

# Template-induced formation of heterobidentate ligands and their application in the asymmetric hydroformylation of styrene†

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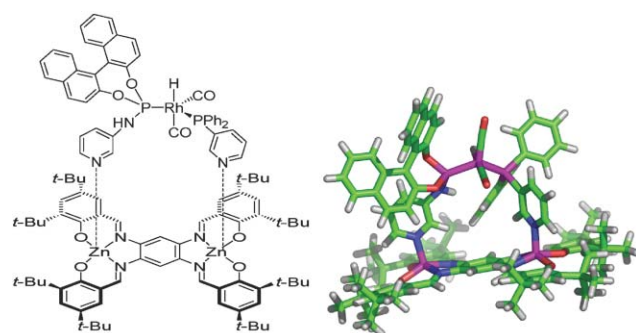
We report the template-induced formation of chelating heterobidentate ligands by the selective self-assembly of two *different* monodentate ligands on a rigid bis-zinc(II)-salphen template with two *identical* binding sites; these templated heterobidentate ligands induce much higher enantioselectivities (up to 72% ee) in the rhodium-catalyzed asymmetric hydroformylation of styrene than any of the corresponding homobidentate ligands or non-templated mixed ligand combinations (up to 13% ee).

Homobidentate and heterobidentate ligands comprise a very important class of ligands in homogeneous transition metal catalysis,<sup>1</sup> but compared to monodentate ligands<sup>2,3</sup> their synthesis is more tedious. Supramolecular (hetero)bidentate ligands<sup>4</sup> do not suffer from these synthetic disadvantages and therefore represent an important new class of ligands that is well-suited for combinatorial approaches. In the supramolecular approach two monodentate ligands are brought together by a self-assembly process using non-covalent interactions such as hydrogen bonds or dynamic metal–ligand interactions. Two monodentate ligands can be assembled by using ligands with complementary binding motifs,<sup>5</sup> or alternatively a template can be used that contains binding sites for the assembly of two monodentate ligands.<sup>6</sup>

Herein, we report the template-induced formation of chelating heterobidentate ligands by the selective self-assembly of two *different* monodentate ligands on a rigid bis-zinc(II)-salphen

template with two *identical* binding sites (Fig. 1). These templated heterobidentate ligands induce much higher enantioselectivities in the rhodium-catalyzed asymmetric hydroformylation of styrene than their non-templated analogues.

The building blocks used in this contribution (**1–3**, **a–h**) were all prepared in a straightforward manner.<sup>7</sup> The formation of bidentate phosphorus ligands takes place *in situ* by selective coordination of the nitrogen donor atom of ligand **a–h** to the zinc atoms of the bis-Zn-salphen template **3**, and the phosphorus donor atoms are still available for complexation to palladium or rhodium.<sup>8</sup> Titration experiments in toluene monitored by UV-vis spectroscopy revealed that the bis-Zn-salphen template binds two ligands **a** with corresponding binding constants of  $K_1 = 2.4 \times 10^4 \text{ M}^{-1}$  and  $K_2 = 1.5 \times 10^4 \text{ M}^{-1}$ . The formation of templated homobidentate palladium complexes such as  $[\text{Pd}(\text{CH}_3\text{Cl})(\mathbf{3}(\mathbf{a})_2)]$  and  $[\text{Pd}(\text{CH}_3\text{Cl})(\mathbf{3}(\mathbf{b})_2)]$  was evidenced by  $^{31}\text{P}$  NMR studies.<sup>7</sup>

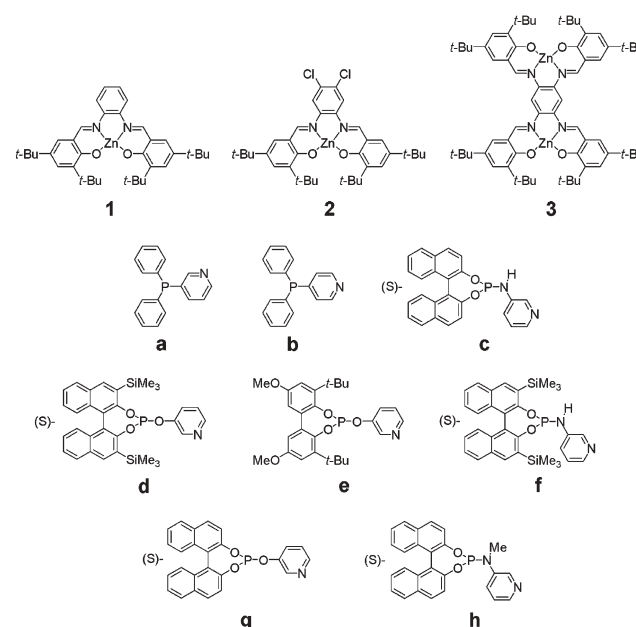


**Fig. 1** Schematic representation (left) and molecular modeling picture (right) of the templated heterobidentate complex  $[\text{HRh}(\text{CO})_2(\mathbf{3}(\mathbf{a} + \mathbf{c}))]$  (green = C, white = H, blue = N, red = O, purple = P, purple = Rh and purple = Zn).

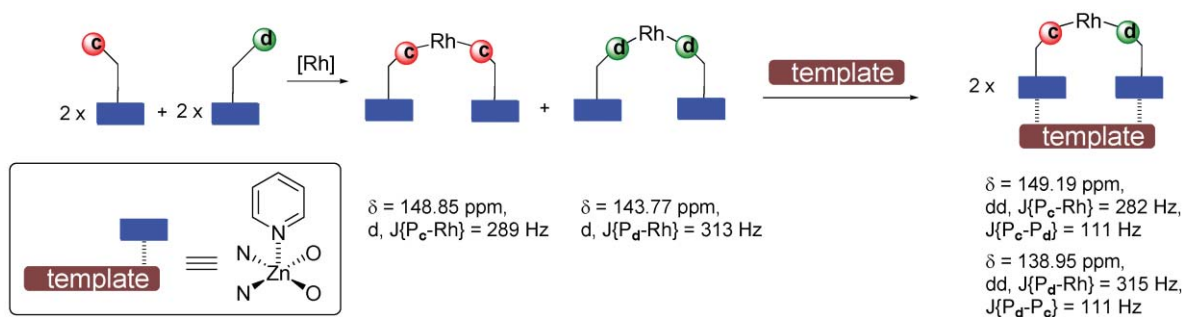
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Since template **3** contains two identical binding sites, the use of mixtures of ligands in the presence of the template was expected to lead to mixtures of complexes, in analogy to the work of Reetz and of de Vries and Feringa.<sup>3</sup> Remarkably, a mixture of **c** + **d** in the presence of the rhodium-precursor  $[\text{Rh}(\text{acac})(\text{CO})_2]$  and the bis-zinc(II)-salphen template **3** showed exclusive formation of the templated heterobidentate catalyst assembly  $[\text{Rh}(\text{acac})\text{CO}(\mathbf{3}(\mathbf{c} + \mathbf{d}))]$ . The corresponding homocombinations were not observed at all by  $^{31}\text{P}$  NMR spectroscopy (Scheme 1).<sup>7</sup> In contrast, in the absence of template, only the two homocombinations

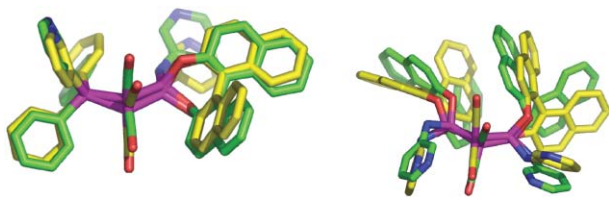


**Scheme 1** Schematic representation of the selective formation of templated heterobidentate rhodium complexes.

$[\text{Rh}(\text{acac})\text{CO}(\mathbf{c})_2]$  and  $[\text{Rh}(\text{acac})\text{CO}(\mathbf{d})_2]$  were formed, and the heterocombination  $[\text{Rh}(\text{acac})\text{CO}(\mathbf{c})(\mathbf{d})]$  could not be detected at all.<sup>7</sup> Likewise, when the mono-zinc(II)-salphen building block **1** was used, exclusive formation of the homocomplexes was observed.<sup>7</sup>

There are no electronic changes of the metal complexes in going from the non-templated to the templated state, indicating that the selective formation of heterobidentate ligated metal complexes must be sterically driven. Molecular modeling studies at the PM3 level show that the reorganization energy of the metal complexes in going from the non-templated to the templated state is much higher for the bulky ligands than for non-bulky ligands. For example, the energy to reorganize  $\text{HRh}(\text{CO})_2(\mathbf{c})_2$  such that it can coordinate to the template with the two pyridyl groups is 8.6 kcal/mol, whereas for  $\text{HRh}(\text{CO})_2(\mathbf{a})_2$  and  $\text{HRh}(\text{CO})_2(\mathbf{a})(\mathbf{c})$  this is 4.9 and 4.7 kcal/mol, respectively.<sup>7</sup> This is clearly visible in the structural changes (Fig. 2) and it suggests that the selective formation of heterobidentate ligated complexes is disadvantaged if both ligands are very bulky, which is supported by the catalysis data (*vide infra*).

The templated heterobidentate ligand assemblies were studied in the rhodium-catalyzed asymmetric hydroformylation of styrene (Table 1). Rhodium complexes based on ligand **c** (entries 1–3) all showed a low conversion whereas the rhodium complexes based on ligand **d** (entries 4–6) all gave full conversion and a low enantiomeric excess of the product (13%). Surprisingly, the catalyst based on the templated heterobidentate ligand **3(c + d)** gave much higher ee (55%) at slightly lower conversion (entry 9). Control experiments using mixed ligand combinations **c + d** and **1c + 1d** (entries 7 and 8) gave low ee (approximately 10%) and full conversion, indicating that the template **3** plays a crucial role. These results are completely in line with the NMR data and support the formation of the templated heterobidentate (**3(c + d)**) catalyst assembly under catalytic conditions, which is also the most selective of the series.



**Fig. 2** Preorganization of  $\text{HRh}(\text{CO})_2(\mathbf{a})(\mathbf{c})$  (left) and  $\text{HRh}(\text{CO})_2(\mathbf{c})_2$  (right) adjusting from the non-templated (green) to the templated (yellow) state.

Templated heterobidentate ligands were also formed by other ligand building blocks, as is clear from the catalysis results. For example, the bis-zinc(II)-salphen templated heterobidentate ligand (**3(c + a)**) provided a rhodium catalyst that gave the product with high enantioselectivity of 72% ee (entry 12), whereas the non-templated catalysts based on these ligands (entries 10 and 11) provide the product almost in racemic form. The combinations of **c/e**, **c/b**, **c/f** and **f/g** all gave similar enhanced enantioselectivities in the presence of the template (entries 15–18).<sup>7</sup> As predicted by the molecular modeling studies, the approach does not work for a combination of two sterically hindered ligands. For example, phosphite **d** and phosphoramidite **f** provide the product in low ee, also in the presence of a template (entry 19).<sup>9</sup>

**Table 1** Asymmetric Rh-catalyzed hydroformylation of styrene<sup>a</sup>

Entry	Ligands	Template	% conv. <sup>b</sup>	b/l <sup>c</sup>	% ee <sup>d</sup>
homocombinations					
1	<b>c/c</b>	—	< 1	—	—
2	<b>c/c</b>	<b>1</b>	< 1	—	—
3	<b>c/c</b>	<b>3</b>	< 1	—	—
4 <sup>e</sup>	<b>d/d</b>	—	> 99	12.2	11
5 <sup>e</sup>	<b>d/d</b>	<b>1</b>	> 99	12.5	11
6 <sup>e</sup>	<b>d/d</b>	<b>3</b>	> 99	13.5	13
heterocombinations					
7	<b>c/d</b>	—	> 99	12.0	10
8	<b>c/d</b>	<b>1</b>	> 99	12.3	10
9	<b>c/d</b>	<b>3</b>	66	9.90	55
10	<b>c/a</b>	—	33	8.02	0
11	<b>c/a</b>	<b>2</b>	20	8.40	4
12	<b>c/a</b>	<b>3</b>	19	9.20	72
13	<b>c/e</b>	—	28	7.56	0
14	<b>c/e</b>	<b>2</b>	21	9.26	6
15	<b>c/e</b>	<b>3</b>	20	8.21	55
16	<b>c/b</b>	<b>3</b>	12	3.92	57
17 <sup>f</sup>	<b>c/f</b>	<b>3</b>	2.0	4.20	61
18 <sup>f</sup>	<b>f/g</b>	<b>3</b>	1.3	4.20	53
19 <sup>f</sup>	<b>d/f</b>	<b>3</b>	84	16.0	6
20 <sup>g</sup>	<b>d/h</b>	—	97	11.3	3
21 <sup>g</sup>	<b>d/h</b>	<b>1</b>	93	12.4	3
22 <sup>g</sup>	<b>d/h</b>	<b>3</b>	21	5.30	4

<sup>a</sup>  $[\text{Rh}(\text{acac})(\text{CO})_2] = 1.0$  mmol/l in toluene, [phosphorus] = 10 mmol/l, styrene/rhodium = 1000, pressure = 20 bar ( $\text{CO}/\text{H}_2 = 1/1$ ), temperature = 40 °C. <sup>b</sup> Percentage conversion; the reaction was stopped after 87 h. <sup>c</sup> Ratio of branched to linear product. <sup>d</sup> In all cases the *S* enantiomer of the product was formed. <sup>e</sup> 16 h. <sup>f</sup> 20 h. <sup>g</sup> 48 h.

Remarkably, all ligands that gave high ee had at least one ligand with a  $R_2P-N(H)-R_1$  moiety. Control experiments with rhodium complexes based on a methylated phosphoramidite ligand **h** and a bulky phosphite ligand **d** (**ee**-isomer)<sup>10</sup> all gave low ee (templated or not), suggesting a non-innocent role for the N–H moiety (entries 20–22).<sup>7</sup>

To get more information on the structure of the complex formed under hydroformylation conditions we performed high-pressure IR and NMR spectroscopy studies. High-pressure IR data indicate the formation of the heteroligated  $HRh(CO)_2(3(c + d))$  complex in which both phosphorus donor atoms coordinate in the equatorial plane of the trigonal bipyramidal rhodium complex.<sup>7</sup> The IR spectrum shows two absorption bands for the carbonyl ligands at 2056 and 2008  $cm^{-1}$ , typical of an **ee** isomer.<sup>11</sup> In contrast, the non-templated mixed ligand combination showed the presence of various rhodium-complexes in the reaction mixture.<sup>7</sup> Additional support for the formation of the **ee**-isomer of  $HRh(CO)_2(3(c + d))$  complex was obtained from high-pressure NMR data<sup>7</sup> showing coupling constants of  $J\{Rh-P_c\} = 216$  Hz and  $J\{Rh-P_d\} = 253$  Hz, typical of a complex containing an equatorial amidite<sup>12</sup> and an equatorial phosphite<sup>13</sup> respectively. It was previously demonstrated that the coordination of the ligands in an **ee** disposition is an important prerequisite for the formation of (enantio)selective Rh-catalysts.<sup>14</sup> These templated heterobidentate ligands coordinating in a **ee**-fashion are a promising class of ligands through variation of the substituents in the equatorial plane.

In summary, we have shown, for the first time, a template-induced selective formation of a chelating heterobidentate ligand. This heterobidentate ligand is formed by self-assembly of two different monodentate ligands on a bis-zinc(II)-salphen template molecule that contains two identical binding sites. These templated heterobidentate ligands gave rise to catalysts that provided much higher enantioselectivities (up to 72% ee) in the asymmetric rhodium catalyzed hydroformylation of styrene than any of the corresponding homobidentate ligands or non-templated mixed ligand combinations (up to 13% ee). With the experiments described herein we have introduced a new method for the easy preparation of heterobidentate ligands that can be used for asymmetric catalysis. We are currently exploring this strategy in a combinatorial fashion for various asymmetric transformations.

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