Coordination Chemistry

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Supramolecular Control of Ligand Coordination and Implications in Hydroformylation Reactions**

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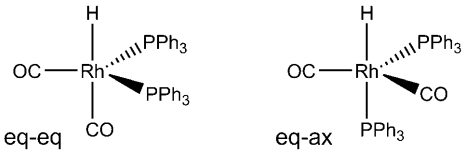
Coordination chemistry and organometallic chemistry have intensely fuelled the field of transition metal catalysis, and knowledge-based ligand design is, next to combinatorial and high-throughput experimentation, a leading approach to develop new catalytic systems. For the industrially important hydroformylation reaction, ligand effects have been studied in detail, also with the aid of high-pressure spectroscopy techniques, (for example, HP NMR and HP-IR).[1] The active species in this reaction is a trigonal bipyramidal complex, with a hydride on the axial position. The classical Wilkinson's dissociative mechanism, based on triphenyl phosphine as ligand, is widely accepted and explains most observations made to date. Two coordination complexes have been observed with either the ligands coordinated in the equatorial–equatorial (eq-eq) or in the equatorial–axial (eq-ax) mode (Scheme 1).



Scheme 1. Different coordination modes of a triphenylphosphine rhodium catalyst. eq-eq = both equatorial, eq-ax = equatorial/axial.

Van Leeuwen et al. elegantly demonstrated that bidentate phosphorus ligands with wide bite angles predominantly lead to the formation of the eq-eq rhodium complex, resulting in highly selective rhodium-catalyzed hydroformylation of 1-octene, and promoting the formation of the linear aldehyde product.[2] In the field of asymmetric hydroformylation, the most promising class of ligands are hybrid phosphines and phosphites or phosphoroamidites.[3] A real breakthrough in this field was achieved by Takaya, Nozaki et al. with the discovery of Binaphos, which gives *ee* values of up to 95% for a wide range of substrates.[4] The reason for the exceptionally high enantioselectivity is attributed to the exclusive formation of a single active species, in which the ligand coordinates in eq-ax mode to the transition-metal center.

Monodentate ligands have been much less applied in these transformations, as lower selectivities are anticipated owing to lower control over coordination modes. However, because of their simple structure, their synthesis is generally much less elaborate, making these ligands potentially cheaper and enabling the preparation of large ligand libraries, which are required to rapidly find new active and selective catalysts by rapid screening technologies. Application of very bulky monodentate phosphite (π-accepting) ligands demonstrated that these form very active catalysts that are also active in the hydroformylation of internal alkenes, albeit with significant isomerization.[5] Spectroscopy experiments on such systems indicate that only one phosphite ligand coordinates to the metal center in the equatorial plane. Along the same lines, Breit et al. have reported the use of bulky phosphabenezenes in hydroformylation catalysis.[6] In situ high-pressure NMR investigations demonstrate the prevalent formation of a monophosphine rhodium complex in which the ligand is located in equatorial position whereas the hydride occupies the axial site, which accounts for the reported activity and selectivity.

Recently, we have introduced a ligand-template approach for the supramolecular encapsulation of transition-metal complexes.[7] Ligand-template tris-3-pyridylphosphine coordinates zinc(II) porphyrins exclusively to the nitrogen donor atom, whereas the phosphorus atom coordinates to the catalytically active rhodium. The rhodium complex formed under hydroformylation conditions has only one phosphorus atom coordinated in the equatorial plane, and this catalyst system displayed unprecedented regioselectivity in the hydroformylation of unfunctionalized terminal and internal alkenes. Based on these results, we explored the use of chiral analogues, that is, typically based on the bis(naphthol) skeleton (Scheme 2). Herein, we present the remarkable supramolecular control over the coordination chemistry of these chiral pyridine-containing phosphoroamidite ligands and the effect in the asymmetric rhodium-catalyzed hydroformylation of unfunctionalized internal alkenes by this unusual coordination complex.

Monodentate phosphoroamidites (*S*)-**1a**–**b** were synthesized in just two steps (Scheme 3).[8,9] To ascertain that ligands (*S*)-**1a** bind to two zinc(II) porphyrin building blocks (**2**), we measured the binding constants and performed a Job plot analysis. The UV/Vis titration experiment revealed binding constants of $K_1 = 1.8 \times 10^3\ \mathrm{L\,mol^{-1}}$ and $K_2 = 1.7 \times 10^3\ \mathrm{L\,mol^{-1}}$ for the first and second porphyrin binding, respectively, to (*S*)-**1a**. The similarity between these constants indicate that the

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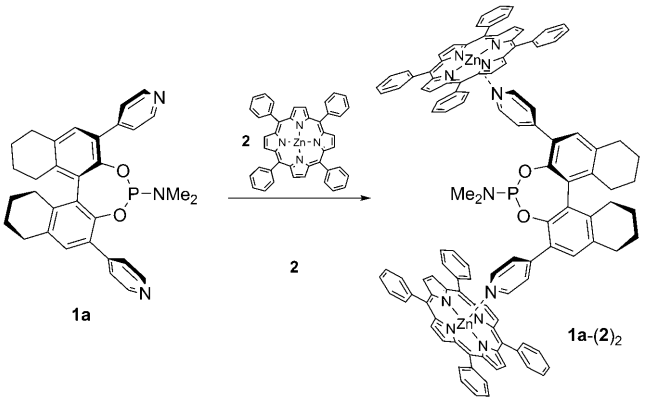
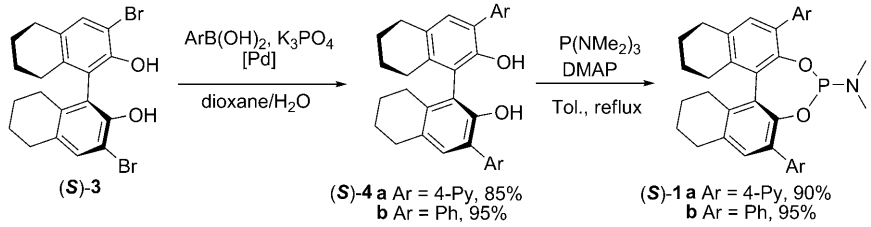


Scheme 2. The assembly of supramolecular ligand based on 4-pyridyl-phosphoroamidite **1a** and tetraphenyl zinc(II) porphyrin **2**.



Scheme 3. Synthesis of phosphoroamidite ligands.

binding events are independent and no cooperativity is observed as previously with the tris-3-pyridylphosphine.[7b] The Job plot analysis of NMR spectroscopy experiments in [D_8]toluene confirmed the formation of a 1:2 complex between (*S*)-**1a** and template **5**.[9]

To investigate the coordination behavior of (*S*)-**1a** to rhodium under catalytically relevant conditions, we studied the complexes formed by high-pressure (HP) NMR spectroscopy. Rhodium complexes were prepared in situ using [Rh(acac)CO_2] as the metal precursor in [D_8]toluene under syngas (H_2/CO 1:1) at a pressure of 5 bar (Figure 1). In line with previously reports, the complex based on bulky ligand (*S*)-**1a** is monoligated [Rh(H)$(CO)_3$**1a**] with the phosphorus ligand in the equatorial position; an hydride signal centered at $\delta = -11.01$ ppm is observed with a small PH coupling typical of such a *cis*-[Rh(H)$(CO)_3$**1a**] complex. Much to our surprise, in the presence of two equivalents of porphyrin **2**, this signal disappears and the HP ^{1}H NMR shows new signals in the hydride region; a double doublet centered at $\delta = -10.3$ ppm with a large phosphorus coupling ($J_{P\text{-}H} = 180$ Hz and $J_{Rh\text{-}H} = 6.1$ Hz) indicating that in this complex the phosphorus donor atom is located *trans* to the hydride. The ^{1}H-{^{31}P} NMR spectrum shows a signal at $\delta = -10.3$ ppm, confirming the large coupling between the phosphorus and the hydride. The 2D ^{1}H-^{31}P NMR spectra also supports the formation of a complex with a very large H-P coupling.[9] To the best of our knowledge, this is the first example of a rhodium complex in which a bulky monodentate ligand is coordinated *trans* to the hydride.

Importantly, we are able to control the ligand coordination mode by addition of a supramolecular template, which triggers the ligand coordination on rhodium from the *cis* position to *trans* position with respect to the hydride. This supramolecular control of *cis* versus *trans* coordination was demonstrated for a variety of systems, extending to zinc(II) salphen templates, and to the 3-pyridyl, bisnaphthol, and phosphoramidite and phosphite analogues of **1a**, showing that this behavior is rather general.[9]

Using high-pressure IR spectroscopy, we studied the formation of complexes *cis*-[Rh(H)$(CO)_3$**1a**] and *trans*-[Rh(H)$(CO)_3$**1a**$(2)_2$] under actual catalytic conditions, using 20 bar of syngas (H_2/CO 1:1) and concentrations identical to

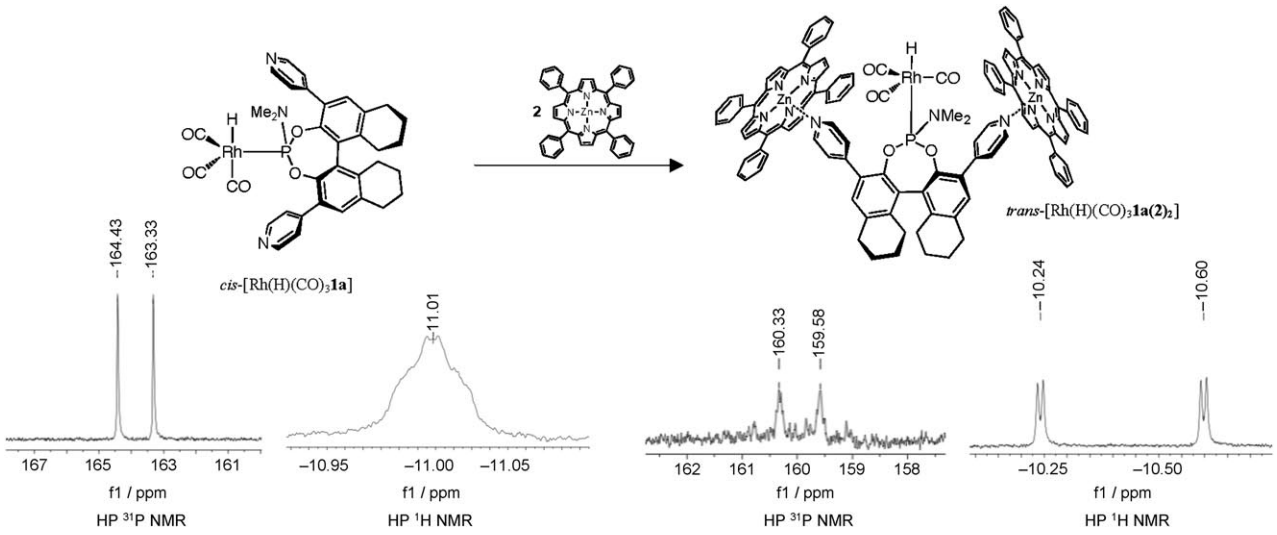
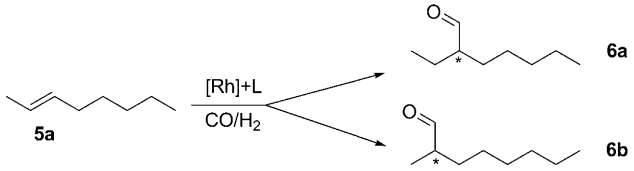


Figure 1. High Pressure NMR spectra of *cis*-[Rh(H)$(CO)_3$**1a**] and *trans*-[Rh(H)$(CO)_3$(**1a**$(2)_2$)].

those in catalysis experiments.[12] In the presence of [Rh(acac)CO_2] and ligand (*S*)-**1a**, the tris(carbonyl) rhodium hydride complex *cis*-[Rh(H)$(CO)_3$**1a**] was obtained, as was evident from the three peaks in the carbonyl region, namely 2054, 2000, and 1982 cm^{-1}. The rhodium complex formed in the presence of (*S*)-**1a** and two equivalents of porphyrin **2** shows three absorption bands that are shifted to higher wavenumbers (2055, 2022, 1998 cm^{-1}),[9] in line what we expected as the CO is a stronger π-accepting ligand than the phosphoroamidite. This change also suggests that CO dissociation from the *trans*-[Rh(H)$(CO)_3$**1a**$(\mathbf{2})_2$] complex might be faster, enhancing the alkene coordination step and possibly increasing the reaction rate.

To find out if the change in coordination mode would affect the catalytic performance, we used both complexes *cis*-[Rh(H)$(CO)_3$**1a**] and *trans*-[Rh(H)$(CO)_3$**1a**$(\mathbf{2})_2$] as catalyst for the asymmetric hydroformylation of internal alkenes.[10,11] We have chosen this reaction as 1) it is very challenging to introduce functional groups in non-functionalized alkenes, so success will lead to new enabling technology; 2) we previously demonstrated that encapsulation can lead to unusual regioselective reactions;[7] and 3) monodentate phosphoramidite ligands have been demonstrated to provide selective rhodium catalyst for the asymmetric hydroformylation of functionalized alkenes.[10c]

The ligand (*S*)-**1a** and (*S*)-**1a**$(\mathbf{2})_2$ as well as some control ligands (PPh_3,(*R*,*S*)-Binaphos and (*S*)-**1b**) were studied in the rhodium-catalyzed asymmetric hydroformylation (AHF) of *trans*-2-octene (**5a**) under syngas (H_2/CO = 1/1) at 20 bar pressure and at 25 °C in toluene (1 mM) (Scheme 4).[9]



Scheme 4. Hydroformylation of *trans*-2-octene.

The challenging character of this reaction is clear from the results obtained with the rhodium catalyst derived from triphenylphosphine, which only gave low conversions and significant amount of isomerization (Table 1, entry 1). The rhodium-catalyst-based (*R*,*S*)-Binaphos (Table 1, entry 2) gave useful conversion (55 %) but no significant ee %.

Complex [Rh(H)$(CO)_3$**1a**] provided the product with an *ee* of 25 %, albeit at relatively low conversion (12 %, Table 1, entry 5) Interestingly, in the presence of the template **2**, and thus with complex [Rh(H)$(CO)_3$**1a**$(\mathbf{2})_2$], an increase in both conversion (54 %) and enantioselectivity (45 %) is observed (Table 1, entry 6). This indicates that the change of coordination mode improves the catalyst performance in this challenging reaction both in terms of activity and selectivity. In line with this finding, we explored a small series of various zinc(II)-based templates, and regardless of the structure of the template, in all cases the *ee* increases to the same 45 %.[9] This suggests that the dominant effect in change of performance is associated to this change in coordination mode. In line with this, control experiments using ligand (*S*)-**1b** (Table 1, entry 3 and 4) that lacks the pyridyl group shows that these complexes give rise to low activity and the product **6a** is produced in low *ee*, regardless of the presence of zinc(II) porphyrin **2**. This demonstrates that template **2** does therefore not interfere directly with the rhodium-catalyzed hydroformylation. Furthermore, the increase in *ee* was also observed when the coordination mode was changed using phosphite and phosphoramidite analogues of **1a**.

Table 1: Results of the hydroformylation of *trans*-2-octene.[a]

Entry	Ligand	Conv. [%][b]	Isom. [%][c]	**6b**/**6a**[b,d]	**6a** *ee* [%][e]
1	PPh_3	6	5	1.24	0
2	(*R*,*S*)-Binaphos	55	4	1.51	0
3	(*S*)-**1b**	12	4	1.42	11 (*R*)[f]
4	(*S*)-**1b**, 2 equiv **2**	11	4	1.45	10 (*R*)[f]
5	(*S*)-**1a**	12	4	1.41	25 (*R*)[f]
6	(*S*)-**1a**$(\mathbf{2})_2$	**56**	**0**	**0.96**	**45** (*R*)[f]

[a] [Rh] = 1 mM in toluene, ligand/rhodium = 9, *trans*-2-octene/rhodium = 200, 25 °C, 20 bar, 84 h. [b] Percentage conversion calculated using the GC method. [c] Percentage isomerization. [d] Ratio of the products **6b** and **6a**. [e] Enantiomeric excess of product **6a**. [f] The absolute configuration was determined by comparing the GC traces with the that from the enantiopure aldehydes (*R*)-**6a** and (*S*)-**6a**. For detailed synthesis of (*R*)-**6a** and (*S*)-**6a**, see the Supporting Information.

To determine whether this unusual template effect in (*S*)-**1a** is more general, we investigated the AHF of a *trans*-2-hexene and *trans*-2-heptene, and the templated ligands also provide higher activity and enantioselectivity for these substrates compared to the non-templated analogues.[9]

In summary, we have presented a new class of monodentate phosphoramidite ligands for which the coordination mode to rhodium can be controlled in a unique supramolecular fashion, providing a new tool to control the activity and selectivity of a transition metal catalyst. In situ high-pressure NMR and IR studies under hydroformylation conditions demonstrate the formation of the first rhodium hydride complex in which the phosphorus donor atom of the ligand is *trans* to the hydride, but only after coordination of zinc(II) porphyrin moieties to the pyridyl moieties of the ligand. In absence of these zinc(II) porphyrins, the common monoligated rhodium hydrido complexes are formed with the ligand in the equatorial plane, in *cis* orientation to the hydride. Interestingly, the supramolecular change to the unusual coordination is reflected in higher activity and selectivity when these complexes are applied to the very challenging asymmetric hydroformylation of unfunctionalized internal alkenes.

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