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Self-assembly of bidentate ligands for combinatorial homogeneous catalysis based on an A–T base pair model*

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Abstract: A new concept for generation of chelating ligand libraries for homogeneous metal complex catalysis based on self-assembly is presented. Thus, self-assembly of structurally simple monodentate ligands in order to give structurally more complex bidentate ligands is achieved employing hydrogen bonding. Based on this concept and on the 2-pyridone/hydroxypyridine tautomeric system, a new rhodium catalyst was identified which operated with excellent activity and regioselectivity upon hydroformylation of terminal alkenes. In order to generate defined unsymmetrical heterodimeric ligands, an A–T base pair analog—the aminopyridine/isoquinolone system—was developed which allows for complementary hydrogen bonding. Based on this platform, a 4×4 phosphine ligand library was screened in the course of the rhodium-catalyzed hydroformylation of 1-octene. A catalyst operating with outstanding activity and regioselectivity in favor of the linear aldehyde was discovered.

Keywords: bidentate ligands; homogeneous catalysis; combinatorial; BINAP; XANTPHOS; 2-pyridone; 2-hydroxypyridine; 6-DPPon; rhodium catalyzed; hydroformylation.

Selectivity control in homogeneous metal complex catalysis relies in many cases on tailor-made ligands which craft the microenvironment at the catalytically active metal center. However, the quest for the ideal ligand giving rise to a catalyst with optimal activity and selectivity is a difficult task. Although rational ligand design has made significant progress, it is still not (and may never be) possible to predict the ligand of choice for a given reaction, substrate, and selectivity problem. This is why combinatorial methods have gained increased importance recently in which catalyst libraries are generated and screened against a particular selectivity/activity problem [1]. However, so far the problematic and rate-limiting step has been the time-consuming ligand synthesis. It is particularly difficult for the important class of bidentate ligands. Prominent examples of bidentate ligands are, for instance, BINAP, which allows for enantioselectivity control for a wide range of catalytic processes [2], and XANTPHOS—a tailor-made ligand in order to control regioselectivity in the course of the industrially important hydroformylation of terminal alkenes [3].

With the goal to facilitate bidentate ligand synthesis and to accelerate the process of ligand discovery, we anticipated constructing a bidentate ligand in a new fashion. Thus, instead of having a co-

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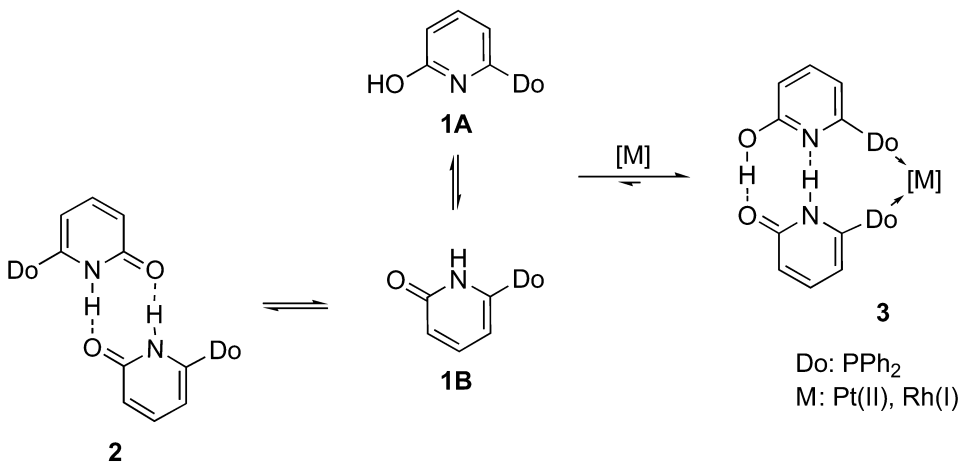
valent connection between the two binding sites, we envisioned a self-assembly process of two monodentate ligands through hydrogen bonding in the presence of a TM (transition-metal) center [4,5].

In this context, we became interested in the 2-hydroxypyridine/2-pyridone (Do = H) (**1A/1B**) tautomeric system (Scheme 1). It is known to exist in the gas phase approximately in a one to one ratio [6]. In solution and the solid state, the system prefers to dimerize as the pyridone tautomer (→**2**). Thus, if one would introduce a donor capable of binding to a metal center we envisioned both ligands to bind to the same metal center in a *cis* geometry in order to allow for hydrogen bonding between the pyridone and its hydroxypyridine tautomer (→**3**). This situation would be equivalent to a bidentate ligand with a noncovalent connection—in this case, hydrogen bonding—between the two donor sites.



Scheme 1 Concept of self-assembly of monodentate to bidentate ligands through hydrogen bonding on the basis of the 6-diphenylphosphanyl-2(1*H*)-pyridone/2-hydroxypyridine (**1**) tautomer system.

In fact, reaction of 6-diphenylphosphanyl-2(1*H*)-pyridone (6-DPPon) with [Cl_2Pt(COD)] lead to the quantitative formation of *cis*-[Cl_2Pt(6-DPPon)$_2$] (**3**, M = $PtCl_2$). The X-ray structure of this complex revealed the expected hydrogen-bonding interaction between pyridone and hydroxypyridine, thus rendering (6-DPPon)$_2$ a bidentate ligand (Fig. 1) [4].

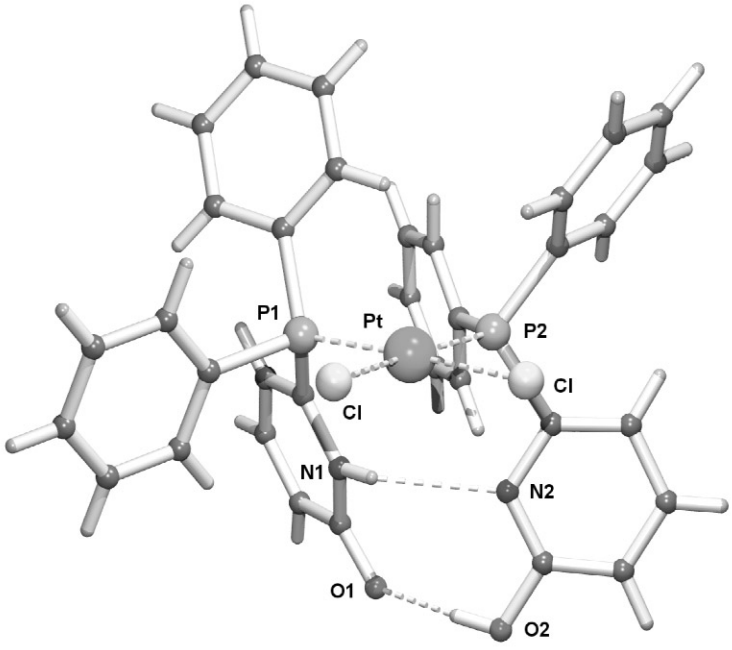
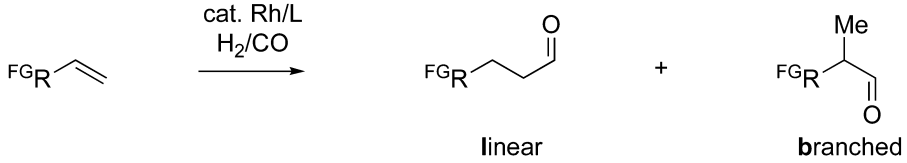


Fig. 1 X-ray plot of *cis*-[Cl_2Pt(6-DPPon)$_2$] (**3**).

Nevertheless, it was completely unclear whether this chelating geometry would be of any meaning for a catalytic reaction. To learn about the 6-DPPon ligand's properties in catalysis, we chose the rhodium-catalyzed hydroformylation of terminal alkenes (see eq. 1) for which a strong chelation effect is well established [3]. Thus, only tailor-made bidentate ligands such as XANTPHOS and others allow for high levels of regioselectivity in favor of the linear aldehyde (see Table 1, entries 3 and 4). A typical result with a monodentate ligand is depicted for triphenylphosphine (Table 1, entries 1 and 2) with rather low regioselectivity for the hydroformylation of 1-octene. Conversely, from the data of entries 5 and 6 in Table 1 it is obvious that a rhodium catalyst derived from the 6-DPPon ligand behaves as a chelating ligand. High linearity in combination with high catalyst activity was observed. Furthermore, this catalyst turned out to be compatible with a wide range of functional groups, even those capable of hydrogen bonding (Table 2). In all cases, excellent *n*-selectivity and catalyst activity was noted. However, switching from toluene as the standard solvent to protic solvents such as methanol lead to a significant decrease in regioselectivity, which may be due to disrupture of the hydrogen-bonding network of the 6-DPPon ligand (Table 2, entries 9 and 10) [4].



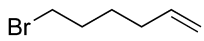
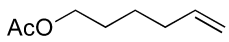
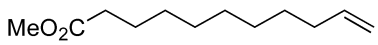
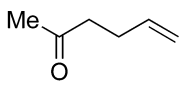
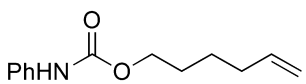
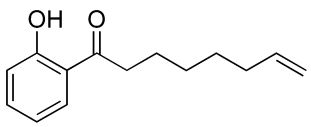
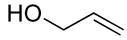
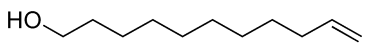
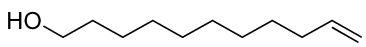
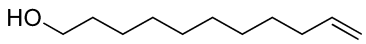
(1)

Table 1 Hydroformylation of 1-octene[a].

Entry	Ligand	T (°C)	Conv. (%)[b]	Isom. (%)[b]	l:b[b]
1	PPh_3	65	22	0.3	73:27
2	PPh_3	80	98	9	72:28
3	*t*-Bu-XANTPHOS	65	6	1	98:2
4	*t*-Bu-XANTPHOS	80	31	2	98:2
5	**1**	65	56	3	97:3
6	**1**	80	96	8	96:4

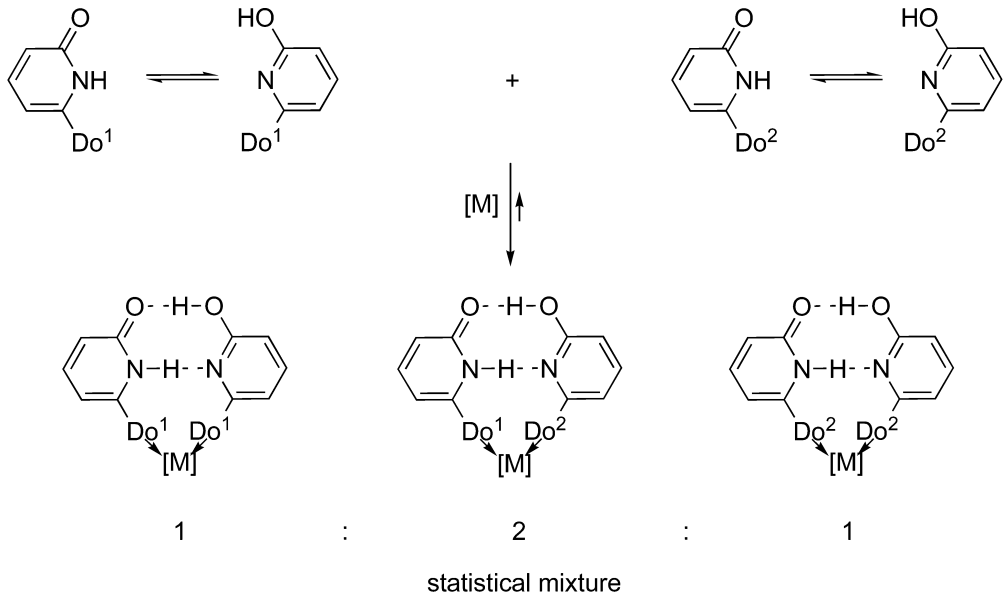
[a]Reaction parameters: Rh:L:1-octene (1:20:7000), c_0(1-octene) = 1.4 M, 4 h, toluene, 10 bar H_2/CO (1:1).
[b]Determined by GC analysis.

Table 2 Regioselective hydroformylation of functionalized terminal alkenes with the rhodium/6-DPPon (**1**) catalyst in comparison to the standard industrial rhodium/PPh_3 catalyst.

Entry[a]	Substrate	l:b[b] (L = **1**)	l:b[b] (L = PPh_3)
1		97:3	72:28
2		96:4	71:29
3		97:3	74:26
4		94:6	71:29
5		96:4	69:31
6		95:5	70:30
7[c]		95:5	89:11
8		96:4	77:23
9	 MeOH as solvent	83:17	77:23
10	 + 0.5 equiv AcOH	81:19	–

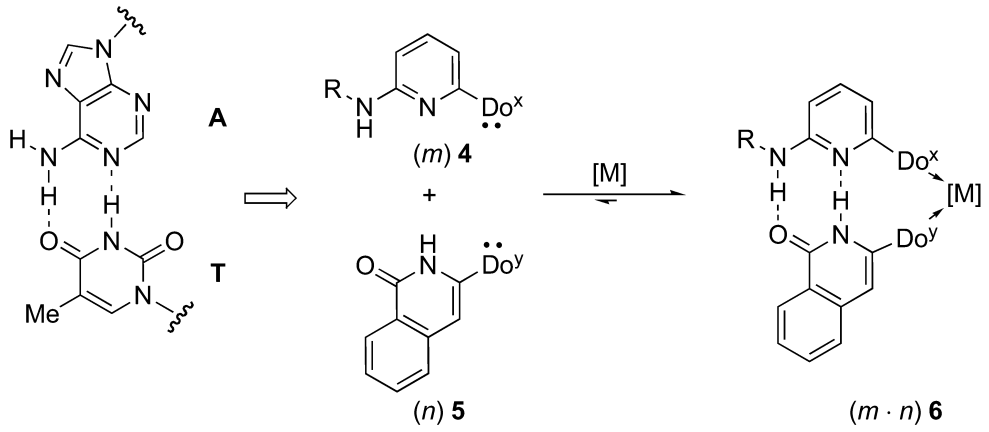
[a]Reaction parameters: Rh:L:alkenic substrate (1:20:1000), c_0(alkene) = 0.7 M, toluene, 10 bar H_2/CO (1:1), 70 °C. Full conversion was reached in every case after 20 h.
[b]Determined by GC and NMR analysis of crude reaction mixture after 20 h.
[c]Isolated as the corresponding γ-lactol.

Hence, self-assembly of monodentate to bidentate ligands through hydrogen bonding is, in fact, possible and has provided one of the most efficient catalysts for *n*-selective hydroformylation of functionalized terminal olefins. Even more, the self-assembly approach would now allow for a truly combinatorial approach for ligand library generation. Thus, mixing of *m* ligands of a set L1 with *n* ligands of a set L2 would generate *m* times *n* bidentate ligands. However, since the two tautomers—the hydroxypyridine **1A** and the pyridone **1B**—equilibrate rapidly, mixing of two pyridone ligands with different donor sites would result in the formation of mixtures [7] of the heterodimeric and the two homodimeric catalysts (Scheme 2).



Scheme 2 Statistical mixture of homo- and heterodimeric complexes formed upon mixing of two different pyridone ligands in the presence of a metal salt.

Hence, a clear-cut delineation of structure activity and structure selectivity relations, which is the prerequisite for an intelligent ligand library design, would be impossible. Thus, a situation in which the heterodimeric complex would form exclusively, would be most desirable. In order to achive this goal, the self-assembly of two complementary species through hydrogen bonding—a principle employed by nature in DNA base pairing—would become mandatory. Thus, an A–T base pair model relying on the aminopyridine (**4**)/isoquinolone (**5**) platform was selected to serve for a specific heterodimeric ligand assembly (Scheme 3) [8].



Scheme 3 An A–T base pair model as a complementary platform for specific self-assembly of heterodimeric bidentate ligands.

In fact, mixing two phosphine ligands based on this platform in the presence of the metal salt $[Cl_2Pt(COD)]$ lead to the quantitative formation of the heterodimeric complex *cis*-$[Cl_2Pt($**6aa**$)]$ (Do^x = Do^y = PPh_2) exclusively. An X-ray structure of this complex shows the expected hydrogen-bonding network reminiscent of the Watson–Crick base pairing of A and T in DNA (Fig. 2) [8]. From NMR studies, it seems obvious that a similar structural situation occurs in solution, too. Thus, on the basis of this

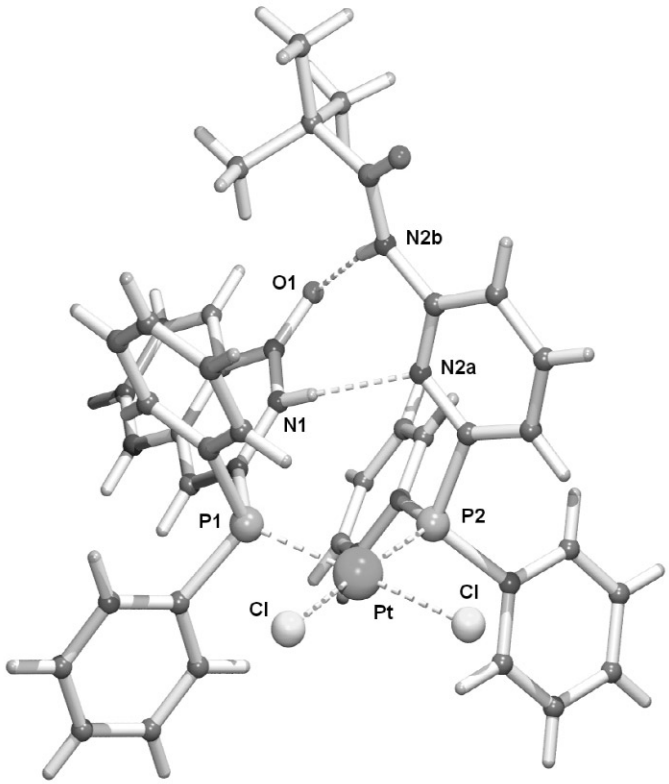
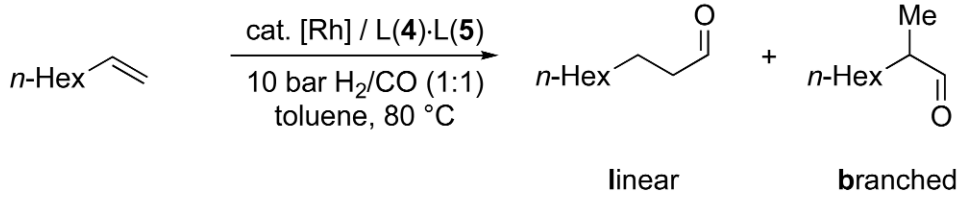
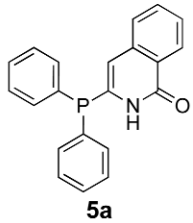
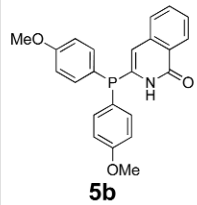
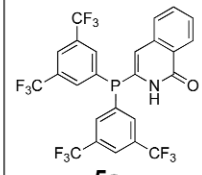
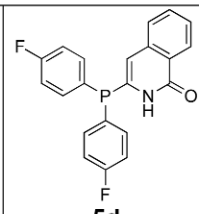
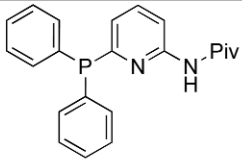
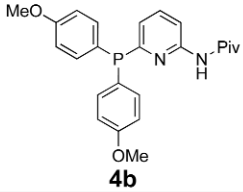
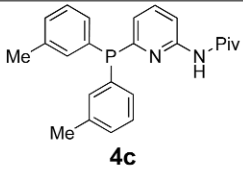
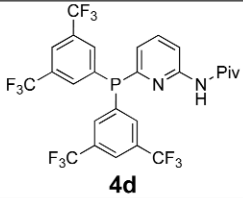


Fig. 2 X-ray plot of *cis*-$[Cl_2Pt($**6aa**$)]$ (Do^x = Do^y = PPh_2).

platform the first 4 × 4 self-assembled ligand library based on hydrogen bonding was generated and explored for regioselective hydroformylation of terminal alkenes (exemplarily for 1-octene). This study allowed us to identify a catalyst (**4d**/**5d**) which operated with truly outstanding activity and regioselectivity (see Table 3) [8].

Table 3 4 × 4 ligand matrix of aminopyridine (**4a–d**)/isoquinolone (**5a–d**) derived self-assembled bidentate ligands in the [Rh]-catalyzed hydroformylation of 1-octene[a].



L	 **5a**	 **5b**	 **5c**	 **5d**
 **4a**	2425 h^{-1} [b] 94:6 [c]	1040 h^{-1} 94:6	2732 h^{-1} 96:4	2559 h^{-1} 95:5
 **4b**	2033 h^{-1} 93:7	1058 h^{-1} 92:8	1281 h^{-1} 96:4	1772 h^{-1} 94:6
 **4c**	3537 h^{-1} 94:6	1842 h^{-1} 93:7	1808 h^{-1} 96:4	2287 h^{-1} 94:6
 **4d**	7439 h^{-1} 96:4	2695 h^{-1} 95:5	7465 h^{-1} 94:6	**8643 h^{-1}** **96:4**

[a]Reaction conditions: [$Rh(CO)_2$acac], [Rh]:L(**4**):L(**5**):1-octene = 1:10:10:7500, 10 bar H_2/CO(1:1), toluene (c_0(1-octene) = 2.91 M), 5 h. Catalyst preformation: 5 bar CO/H_2(1:1), 30 min, rt to 80 °C.

[b]Turnover frequency (TOF) was calculated as (mol aldehydes) × (mol catalyst)$^{-1}$ × (t/h)$^{-1}$ at 20–30 % conversion, determined by GC analysis.

[c]Regioselectivity: **l**inear to **b**ranched determined by GC analysis.

Extension of this concept to asymmetric catalysis is obvious, and investigations in this area are currently being pursued in these laboratories.

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