Supramolecular PhanePhos-analogous ligands through hydrogen-bonding for asymmetric hydrogenation†

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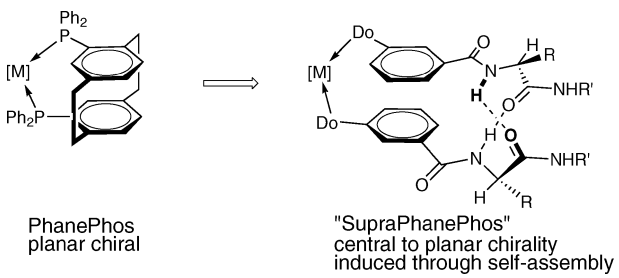
PhanePhos-analogous phosphorous ligands have been generated *via* self-assembly through hydrogen-bonding, and studied in rhodium-catalyzed asymmetric hydrogenation (up to 99% ee).

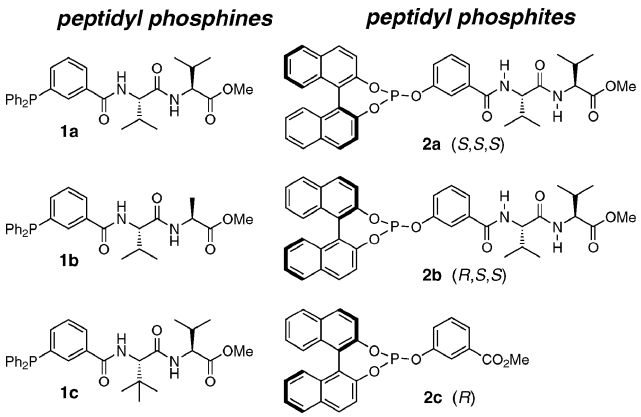
In the past 30 years the field of asymmetric transition metal catalysis has been dominated by chiral bidentate ligands.[1] However, the work of Feringa, de Vries *et al.*,[2] Reetz and Mehler,[3] and Pringle *et al.*[4] has demonstrated that monodentate phosphorus-based ligands can be successfully applied as well.[5] Monodentate ligands are particularly attractive due to their relative ease of preparation in comparison with their bidentate counterparts.

A prominent chelating ligand system for highly enantioselective rhodium-catalyzed asymmetric hydrogenation is the PhanePhos ligand developed by Pye and Rossen *et al.*[6] Unfortunately, access to this system requires a multistep synthesis. We[7] and others[8] recently demonstrated that bidentate ligands can be constructed by a self-assembly process of monodentate ligands mediated through hydrogen-bonding.[9] Thus, we wondered whether a simple monodentate ligand could be designed that would self-assemble in the presence of a transition metal center to provide a planar chiral Phane-like structure. Inspection of molecular models suggested that *meta*-carboxypeptidyl substituted triarylphosphines (Do = PPh_2) or phosphites (Do = $OP(OAr)_2$) might be suitable candidates. An interligand helical hydrogen-bonding network as indicated in Scheme 1 could be expected. This in turn might induce a planar chiral π-stacking arrangement of the two *meta*-substituted arene rings which resembles the planar chiral element found in PhanePhos.



Scheme 1 Schematic representation of "SupraPhanePhos".

Herein, we report the preparation of ligands **1**–**2**, their self-assembly properties and structures in solution and the solid-state as well as on their application to rhodium(I)-catalyzed asymmetric hydrogenation.



The synthesis of the ligands was straightforward, employing conventional solution-phase peptide synthesis procedures[10,11] (for details see ESI†).

Coordination properties of ligands **1** and **2** were investigated upon reaction with *cis*-$[Cl_2Pt(cod)]$ and $[Rh(cod)_2]BF_4$. The thus-formed complexes were studied by 2D ^1H, ^{31}P and ^{13}C NMR spectroscopy and ESI-MS, which in all cases proved the formation of *cis*-$[Cl_2PtL_2]$ and $[Rh(cod)L_2]BF_4$ species (see ESI†). Suitable single crystals for X-ray crystal-structure analysis could be obtained for *cis*-$[Cl_2Pt(\mathbf{1b}\cdot\mathbf{1b})]$. As shown in Fig. 1, the *cis*-coordinated phosphine ligands are linked by pairs of interligand N–H···O=C hydrogen bonds of the peptidyl side chain which adopt a helical conformation. Interestingly, the *meta*-substituted arene rings of the two neighbouring phosphine ligands adopt a planar chiral Phane-type conformation. This π–π interaction (~3.30 Å) is also expected to additionally contribute to the stabilization of the supramolecular metal-induced ligand assembly.[12] Additionally, a hydrogen-bonding intermolecular network is formed between the homodimeric complexes in the crystalline state.

NMR spectra indicate that a similar geometry is prevalent in solution in aprotic solvents such as $CDCl_3$ as well. Thus, the $^1J_{P,Pt}$ = 3659 Hz obtained from the ^{31}P NMR spectrum is typical for the *cis*-coordination of two phosphines at the platinum center.[14] The proton NMR spectrum of the complex displays well-resolved sharp resonances, which rules out the

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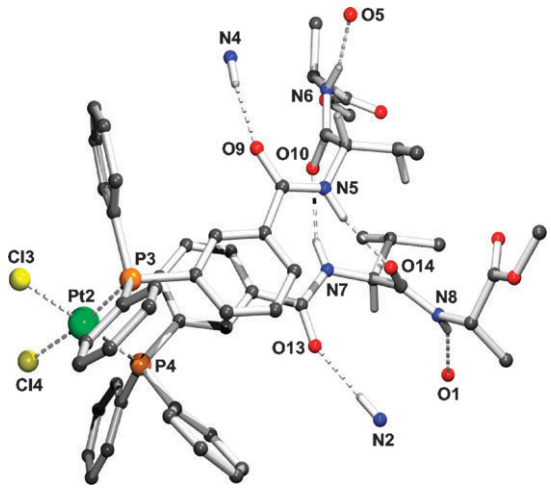


Fig. 1 PLATON[13] plot of *cis*-[Cl_2Pt(**1b** · **1b**)] in the solid-state at 100 K.‡ Selected interatomic distances (Å) and angles (°) of one independent complex in the asymmetric unit: Pt2–P3 2.268(2), Pt2–P4 2.244(2), N5···O14 2.926(8), O10···N7 2.913(9), N4···O9 2.856(9), O5···N6 2.890(9), O13···N2 2.872(9), N8···O1 2.836(9); P3–Pt2–P4 98, N5–H···O14 159, N7–H···O10 167, N4–H···O9 159, O5···H–N6 177, O13···H–N2 166, N8–H···O1 168. O1 and N2 belong to the 2nd independent complex in the asymmetric unit, whereas N4 and O5 belong to the 2nd independent complex in an adjacent cell (symmetry operation: $x + 1, y, z$). Pt green, C dark gray, H light gray, N blue, P orange, O red, Cl yellow. Irrelevant H atoms bound to C atoms and disordered ethyl acetate solvent molecules in the lattice were omitted for clarity.

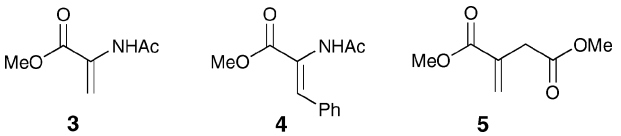
formation of large, disordered aggregates and suggests the formation of well-defined supramolecular species with a distinct predominant conformation. Analysis of the solution structures of peptides **1** before and after coordination of Pt^{II} confirm a change in the chemical shifts and in the NH,C_αH-coupling constants of the amide protons on complexation, and indicate a conformational change induced by the metal.† Compared with the free ligand, the observed significant low field shift of the N–H proton of the amino acid attached to the P-aryl moiety (*e.g.* for **1a**: $\Delta\delta$ = 1.43 ppm) is indicative of strong H-bonding.[15] In contrast, the amide proton of the terminal amino acid did not show a significant downfield shift (*e.g.* for **1a**: $\Delta\delta$ = 0.15 ppm). Both observations suggest that the relatively rigid helical structure and π-stacking of the self-assembled peptide-based complexes is maintained, but the intercomplex hydrogen-bonding network pattern found in the crystalline state is not persistent in solution.

In order to obtain some information on the potential of these supramolecular complexes as chiral catalysts, Rh-catalyzed enantioselective hydrogenation of methyl *N*-acetyl dehydro-amino acids (**3**, **4**) and dimethyl itaconate (**5**) was investigated in CH_2Cl_2 at room temperature under 1 atm of H_2 (Table 1). All rhodium–phosphine complexes [Rh(cod)(**1** · **1**)]BF_4 were catalytically active (full conversions after less than six hours, entries 1–3, 8–10 and 15–16). However, the enantioselectivities remained moderate (up to 51% ee, entry 1).

It has been shown that some of the results obtained with chelating phosphines can be matched by the use of bidentate phosphinites,[16] phosphonites,[17] phosphites,[18] or phosphoroamidites.[2] Therefore we expected that replacement of the achiral phosphine functionality (Do = PPh_2) with a chiral BINOL-based phosphite group (Do = $OP(OAr)_2$) may enhance asymmetric induction of the catalyst when a matching between the chirality of the peptide backbone and the chirality of the phosphite moiety is reached. Thus, the peptidyl phosphite ligands **2a–c** were studied next. Ligand **2c** is unable to form the self-assembly structure through hydrogen bonding. Hence, results obtained with this ligand would provide information on the role of the self-assembly structure with respect to the ligands' ability to induce enantioselectivity.

Hydrogenation of methyl 2-*N*-acetamido acrylate (**3**), with [Rh(cod)(**2a** · **2a**)]BF_4, gave the (*R*)-hydrogenation product with 90% ee (entry 4). Conversely, on employing the diastereomeric phosphite ligand **2b** under identical conditions the reaction was faster (100% conversion after 2.5 h) and gave the (*S*)-configured hydrogenation product in quantitative yield and an excellent ee of 99% (entry 5). Hence, **2b** represents the "matched" peptidyl phosphite ligand. On the other hand, control phosphite **2c** gave an ee of only 82%, which clearly indicates the importance of the peptidyl side chains for enantioinduction. The same conclusion can be drawn from the result of the hydrogenation experiment with ligand **2b** in a H-bond disrupting solvent such as methanol (entry 6).

Table 1 Rh-catalyzed enantioselective hydrogenation of substrates **3**–**5**[a]



Entry	Ligands	Substrate	Time/h	Conv.[b] (%)	ee[c] (%) (*S*)
1	**1a** · **1a**	**3**	<6	100	51
2	**1b** · **1b**	**3**	<6	100	32
3	**1c** · **1c**	**3**	<6	100	32
4	**2a** · **2a**	**3**	24	98	90 (*R*)
5	**2b** · **2b**	**3**	2.5	100	99
6	**2b** · **2b**	**3**	<6	100	77[d]
7	**2c** · **2c**	**3**	<6	100	82
8	**1a** · **1a**	**4**	<6	100	46
9	**1b** · **1b**	**4**	<6	100	30
10	**1c** · **1c**	**4**	<6	100	39
11	**2a** · **2a**	**4**	27	18	85 (*R*)
12	**2b** · **2b**	**4**	<6	100	98
13	**2c** · **2c**	**4**	<6	100	75
14	**1a** · **1a**	**5**	19	79	13 (*R*)
15	**1b** · **1b**	**5**	<6	100	15 (*R*)
16	**1c** · **1c**	**5**	<6	100	3 (*R*)
17	**2a** · **2a**	**5**	20	25	82
18	**2b** · **2b**	**5**	6	44	85 (*R*)
19	**2c** · **2c**	**5**	<6	100	97 (*R*)

[a] Reaction conditions: [Rh] : L_1 : L_2 : substrate = 1 : 1.2 : 1.2 : 100, $p(H_2)$ 1 bar, CH_2Cl_2 (0.1 M substrate), room temperature. [b] Conversion determined by ^{1}H NMR spectroscopy. [c] ees for products of **3**, **5** and **4** determined by chiral GC (Hydrodex-β-TBDAc and GT-A, trifluoroacetyl-γ-cyclodextrin) and chiral HPLC (Chiralpak AD), respectively. [d] MeOH as solvent.

Similar good results were obtained for the phenylalanine precursor **4** (entries 8–13, up to 98% ee). Conversely, in the case of dimethyl itaconate (**5**), the classical monodentate phosphite ligand **2c** performed with best results (97% ee, entry 19). This again proves that there exists no ideal catalyst for all substrates.

In conclusion, a new class of supramolecular PhanePhos-analogous ligands formed through self-assembly *via* hydrogen-bonding between peptidyl side chains was successfully applied in rhodium-catalyzed asymmetric hydrogenation. Both the reactivity and enantioselectivity observed are comparable to the best results obtained with common monodentate or bidentate Rh–phosphite catalysts,[1] and match the results achieved by PhanePhos-type ligands.[6,19]

Taken together, our experimental findings support the conclusion that helical secondary structures are important elements for significant catalyst activity and enantioselectivity. In summary, salient features of these catalysts, such as their ease of preparation from readily accessible and modular building blocks, the inherent combinatorial possibilities of this supramolecular approach, as well as the excellent levels of stereocontrol, render these ligand systems attractive for practical asymmetric synthesis.

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‡ CCDC 661682. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b716529c

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