Combinatorial Catalysis

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Self-Assembly of Bidentate Ligands for Combinatorial Homogeneous Catalysis: Methanol-Stable Platforms Analogous to the Adenine–Thymine Base Pair**

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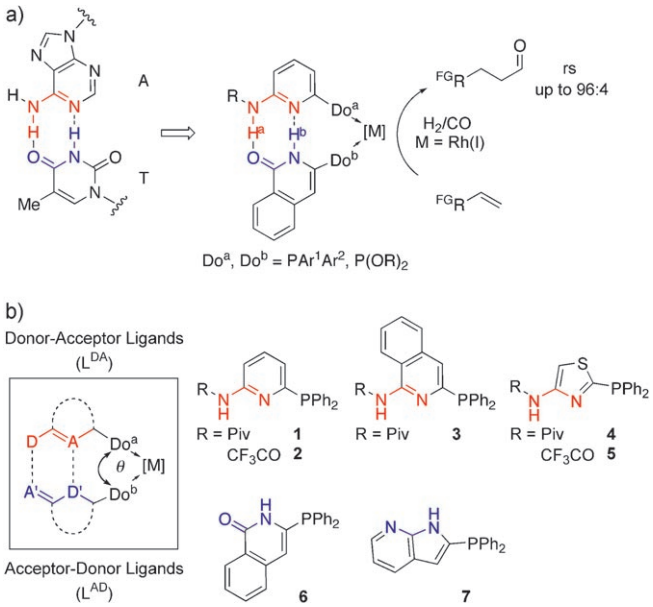
Tailor-made ligands are essential for efficient selectivity control in homogeneous metal-complex catalysis. Since the theoretical prediction of an optimal ligand for a given reaction, substrate, and desired selectivity is impossible, combinatorial approaches have emerged to accelerate catalyst discovery.[1] However, these approaches still suffer from limited access to structurally diverse and meaningful ligand libraries. The problem is particularly acute for the important class of bidentate ligands, for which the synthesis, in many cases, involves nontrivial operations that are unsuited for automation. Even more difficult is the synthesis of nonsymmetric bidentate ligands with two different donor sites.

As a solution to this problem, we recently introduced an alternative to the classical bidentate-ligand synthesis, the self-assembly of monodentate to bidentate ligands through complementary hydrogen bonding.[2–4] Thus, on the basis of a platform analogous to the A–T base pair, the aminopyridine–isoquinolone system, libraries of achiral and chiral phosphine and phosphonite ligands were evaluated (Scheme 1a). From these studies, excellent catalysts for regioselective hydroformylation,[5] anti-Markovnikov hydration of alkynes,[6] as well as asymmetric hydrogenation[7] have emerged. In all cases, combinatorial ligand variations were achieved by changing the donor site ($Do^{a/b}$ in Scheme 1a) on the aminopyridine–isoquinolone platform. It was unclear whether this approach would be restricted to the aminopyridine–isoquinolone self-assembly system, or whether, indeed, a variation of the A–T base-pair analogous platform would also be possible (Scheme 1b). It was reasonable to expect that any change of the platform geometry or the hydrogen-bonding system would have an immediate impact on the ligand bite angle (θ) and the coordination geometry at the metal center, and thus, an important influence on the catalyst performance.[8]



Scheme 1. a) A platform analogous to the A–T base pair for the self-assembly of monodentate to bidentate ligands for hydroformylation catalysts. b) A library of ligands with complementary hydrogen-bonding motifs. rs = regioselectivity. FG = functional group. D = hydrogen-bond donor. A = hydrogen-bond acceptor. Piv = pivaloyl.

Herein, we report on the development of the first library of self-assembled ligands based on new heterocyclic platforms analogous to the A–T base pair. From a first evaluation of this new library of self-assembled phosphine ligands, an extremely regioselective hydroformylation catalyst emerged, in which the ligand's behavior was bidentate, even in protic solvents such as methanol.

As A-analogous donor–acceptor ligands (L^{DA} in Scheme 1b), the heterocycle-functionalized phosphines **1**–**5** were chosen. As T-analogous acceptor–donor ligands (L^{AD} in Scheme 1b), we selected the known isoquinolone **6** and the new 7-azaindole **7**. The preparation of the ligands is described in the Supporting Information.

The coordination properties of all 10 possible ligand combinations were studied through the NMR spectroscopic investigation of the corresponding platinum complexes $[Cl_2Pt(L^{DA})(L^{AD})]$ (Table 1). ^{31}P NMR spectroscopy showed, in all cases, the selective formation of a defined complex with a heterodimeric ligand. In the ^{31}P NMR spectra, an AB spin system with a $^2J(P,P)$ coupling constant of 14.8–17.2 Hz was detected, indicating that two non-equivalent phosphorus atoms are bound to a single platinum nucleus. The $^1J(P,Pt)$

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Table 1: ^{31}P and ^{1}H NMR spectroscopic data for the *cis*-[$Cl_2Pt(L^{DA})(L^{AD})$] complexes of the donor–acceptor (L^{DA}; **1**–**5**) and acceptor–donor ligands (L^{AD}; **6**, **7**).

L^{DA}/L^{AD}	^{31}P NMR					^{1}H NMR	
	δ_1 [ppm]	^{1}J(P,Pt) [Hz]	δ_2 [ppm]	^{1}J(P,Pt) [Hz]	^{2}J(P,P) [Hz]	$\delta(H^a)$ [ppm][a]	$\delta(H^b)$ [ppm][b]
1/6	11.3	3507	13.0	3684	14.8	10.4	11.1
2/6	8.7	3463	16.0	3691	14.8	12.5	11.0
3/6	10.4	3704	13.3	3596	14.8	10.7	11.7
4/6	10.6	3512	11.5	3770	14.8	10.7	12.1
5/6	10.3	3495	13.0	3778	14.8	12.6	12.1
1/7	2.9	3667	9.3	3537	14.8	10.3[c]	12.3[c]
2/7	4.8	3674	7.2	3426	14.8	13.4[c]	12.6[c]
3/7	2.1	3687	10.9	3613	14.8	10.8[c]	13.0[c]
4/7	2.3	3608	5.9	3535	14.8	10.0[c]	12.4[c]
5/7	3.3	3608	5.6	3539	17.2	13.2[c]	12.9[c]

[a] H^a is from the donor group of L^{DA}; see Scheme 1 a. [c] H^b is from the donor group of L^{AD}; see Scheme 1 a. [c] The assignment of $\delta(H^a)/\delta(H^b)$ is interchangeable.

coupling constants are all greater then 3000 Hz (Table 1), as is typical for *cis*-diphosphine platinum(II) complexes.[9,10] The ^{1}H NMR spectra revealed nuclear Overhauser effect (NOE) contacts between the protons involved in hydrogen bonding. Hence, in solution, all 10 ligand combinations form hydrogen-bonding platforms analogous to the A–T base pair. Furthermore, the existence of defined *cis*-heteroleptic complexes in the solid state was confirmed by the analysis of the crystal structures of [Cl_2Pt(**4**/**6**)] and [Cl_2Pt(**3**/**7**)] by X-ray diffraction (Figure 1).

To probe the influence of the self-assembled platforms on the catalyst properties, we studied the rhodium-catalyzed hydroformylation of terminal alkenes. We chose this reaction because a strong chelating effect is well-established and is indicative of the ligand binding properties of the kinetically competent catalyst,[11] and because it has enormous industrial importance.[12] 1-Octene was chosen as the test substrate.

In a first set of experiments, all the ligands were evaluated independently. The regioselectivities were on the order of 75:25 to 81:19, which is the typical result for a monodentate triarylphosphine rhodium catalyst.[13] Next, all 10 possible ligand combinations were studied, and the results of these hydroformylation experiments are given in Table 2. The regioselectivies observed (89:11 to >99:1) confirm that, in all cases, bidentate-ligand catalysts are the kinetically competent catalyst species.

Interestingly, in all of the relevant ligand combinations, going from the pivaloyl substituent to a trifluoroacetyl group led to an increase in regioselectivity (**1/6** vs. **2/6**, **1/7** vs. **2/7**, **4/6** vs. **5/6**, and **4/7** vs. **5/7**). This trend is consistent with an increase of hydrogen-bond strength, as reflected in the downfield chemical shift of the amide proton H^a in the ^{1}H NMR spectra of the corresponding *cis*-[$Cl_2Pt(L^{DA})(L^{AD})$] complexes (Table 1). Among all the ligand combinations, the catalysts derived from the thiazole–isoquinolone (**5/6**) and from the thiazole–7-azaindole (**5/7**) systems were the best. In these cases, regioselectivities greater than 99:1 in favor of the linear aldehyde were observed, even at a reaction temperature of 80 °C. One explanation could be that going from the six-membered aminopyridine systems **1**–**3** to the five-membered thiazole heterocycles **4** and **5** might result in stronger hydrogen bonds and, hence, in a more rigid self-assembled system. If this notion is correct, it should be interesting to see whether the new platforms incorporating the thiazole system remain intact in a protic solvent environment (e.g., methanol). Indeed, previous studies showed that the hydrogen-bonding network of the first generation of self-assembled ligands is interrupted through interaction with methanol,[2] which limits their application range in homogeneous catalysis.

Thus, the rhodium-catalyzed hydroformylation of 1-octene employing the self-assembled platforms was studied in methanol, and the results were compared to those obtained in toluene (Table 3). As expected, the first-generation platform **1/6** showed a significant drop in regioselectivity on going from toluene (94:6) to methanol (82:18). The drop in regioselectivity is indicative of a disruption of the hydrogen-bonding

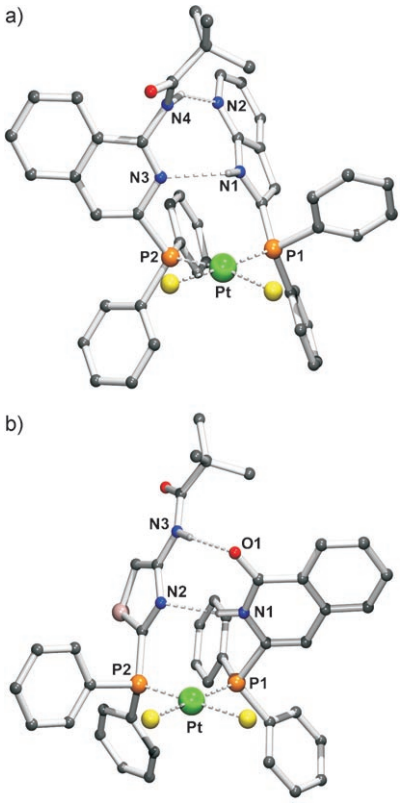
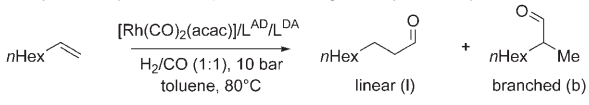


Figure 1. a) PLATON plot of the structure of *cis*-[Cl_2Pt(**3**/**7**)] in the solid state. Selected interatomic distances [Å] and angles [°]: Pt—P1 2.2417(6), Pt—P2 2.2517(6), N1···N3 2.910(3), N4···N2 2.987(3); P1-Pt-P2 99.01(2), N1—H···N3 129.0, N4—H···N2 153.7. b) PLATON plot of the structure of *cis*-[Cl_2Pt(**4**/**6**)] in the solid state. Selected interatomic distances [Å] and angles [°]: Pt—P1 2.2609(5), Pt—P2 2.2331(6), N1···N2 2.992(3), N3···O1 3.038(3); P1-Pt-P2 97.42(2), N1—H···N2 159.0, N3—H···O1 166.0. Pt green, C dark gray, H light gray, N blue, P orange, O red, S pink, Cl yellow; H atoms bound to C atoms are omitted for clarity.

Table 2: Turnover frequencies (TOF)[b] [h^{-1}] and linear:branched (l:b) regioselectivities[c] of the rhodium-catalyzed hydroformylation of 1-octene for a 5×2 matrix of self-assembled bidentate ligands derived from donor–acceptor (L^{DA}; **1**–**5**) and acceptor–donor ligands (L^{AD}; **6**, **7**).[a]



$L^{DA}\rightarrow$ / $L^{AD}\downarrow$	**1**		**2**		**3**		**4**		**5**	
	TOF	l:b	TOF	l:b	TOF	l:b	TOF	l:b	TOF	l:b
6	2465	94:6	3396	96:4	2341	95:5	3890	98:2	3888	>99:1
7	2713	89:11	4356	96:4	3205	95:5	3233	95:5	2318	99:1

[a] Reaction conditions: $[Rh(CO)_2(acac)]$ (acac = acetylacetonato):L^{AD}:L^{DA}:1-octene = 1:10:10:7500, 10 bar H_2/CO (1:1), toluene, 80 °C, 5 h; catalyst preformation: 5 bar H_2/CO (1:1), 30 min, RT→80 °C. [b] Calculated as TOF [h^{-1}] = (mol aldehydes) × (mol catalyst)$^{-1}$ × (time [h])$^{-1}$ at a reaction time of 30 min; determined by GC. [c] The ratio of linear to branched aldehyde products; determined by GC.

Table 3: Linear:branched (l:b) regioselectivities of the rhodium-catalyzed hydroformylation of 1-octene in toluene and in methanol for self-assembled ligands derived from donor–acceptor (L^{DA}; **1**, **2**, **4**, **5**) and acceptor–donor ligands (L^{AD}; **6**, **7**).[a]

L^{DA}/L^{AD}	l:b[b]	
	in toluene	in MeOH
1/6	94:6	82:18
2/6	96:4	79:21
5/7	99:1	85:15
4/6	98:2	97:3
5/6	99:1	96:4

[a] Reaction conditions: $[Rh(CO)_2(acac)]$:L^{DA}:L^{AD}:1-octene = 1:10:10:1000, 10 bar H_2/CO (1:1), 80 °C 20 h. [b] The ratio of linear to branched aldehyde products; determined by GC and ^{1}H NMR spectroscopy on crude reaction mixtures after a reaction time of 20 h; complete conversion was reached in all cases.

network between ligands **1** and **6**, which forces the system to behave as a monodentate triarylphosphine rhodium catalyst.[13] The same holds for the ligand combination **2**/**6** and **5**/**7**. However, for the thiazole systems **4**/**6** and **5**/**6**, high regioselectivities were observed in toluene and in methanol. Hence, for the first time, we could identify complementary self-assembled platforms that operate as bidentate ligands, even in a protic solvent.

In conclusion, the combinatorial self-assembly of monodentate to bidentate ligands for homogeneous catalysis is a very promising approach to the development of new and better catalysts. Herein, we have demonstrated that variation of the heterocyclic self-assembly platform has an enormous impact on the properties of the resulting catalyst. New hydroformylation catalysts with excellent activities and outstanding regioselectivities, even in protic solvents such as methanol, were identified. This result is an important extension of the application range of self-assembled catalysts based on hydrogen bonding. New applications in homogeneous catalysis are expected to emerge soon.

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[13] Under identical conditions (Table 2), a turnover frequency of 1312 h^{-1} and a linear:branched regioselectivity of 76:24 in the rhodium-catalyzed hydroformylation of 1-octene were measured for triphenylphosphine.

