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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-(diphenylphosphino)isophthalic acid bioconjugates, Lig-[R]$_2$. In addition to symmetrically disubstituted conjugates with amino acids (**1a-1e** and **4f-4g**), peptides (**2a-2e** and **3a-3b**) or amines (**4a-4e**), a convenient one pot two step procedure for the synthesis of conjugates **5a-g** bearing two different substituents is reported. The 28 prepared phosphanes **1-5** are used as monodentate ligands in the rhodium(I) catalyzed hydrogenation of 2-acetamidoacrylate or (*Z*)-acetamidocinnamate. Ligand with small side chain substituents Lig-[Ala-OMe]$_2$ **1a** revealed highest selectivity with up to 84 % ee. The catalysts presented herein are models of artificial metalloenzymes where the secondary 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).

Introduction

The catalysis of chemical reactions has an enormous impact in industry since the production of many important chemicals involves a 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 gain 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 if compared to monodentate ligands, but moderate to excellent selectivity in catalytic hydrogenation can be achieved with monodentate phosphane ligands as well.[10,11] The advantages of monodentate ligands are easier synthesis and straightforward structural variations (ligand libraries), for fine-tuning of catalytic properties.

Chiral metal complexes are used as homogeneous asymmetric catalysts very frequently. The importance of the incorporation of the chiral information as close as possible to the coordination sphere of the catalytic metal is widely accepted. Within our work, we challenge this fundamental principle and use a catalytically active metal centre that is only prochiral.[16] The chiral information is transmitted by "backdoor induction" *via* 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 secondary 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 *via* an assembly metal (Ti).[19] In this work, we present a comprehensive study using amino acid substituted triphenylphosphane bioconjugates **III** based on 5-(diphenylphosphino)isophthalic acid as monodentate ligands in rhodium(I) catalyzed asymmetric hydrogenation. When compared to **I** or **II**, ligands **III** contain one additional amino acid substituent allowing more supramolecular interactions that could stabilize the catalytic [Rh(**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] reacting 5-(diphenylphosphino)-isophthalic acid[20] with *N*-unprotected amino acids, dipeptides or tripeptides using standard peptide coupling conditions in solution (Scheme 1).

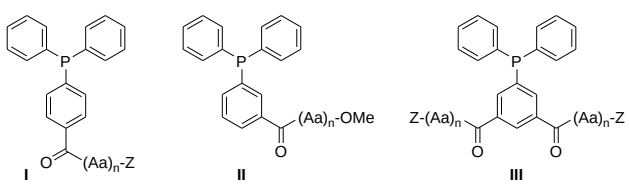

Figure 1. Amino acid substituted monodentate triphenlyphosphane ligands **I** and **II** reported previously,[16-18] and ligands **III** studied in this paper; Aa = amino acid, Z = OMe or NH$_2$, *n* = 1, 2 or 3.

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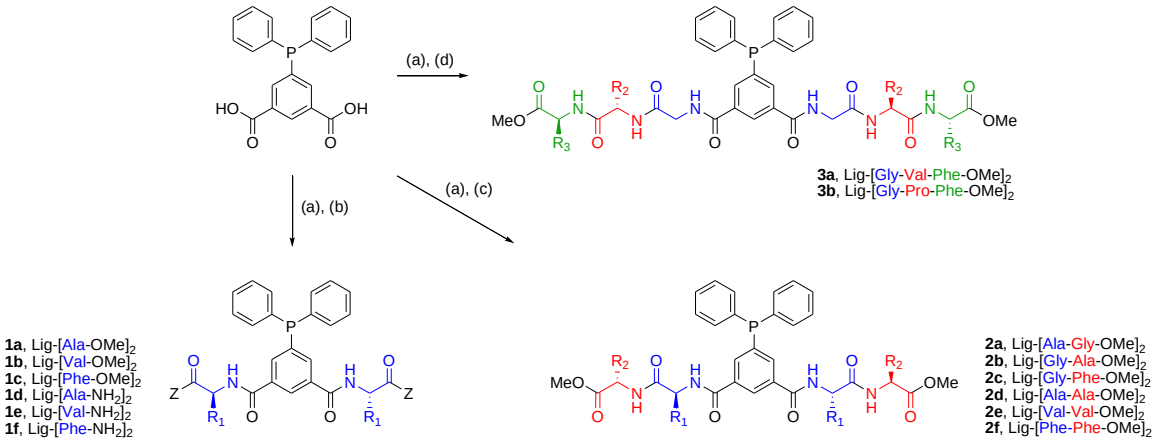
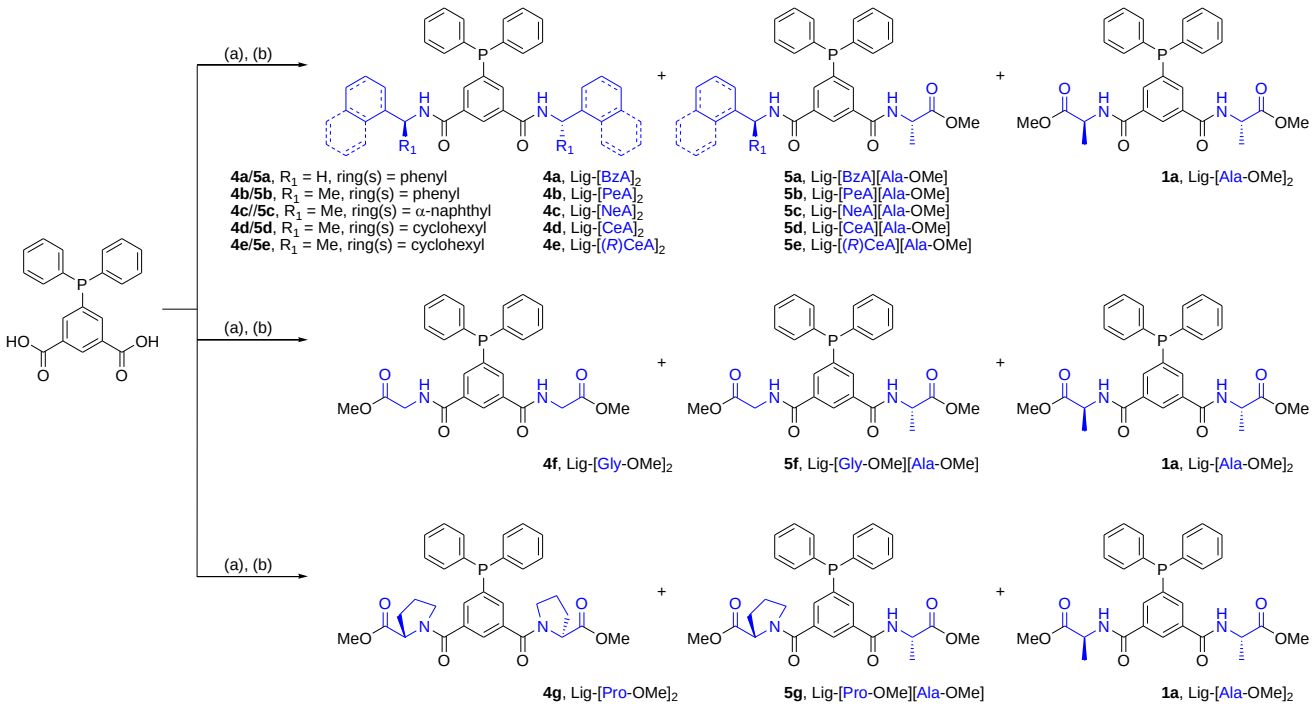


Scheme 1. Synthesis of ligands Lig-[Aa$_1$-Z]$_2$ **1**, Lig-[Aa$_1$-Aa$_2$-OMe]$_2$ **2** and Lig-[Aa$_1$-Aa$_2$-Aa$_3$-OMe]$_2$ **3**, Z = OMe or NH$_2$. Reaction conditions: (a) TBTU / HOBt / DIPEA, DCM, r. t., 15h, (b) H-Aa$_1$-Z, (c) H-Aa$_1$-Aa$_2$-OMe, (d) H-Aa$_1$-Aa$_2$-Aa$_3$-OMe.

Unsymmetrically substituted ligands Lig-[NH-R][Ala-OMe] **5a-e** and Lig-[Aa$_1$-OMe][Ala-OMe] **5f-g** were prepared starting from 5-(diphenylphosphino)isophthalic acid using a one pot two step approach[21-23] (Scheme 2). First, 5-(diphenylphosphino)isophthalic acid was activated with one equiv. of coupling reagent and reacted 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 one 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 gives 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 later (**5a-g**).[21] The three products can be separated by column chromatography if the employed amino acids or amines differ sufficiently in polarity and hydrophobicity.[24] Seven one pot reactions have been performed. As expected, during chromatographic purification the unsymmetrical products **5a-g** are eluted in between the two corresponding symmetrical products **4a-g** and **1a**. Ligands **5a-g** were isolated in up to 29 % yield, which is in good accordance with previous work.[21]

Ligands **1**-**5** were characterized by ^{1}H–, ^{13}C– and ^{31}P–NMR spectroscopy, 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 that has some double-bond character and is planar.[16,25] ^{13}C–NMR spectra ($CDCl_3$) reveal 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**.

Precatalytic Rh(I) Complexes. Complexation of ligands **1**-**5** with [Rh(COD)(CH$_3$CN)$_2$]BF$_4$ was performed *in situ*; the obtained precatalytic complexes were studied by ESI mass spectrometry, NMR and CD spectroscopy.



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**. Reaction conditions: (a) HBTU (1 eq.), HOBt (1 eq.), DIPEA (4 eq.), NH$_2$-R or H-Aa$_1$-OMe (0.5 eq.) and H-Ala-OMe (0.5 eq.), DCM, r. t., 15 h; (b) HBTU (1 eq.), HOBt (1 eq.), DIPEA (4 eq.), NH$_2$-R or H-Aa$_1$-OMe (0.5 eq.) and H-Ala-OMe (0.5 eq.), DCM, r. t., 15 h. For an explanation of the non-standard three letter labels see Abbreviation section.

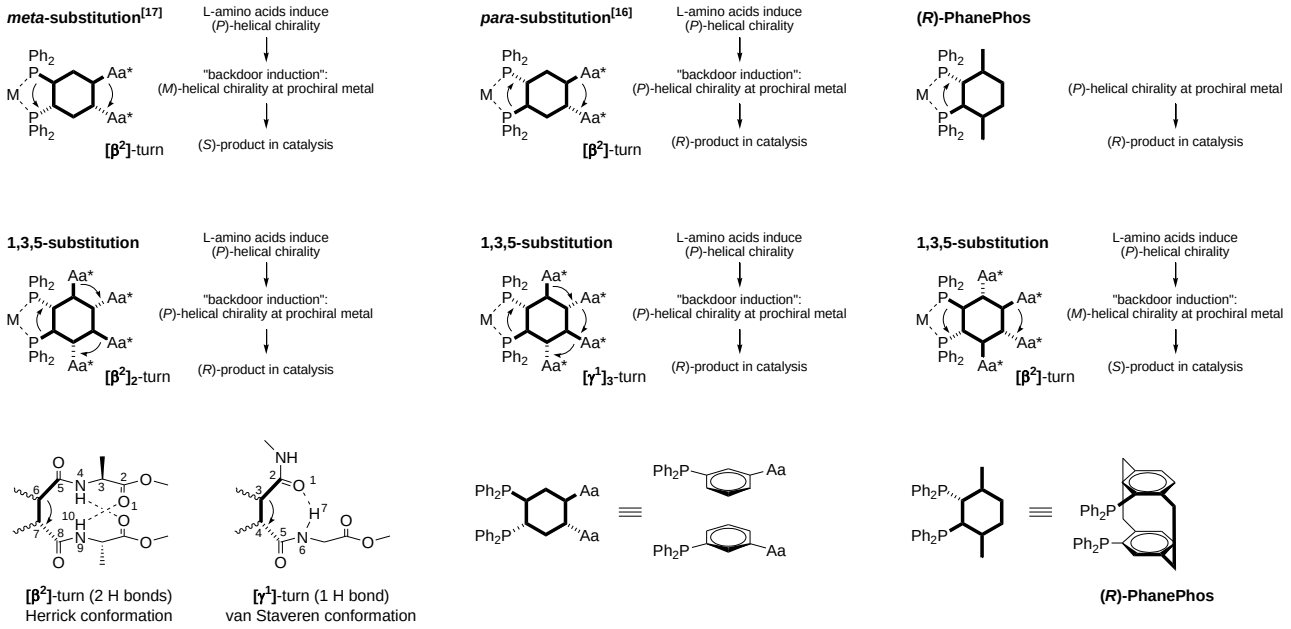


Figure 2. Proposed sterochemical analysis. Schematic representation (top view) of conformations in $[Rh(Lig\text{-}R)_2]^+$ complexes containing ligands with various substitutions pattern; (*R*)-PhanePhos is included for comparison. The upper central aromatic rings are indicated in bold; the arrows indicate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

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

^1H NMR spectra reveal the absence of amide resonances in $[Rh(COD)(Lig\text{-}R)_2]BF_4$ below a chemical shift $\delta = 7$ ppm in a non hydrogen bonding solvent ($CDCl_3$), strongly indicating the presence of *intra*molecular hydrogen bonding. *Intra*molecular H-bonding is an indication of a folded conformation of the studied Rh(I). In addition, a folded conformation of the studied square-planar 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 VIS region strongly 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. 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**) using $[(COD)Rh(Ph_2P\text{-}C_6H_4\text{-}Aa_n)_2]BF_4$ 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 10-membered rings, Herrick conformation **[β²]**, and (ii) a γ-turn involving one hydrogen bonded 7-membered ring, van Staveren conformation **[γ¹]**.

Based on this proposed 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 $\mathbf{[\beta^2]_2}$ is based on two β-turns containing a total of four *intra*molecular hydrogen bonds, while the second conformation $\mathbf{[\gamma^1]_3}$ is based on three γ-turns and contains altogether three hydrogen bonds. The third conformation contains one β-turn involving two hydrogen bonds, **[β²]**. Although the two Aa-stands adjacent to the phosphane groups of **[β²]** are too far away for strong *intra*molecular H-bonding to the neighboring Aa-strands, weak H-bonding interactions are possible as found in closely related amino acids 1,3,5-trisubsituted benzenes,[30,31] see Supporting information. 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.

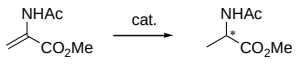
It is important to note that in asymmetric hydrogenation, according to the stereochemical analysis proposed in Fig. 3, an excess of the (*R*)-product is expected if conformations $\mathbf{[\beta^2]_2}$ or $\mathbf{[\gamma^1]_3}$ are dominant, while an excess of the (*S*)-product is expected if conformation **[β²]** is preferred. In addition, an excess of (*R*)-product is expected if the commercially available (*R*)-PhanePhos[32] is used as hydrogenation catalyst, see 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, RT, –5 °C, and –20 °C (Table 1).

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

As expected, the selectivity was higher at lower temperature if compared to room temperature; the Δee was, however, less than 10 %. Decreasing the concentration in DCM by one order of magnitude revealed a small change in selectivity, $\Delta ee \leq 5\%$ (Table 1, runs 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. Generally, the selectivity in MeOH decreases; the decrease is significant for

Table 1. Rh(I) catalyzed asymmetric hydrogenation of **S1** using ligands **1-3**.[a]



S1 **P1**

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

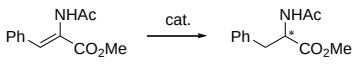
[a] Reaction conditions: [Rh] : ligand : substrate = 1 : 2.4 : 100, $p(H_2)$ = 1 bar, DCM (0.1 M substrate). [b] Reaction time: 2h (RT), overnight (–5 °C) or 3d (–20 °C). [c] Determined by ^{1}H NMR. [d] Determined by GC (Beta Dex 225). [e] Diluted DCM solution (10 ×). [f] MeOH was used as solvent. [g]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

1a, **1c**, **2a** and **3b** (about half of the original value), but only small for **2b** and **2d** (Δee is 10% or less). The relatively good selectivity in MeOH indicates stable secondary structures, particularly for **2b** and **2d**, comparable to peptides that can preserve their conformation even in a highly hydrogen bond competitive solvent like water.

Similar results were obtained for the corresponding ester or amide derivatives, with amides giving slightly higher selectivity. However, triphenylphosphane ligands with a terminal amide group have the tendency to form gels[16] and are more difficult to subject to 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

Table 2. Rh(I) catalyzed asymmetric hydrogenation of **S2** using ligands **1**.[a]



S2 **P2**

Run	Ligand	Press. / bar	Time / h	Conv.[b] / %	ee[c] % (*S*)
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, RT, DCM (0.1 M substrate). [b] Determined by ^{1}H NMR. [c] Determined by GC (L-chirasil-Val).

stable supramolecular complex $[Rh(Lig)_2]^+$ and higher selectivity in catalysis.[16,33] However, results obtained in catalysis do not support this reasoning for the crowded Rh(I) complexes derived from ligands **2** or **3** (Table 1); smaller ligand **1a** remains most selective in the studied asymmetric hydrogenation.

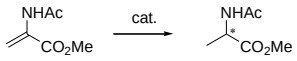
Other selectivity trends obtained with ligands **1** could be confirmed with ligands **2** or **3**. A rather small improvement of selectivity was found at lower temperature. In addition, small amino acids Gly or Ala at Aa_1 position give the best results (ligands **2a**, **2b** and **2d**), while side chain 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, runs 19 and 20, Table 1), despite having unsubstituted Gly at Aa_1.

Next, asymmetric hydrogenation of methyl (*Z*)-acetamido-cinnamate (**S2**) was examined using ligands Lig-[Aa_1-Z]$_2$ **1** (Table 2). Selectivity trends observed in hydrogenation of **S1** were preserved with **S2**; highest selectivity was obtained with Ala-derivatives **1a** or **1d**, up to 75 % ee, although 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. The selectivity obtained at atmospheric pressure is retained at elevated pressure.

Binary mixtures of monodentate phosphane ligands can lead to higher yields and selectivity in metal catalyzed asymmetric reactions than the individual ligands alone.[34] In addition, using an excess of the more selective ligand minimizes the formation of the less selective homo-complex $[ML_2L_2]$. An increase in selectivity should be observed if 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, runs 1-4). In addition, a binary mixture of most selective **1a** with other chiral ligands did not improve the selectivity obtained using only one single ligand (Table 3, runs 5-9). However, if binary mixtures of ligands Lig-[Ala-Gly-OMe]$_2$ **2a** and Lig-[Gly-Ala-OMe]$_2$ **2b** were used in catalysis (Table 3, runs 10-12), a small improvement was obtained in comparison to the results obtained using only one ligand (Table 1, runs 15 and 17).

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



S1 **P1**

Run	L1 / L2	n_{L1} : n_{L2}	Conv.[b] / %	ee[c] % (*S*)
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, RT, 2h, DCM (0.1 M substrate). [b] Determined by ^{1}H NMR. [c] Determined by GC (Beta Dex 225).

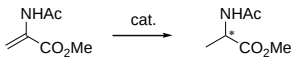
Products **P1** or **P2** with predominantly (*S*)-configuration were obtained with most of the examined catalysts; the few exceptions are limited to Val or Phe derivatives with low selectivity. According to the stereochemical analysis in the previous chapter, catalytic results support a preference for **[β²]** conformation. Our stereochemical analysis is further supported by results obtained 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 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). Since, in those cases, not all hydrogen bonding patterns of the catalytically active complex are possible, the obtained results can contribute to the understanding of the stereochemical outcome. Diamines **4b**–**4e** lack the ester carbonyl group and the otherwise preferred **[β²]** conformation can't be formed. Consequently, the obtained selectivity is rather low, only up to 34 % (runs 2–4, Table 4). Proline derivative **4g** contains no amide protons and the selectivity is very low (10 % ee, run 6, Table 4). Unsymmetrical ligands **5a–f** are capable of forming **[β²]** conformation and show moderate selectivity, (47–68 % ee, runs 7-12, Table 4). Particularly interesting is the rather low selectivity of derivative **5g** (29 % ee, run 13, Table 4), were **[β²]** conformation can be formed, but without the weak supporting H-bonding, due to the lack of Pro amide protons. As expected, catalysis using achiral ligands **4a** or **4f** gave quantitative yield but without selectivity (Table 4, runs 1 and 5).

Conclusions

This paper describes the solution phase synthesis of monodentate triphenylphosphane ligands disubsituted 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 symmetrical substituted analogues Lig-[NH-R or Aa_1-OMe]$_2$ **4** are prepared using a convenient one pot two step protocol.

Table 4. Rh(I) catalyzed asymmetric hydrogenation of **S1** using ligands **4** and **5**.[a]



S1 **P1**

Run	Ligand	Conv.[b] / %	ee[c] % (*S*)
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, RT, 2h, DCM (0.1 M substrate). [b] Determined by ^{1}H NMR. [c] Determined by GC (Beta Dex 225). [d] Catalysis using enatiomer **4e** yields **(*R*)-P1** with 34 % ee.

In situ prepared supramolecular Rh(I) complexes [Rh(COD)-(Lig-R)$_2$]BF_4 with ligands Lig-R = **1**–**5** were used as catalysts in the asymmetric hydrogenation of methyl 2-acetamidoacrylate (**S1**) or (*Z*)-acetamidocinnamate (**S2**). The selectivity obtained depends strongly on the distant amino acid or amine substituents, spanning the range from 84 % ee (**1a**, Table 1, run 3) to 4 % ee (**4b**, Table 4, run 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 side chain substituents. Attempts to use even smaller substituents did not improve the selectivity in catalysis, as can be seen for example 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]$_2$ (Table 3, runs 1-4) or Lig-[Ala-Gly-OMe]$_2$ **2a** and Lig-[Gly-Ala-OMe]$_2$ **2b** (Table 3, runs 10-12).

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

Experimental Section

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

Ligands 1-3, general procedure. 5-(Diphenylphosphino)isophthalic acid, TBTU (2 eq.), HOBt (2 eq.) and DIPEA were stirred at room temperature in DCM. After 1 h, *N*-unprotected amino acid or peptide (3-4 eq.) was added to the reaction mixture and stirring was continued overnight (approximately 15 h). The reaction mixture was then washed with $NaHCO_3$ (sat., aq.), citric acid (10 %, aq.) and NaCl (sat., aq.), dried over Na_2SO_4, filtered, evaporated in vacuum and purified by automated flash chromatography on a prepacked silica column.

Catalytic hydrogenation of methyl 2-acetamidoacrylate, S1. (a) **Catalysis at RT**: An oven dried two neck round bottomed flask (10 mL) under nitrogen atmosphere 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 DCM 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 gas and the substrate (45 mg, 0.3 mmol) was added in one portion and vigorously stirred with 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 (e.e.) was determined by chiral fused silica capillary column *Beta Dex 225* (conditions: isocratic 140, or 150 °C; 100 kPa head column pressure; eluting order: substrate, (*R*)-product, (*S*)-product). (b) **Catalysis at low temperature**: Following the procedure for reactions at RT, before substrate addition, reaction flask was placed in a thermo-container filled with technical ethanol (or isopropanol), cooled by cryostat device to –5 °C or –20 °C, and stirred vigorously overnight.

Catalytic hydrogenation of methyl (*Z*)-acetamidocinnamate, S2. (a) **Catalysis at atmospheric pressure**: The procedure is followed as for **S1**, using 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; $t_r(R)$ = 18.30 min, $t_r(S)$ = 18.75, t_r(substrate) = 32.39 min). (b) **Catalysis at high pressure**: In an Eppendorf vial, Rh precursor and the ligand were dissolved in DCM (0.5 mL) each and mixed. The yellow solution was added in a 10 mL beaker containing the substrate and DCM (4mL). This was tightly sealed in an autoclave and purged 3 times with H_2 (13 bar) and finally stirred at 13 bar for 2 h. The product was analyzed as written above.

Abbreviations. Amino acids were abbreviated by three letter codes or one letter codes (for spectral assignation). The following non-standard abbreviations were used: H-**BzA** = H-**NH-CH$_2$-C$_6$H$_5$** (benzylamine), H-**PeA** = H-**NH-CH(CH$_3$)-C$_6$H$_5$** (phenylethylamine), H-**NeA** = H-**NH-CH(CH$_3$)-C$_{10}$H$_7$** (α-naphtylethylamine) and H-**CeA** = H-**NH-CH(CH$_3$)-C$_6$H$_{11}$** (cyclohexylethylamine), see Scheme 2 for structures.

Supporting Information (see footnote on the first page of this article).

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