas sidechain substitutions at the β- or γ-carbon atom of Aa_1 cause a significant decrease in selectivity (ligands **2e** and **2f**). A notable exception is the low selectivity obtained for ligand Lig-[Gly-Phe-OMe]$_2$ (**2c**) (up to 12% *ee*; Table 1, Entries 19 and 20), despite having unsubstituted Gly at Aa_1.

Asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate (**S2**) was then examined by using ligands Lig-[Aa_1-Z]$_2$ (**1**) (Table 2). Selectivity trends observed in hydrogenation of **S1** were preserved with **S2**, and the highest selectivity was obtained with Ala derivatives **1a** or **1d** (up to 75% *ee*), albeit slightly lower than with **S1**. Elevated hydrogen pressure (13 bar) was needed to obtain high chemical yields of **P2** after 2 h; the yield of **P2** obtained for catalysis performed at atmospheric pressure after 20 h was low.

Table 1. Rh^I-catalyzed asymmetric hydrogenation of **S1** by using ligands **1**–**3**.[a]

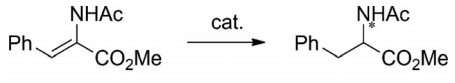


S1 **P1**

Entry	Ligand	Temp. [°C][b]	Conv. [%][c]	*ee* (*S*) [%][d]
1	**1a/1a**	r.t.	> 98	76 (80[e])/35[f]
2	**1a/1a**	–5	> 98	80
3	**1a/1a**	–20	65	84
4	**1b/1b**	r.t.	> 98	25
5	**1b/1b**	–5	> 98	26
6	**1c/1c**	r.t.	> 98	54/19[f]
7	**1c/1c**	–5	94	59
8	**1d/1d**	r.t.	98	80
9	**1d/1d**	–5	48	81
10	**1d/1d**	–20	4	n.d.[g]
11	**1e/1e**	r.t.	> 98	34
12	**1e/1e**	–5	85	41
13	**1f/1f**	r.t.	> 98	63
14	**1f/1f**	–5	76	70
15	**2a/2a**	r.t.	> 98	72/63[f]
16	**2a/2a**	–5	98	76
17	**2b/2b**	r.t.	> 98	68/35[f]
18	**2b/2b**	–5	> 98	73
19	**2c/2c**	r.t.	> 98	12
20	**2c/2c**	–5	> 98	12
21	**2d/2d**	r.t.	> 98	71 (76[e])/68[e]
22	**2d/2d**	–5	97	78
23	**2d/2d**	–20	60	80
24	**2e/2e**	r.t.	> 98	13 (*R*)
25	**2e/2e**	–5	76	12 (*R*)
26	**2f/2f**	r.t.	> 98	43 (*R*)
27	**2f/2f**	–5	67	44 (*R*)
28	**3a/3a**	r.t.	> 98	57
29	**3a/3a**	–5	> 98	68
30	**3b/3b**	r.t.	> 98	36/23[f]
31	**3b/3b**	–5	87	47

[a] Reaction conditions: [Rh]/ligand/substrate = 1:2.4:100, $p(H_2)$ = 1 bar, CH_2Cl_2 (0.1 M substrate). [b] Reaction time: 2 h (r.t.), overnight (–5 °C), or 3 d (–20 °C). [c] Determined by ^1H NMR spectroscopic analysis. [d] Determined by GC analysis (Beta Dex 225). [e] Diluted CH_2Cl_2 solution (10 ×). [f] MeOH was used as solvent. [g] n.d.: not determined.

Table 2. Rh^I-catalyzed asymmetric hydrogenation of **S2** by using ligands **1**.[a]

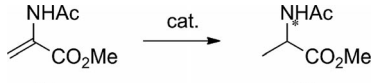


S2 **P2**

Entry	Ligand	Press. [bar]	Time [h]	Conv. [%][b]	*ee* (*S*) [%][c]
1	**1a/1a**	1	20	20	77
2	**1a/1a**	13	2	> 98	75
3	**1b/1b**	1	20	4	39
4	**1b/1b**	13	2	> 98	39
5	**1c/1c**	1	20	37	59
6	**1c/1c**	13	2	> 98	59
7	**1d/1d**	13	2	47	77
8	**1e/1e**	13	2	> 98	37
9	**1f/1f**	13	2	72	66

[a] Reaction conditions: [Rh]/ligand/substrate = 1:2.4:100, room temp., CH_2Cl_2 (0.1 M substrate). [b] Determined by ^1H NMR spectroscopic analysis. [c] Determined by GC analysis (L-Chirasil-Val).

Table 3. Rh^I-catalyzed asymmetric hydrogenation of **S1** by using binary mixtures of ligands **1**–**4**.[a]



S1 **P1**

Entry	L1/L2	n_{L1}/n_{L2}	Conv. [%][b]	*ee* (*S*) [%][c]
1	**1a/4f**	3:1	> 98	69
2	**1e/4f**	3:1	> 98	34
3	**2e/4f**	3:1	> 98	12
4	**2c/4f**	3:1	> 98	13
5	**1a/1b**	3:1	> 98	68
6	**1a/1d**	1:3	> 98	78
7	**1a/2a**	3:1	> 98	76
8	**1a/3b**	3:1	> 98	64
9	**1a/4b**	3:1	> 98	62
10	**2a/2b**	1:1	> 98	74
11	**2a/2b**	3:1	> 98	75
12	**2a/2b**	1:3	> 98	71

[a] Reaction conditions: [Rh]/ligand/substrate = 1:2.4:100, $p(H_2)$ = 1 bar, room temp., 2 h, CH_2Cl_2 (0.1 M substrate). [b] Determined by ^1H NMR spectroscopic analysis. [c] Determined by GC analysis (Beta Dex 225).

The selectivity obtained at atmospheric pressure is retained at elevated pressure.

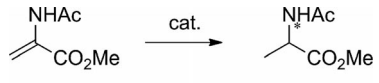
Binary mixtures of monodentate phosphane ligands can lead to higher yields and selectivities in metal-catalyzed asymmetric reactions than the individual ligands alone.[34] In addition, by using an excess of the more selective ligand, the formation of the less selective homo complex $[ML_2L_2]$ can be minimized. An increase in selectivity should be observed when the mixed-ligand complex is more selective. The asymmetric hydrogenation of **S1** with Rh^I complexes derived from binary mixtures is presented in Table 3.

Binary mixtures with achiral ligand Lig-[Gly-OMe]$_2$ (**4f**) and a 3:1 excess of a chiral ligand did not exceed the selectivity obtained with the corresponding chiral ligand alone (Table 3, Entries 1–4). In addition, a binary mixture of most selective **1a** with other chiral ligands did not improve the selectivity obtained by using only one single ligand (Table 3, Entries 5–9). However, when binary mixtures of ligands Lig-[Ala-Gly-OMe]$_2$ (**2a**) and Lig-[Gly-Ala-OMe]$_2$ (**2b**) were used in catalysis (Table 3, Entries 10–12), a small improvement was obtained in comparison to the results obtained by using only one ligand (Table 1, Enrties 15 and 17).

Products **P1** or **P2** with predominantly (*S*) configuration were obtained with most of the examined catalysts; the few exceptions being limited to Val or Phe derivatives with low selectivity. According to the stereochemical analysis described above, catalytic results support a preference for the [β^2] conformation. Our stereochemical analysis is further supported by results obtained by using commercially available (*R*)-PhanePhos as ligand, yielding the expected (*R*)-**P1** (>98% *ee* and >98% yield); reaction conditions are given in Table 1 (for chromatogram see the Supporting Information).

Finally, ligands **4a**–**g** and **5a**–**g** were evaluated in the rhodium(I)-catalyzed hydrogenation of **S1** (Table 4). Some substituents of ligands **4** and **5** lack the ester carbonyl group (amine derivatives) and/or amide hydrogen atoms (Pro derivatives). Because, in these cases, not all hydrogen-bonding patterns of the catalytically active complex are possible, the obtained results can contribute to an understanding of the stereochemical outcome. Diamines **4b**–**e** lack the ester carbonyl group, and the otherwise preferred [β^2] conformation cannot be formed. Consequently, the obtained selectivity is rather low, being only up to 34% (Table 4, Entries 2–4). With proline derivative **4g**, which contains no amide protons, the selectivity was very low (10% *ee*; Table 4, Entry 6). Unsymmetrical ligands **5a**–**f** are capable of forming [β^2] conformations and induced moderate selectivity (47–68% *ee*; Table 4, Entries 7–12). Particularly interesting is the rather low selectivity observed with derivative **5g** (29% *ee*; Table 4, Entry 13), for which the [β^2] conformation can be formed, but without the weak supporting H-bonding, due to the lack of Pro amide protons. As expected, catalysis with achiral ligands **4a** or **4f** gave quantitative yield but without selectivity (Table 4, Entries 1 and 5).

Table 4. Rh^I-catalyzed asymmetric hydrogenation of **S1** by using ligands **4** and **5**.[a]



S1 **P1**

Entry	Ligand	Conv. [%][b]	*ee* (*S*) [%][c]
1	**4a/4a**	> 98	0
2	**4b/4b**	> 98	4 (*R*)
3	**4c/4c**	> 98	18
4	**4d/4d**[d]	> 98	34
5	**4f/4f**	> 98	0
6	**4g/4g**	> 98	10
7	**5a/5a**	> 98	47
8	**5b/5b**	> 98	67
9	**5c/5c**	> 98	68
10	**5d/5d**	> 98	60
11	**5e/5e**	> 98	51
12	**5f/5f**	> 98	54
13	**5g/5g**	> 98	29

[a] Reaction conditions: [Rh]/ligand/substrate = 1:2.4:100, $p(H_2)$ = 1 bar, room temp., 2 h, CH_2Cl_2 (0.1 M substrate). [b] Determined by ^1H NMR spectroscopic analysis. [c] Determined by GC analysis (Beta Dex 225). [d] Catalysis by using enantiomer **4e** yields (*R*)-**P1** with 34% *ee*.

Conclusions

This paper describes the solution-phase synthesis of monodentate triphenylphosphane ligands disubstituted with amino acids Lig-[Aa_1-Z]$_2$ (**1**) (Z = OMe or NH_2), dipeptides Lig-[Aa_1–Aa_2–OMe]$_2$ (**2**) or tripeptides Lig-[Aa_1–Aa_2–Aa_3–OMe]$_2$ (**3**). In addition, unsymmetrically disubstituted Lig-[NH-R or Aa_1-OMe][Ala-OMe] (**5**) and their symmetrically substituted analogues Lig-[NH-R or Aa_1-OMe]$_2$ (**4**) have been prepared by using a convenient one-pot, two-step protocol.

Supramolecular Rh^I complexes [Rh(COD)-(Lig-R)$_2$]BF_4 prepared in situ with ligands Lig-R = **1**–**5** were used as catalysts in the asymmetric hydrogenation of methyl 2-acetamidoacrylate (**S1**) or (*Z*)-α-acetamidocinnamate (**S2**). The selectivity obtained depends strongly on the distant amino acid or amine substituents, spanning the range from 84% *ee* (**1a**; Table 1, Entry 3) to 4% *ee* (**4b**; Table 4, Entry 2), strongly supporting the proposed "backdoor induction" of chirality. For the studied crowded complexes with ligands **1**–**5**, highest selectivity was obtained for Lig-[Ala-OMe]$_2$ (**1a**) with small sidechain substituents. Attempts to use even smaller substituents did not improve the selectivity in catalysis, as can be seen for example by using Lig-[Gly-OMe]-[Ala-OMe] (**5f**) with small Gly at Aa_1 or binary mixtures of Lig-[Gly-OMe]$_2$ (**4f**) and Lig-[Aa_1-OMe]$_2$ (**1a**) (Table 3, Entries 1–4) or Lig-[Ala-Gly-OMe]$_2$ (**2a**) and Lig-[Gly-Ala-OMe]$_2$ (**2b**) (Table 3, Entries 10–12).

To obtain high selectivity, small-molecule catalysts typically need to incorporate the chiral information as close as possible to the catalytically active metal center. Herein, we describe a series of relatively small supramolecular transition-metal catalysts (ca. 1300 g mol^{-1}) for which an ordered chiral outer-coordination sphere allows the use of a prochiral metal center. The presented catalysts are models of artificial metalloenzymes with a minimal functional outer-coordination sphere.

Experimental Section

General Remark: Pure L-amino acids and (*S*)-amines were used except for (*R*)-cyclohexylethylamine.

Synthesis of Ligands 1–3. General Procedure: 5-(Diphenylphosphanyl)isophthalic acid (120 mg, 0.34 mmol), TBTU (212 mg, 0.68 mmol, 2 equiv.), HOBt (90 mg, 0.68 mmol, 2 equiv.) and DIPEA (175 μL, 1.05 mmol) were stirred at room temperature in CH_2Cl_2 (50 mL). After 1 h, *N*-unprotected amino acid or peptide (3–4 equiv.) was added to the reaction mixture, and stirring was continued overnight (ca. 15 h). The reaction mixture was then washed with satd. aq. $NaHCO_3$, aq. citric acid (10%) and satd. aq. NaCl, dried with Na_2SO_4, filtered, concentrated in vacuo, and purified by automated flash chromatography on a prepacked silica column.

Catalytic Hydrogenation of Methyl 2-Acetamidoacrylate (S1). (a) Catalysis at Room Temperature: An oven-dried, two-necked, round-bottomed flask (10 mL) under nitrogen was charged with the ligand (6.6 μmol, 2.2 mol-%) dissolved in dichloromethane (3 mL; distilled, degassed in an ultrasonic bath for 15 min), followed by [(COD)Rh(CH_3CN)$_2$]-BF_4 (1.25 mg, 3 μmol, 1 mol-%) dissolved in dichloromethane (2 mL). Several experiments were performed in diluted CH_2Cl_2 solution (total volume 50 mL instead of 5 mL) or in methanol (total volume 5 mL); see Table 1 for more information. The flask was then flushed with hydrogen, and the substrate (45 mg, 0.3 mmol) was added in one portion and vigorously stirred with a magnetic stirrer. After 2 h, 0.5 mL of the solution was eluted through silica (150 mg) with ethyl acetate (5 mL), and the enantiomeric excess (*ee*) was determined by chiral fused silica capillary column [Beta Dex 225; isocratic 140 or 150 °C; 100 kPa head column pressure; eluting order: substrate, (*R*) product, (*S*) product]. **(b) Catalysis at Low Temperature:** According to the procedure for

reactions at room temp. before substrate addition, the reaction flask was placed in a thermo-container filled with technical ethanol (or 2-propanol), cooled by a cryostat device to –5 or –20 °C, and the mixture was stirred vigorously overnight.

Catalytic Hydrogenation of Methyl (*Z*)-α-Acetamidocinnamate (S2). (a) Catalysis at Atmospheric Pressure: The procedure described for **S1** was used with ligand (13.2 μmol, 2.2 mol-%), [(COD)-$Rh(CH_3CN)_2]BF_4$ (2.50 mg, 6 μmol, 1 mol-%) and **S2** (70 mg, 0.3 mmol). Chiral fused silica capillary column [L-chirasil-Val; conditions: 22 min at 170 °C; 40 °C min^{-1} to 190 °C, 60 kPa head column pressure; t_R = 18.30 (*R*), 18.75 (*S*), 32.39 (substrate) min]. **(b) Catalysis at High Pressure:** In an Eppendorf vial, Rh precursor and the ligand were dissolved in CH_2Cl_2 (0.5 mL each) and mixed. The yellow solution was added to a 10 mL beaker containing the substrate and CH_2Cl_2 (4 mL). This was tightly sealed in an autoclave and purged three times with H_2 (13 bar) and finally stirred at 13 bar for 2 h. The product was analyzed as detailed above.

Abbreviations: Amino acids are abbreviated by three or one letter codes (for spectral assignation). The following non-standard abbreviations were used: H-*BzA* = H-*NHCH$_2$Ph* (benzylamine), H-*PeA* = H-*NHCH(CH$_3$)Ph* (phenylethylamine), H-*NeA* = H-*NHCH(CH$_3$)C$_{10}$H$_7$* (α-naphthylethylamine) and H-*CeA* = H-*NHCH(CH$_3$)C$_6$H$_{11}$* (cyclohexylethylamine); see Scheme 2 for structures.

Supporting Information (see footnote on the first page of this article): Synthetic procedures, NMR, mass and CD spectra of ligands and complexes; gas chromatograms of catalytic products and detailed stereochemical analysis.

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