Supraphos: A Supramolecular Strategy To Prepare Bidentate Ligands

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Bidentate chelating ligands comprise an important class of compounds for the construction of transition metal catalysts.[1] As compared to monodentate ligands,[2] however, the synthesis is generally more complex and time-consuming. This is especially inconvenient for reactions that need intensive ligand-optimization. Methodologies that enable the synthesis of sufficiently large libraries of bidentate phosphorus containing ligands are scarce,[3] and new strategies are required to prepare diverse catalyst libraries that can be used for high throughput experimentation.[4] Here, we report a supramolecular strategy to make bidentate ligands that involves simple mixing of monomeric ligands. A small combinatorial[5] library is used in the palladium-catalyzed allylic alkylation, yielding up to 97% ee.

Traditionally, bidentate ligands are prepared by attaching donor atoms to a ligand backbone. We anticipated that monodentate ligands functionalized with complementary binding motifs could form bidentate ligands by self-assembly (Figure 1). We have shown previously[6] that zinc(II) porphyrins and nitrogen donor ligands form a complimentary motive that is suited for this purpose because the binding is sufficiently strong and selective.[7] For the current project, we prepared six phosphite-functionalized porphyrins (**1**−**6**) that in combination with eight monodentate phosphorus ligands (**b**−**i**) give a library of 48 chelating ligands formed by assembly.

Before studying the ligand library in catalysis, we investigated the coordination behavior of the supramolecular ligands using bidentate ligand **1·b** as a typical example.[8] UV−vis titrations and NMR spectroscopy experiments show that the pyridyl moiety of **b** coordinates to zinc(II) porphyrin **1** selectively with a binding constant in the expected range ($K_{(1·b)} = 3.8 \times 10^3$ M^{-1}). The chelating behavior was proven by the increase in the association constant of **1·b** observed in the presence of [HRh(**a**)$_3$(CO)] ($K = 64.5 \times 10^3$ M^{-1}), corresponding to a chelate effect of 7 kJ/mol.[9]
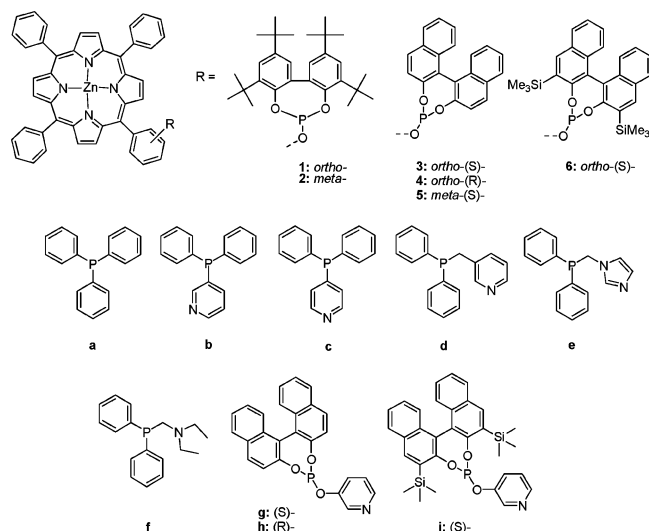
The rhodium carbonyl hydride complex HRh(CO)$_2$(**1·b**) ($\delta = -10.6$ ppm) formed by ligand **1·b** was studied with high-pressure
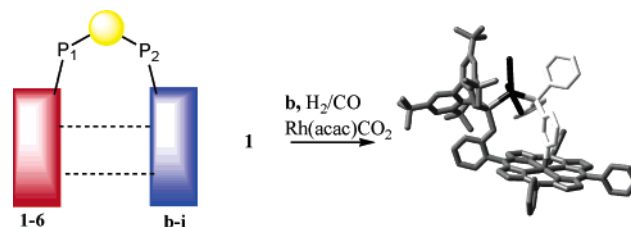

Figure 1. A schematic representation of the supramolecular strategy to form bidentate ligands by assembly and a modeled structure of a rhodium complex [HRh(CO)$_2$(**1·b**)] based on such a bidentate assembly.
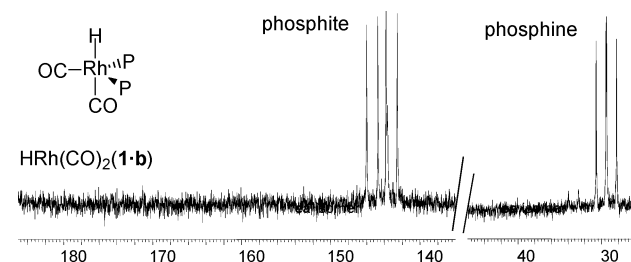
Figure 2. High-pressure ^{31}P NMR spectrum of [HRh(CO)$_2$(**1·b**)] in toluene-d_8.

NMR-spectroscopy in toluene-d_8 under 20 bar of H$_2$/CO. The ^{31}P{^{1}H} NMR spectrum appeared as two doublets of doublets ($\delta = 29.4$ and 144.3 ppm, $J_{Rh-P} = 143$ Hz, $J_{Rh-PO3} = 265$ Hz, $J_{P-PO3} = 153$ Hz) (Figure 2), showing that ligand **1·b** coordinates in a bidentate fashion. These coupling constants indicate that the ligand assembly **1·b** coordinates in an equatorial−equatorial fashion to the rhodium metal center. Importantly, the presence of triphenylphosphine **a** did not influence the formation of this complex, and the addition of **b** to a solution of HRh(CO)$_2$(**1**)PPh$_3$ resulted in the formation of the same complex [HRh(CO)$_2$(**1·b**)], evidencing the chelating behavior of the ligand assembly. The chelating behavior was also reflected in catalysis; in the rhodium-catalyzed hydroformylation[10] of styrene, supramolecular ligand **1·b** shows an increase in selectivity for the branched product (b/l = 10) and a decrease in activity (TOF = 398) of the catalyst as compared to **1** (TOF = 2900, b/l = 2.6). These experiments show that via selective pyridine−zinc interactions two monodentate phosphorus ligands form a chelating bidentate ligand assembly.

The supramolecular ligand library based on monodentate phosphorus ligands **a**−**i** and **1**−**6** was tested in the palladium-catalyzed asymmetric allylic alkylation[11] of *rac*-1,3-diphenyl-2-propenyl acetate using dimethyl malonate as the nucleophile. The matrix of the supramolecular bidentate ligands gave rise to a catalyst library of 60 members just from the mixing of stock solutions of the 16 monodentate ligands. For the tested catalysts, the enantiomeric excess ranged from 85% (*S*) to 86% (*R*) (Table 1). Importantly, the ee depends strongly on the ligand assembly used, both of the components being important.

Table 1. Allylic Alkylation of 1,3-Diphenylallyl Acetate and Dimethyl Malonate at $T = 25\ °C$ Using Different Palladium Catalyst Assemblies: Enantiomeric Excesses Are Given[a]

ligand	1	2	3	4	5	6
	0	0	85 (S)	86 (R)	20 (S)	48 (R)
a	0	0	0	0	0	0
b	0	0	47 (R)	47 (S)	59 (S)	17 (R)
c	0	0	0	0	0	0
d	0	0	40 (S)	38 (R)	11 (R)	33 (S)
e	0	0	23 (S)	23 (R)	10 (S)	5 (S)
f	0	0	4 (S)	3 (R)	22 (R)	0
g	40 (S)	36 (S)	45 (S)	45 (R)	37 (S)	40 (S)
h	40 (R)	34 (R)	42 (S)	43 (S)	43 (S)	39 (R)
i	28 (S)	28 (S)	11 (S)	10 (R)	27 (S)	28 (S)

[a] [[Pd(allyl)Cl]$_2$] = 0.1 mmol/L, [**1−6**] = 0.6 mmol/L, [**a−i**] = 0.6 mmol/L, the reaction was stopped after 24 h, $T = 25\ °C$, complete conversion was obtained in all cases.

Table 2. Allylic Alkylation of 1,3-Diphenylallyl Acetate at $T = -20\ °C$ Using Different Palladium Catalyst Assemblies[a]

ligand	conv. (%)	ee[b] (%)	ligand	conv. (%)	ee[b] (%)
3	56	97 (S)	**4**	54	96 (R)
3·b	100	60 (R)	**4·b**	100	60 (S)
3·c	100	0	**5**	73	42 (S)
3·d	100	44 (S)	**5·b**	40	70 (S)

[a] See Table 1 for conditions. [b] ee = enantiomeric excess.

Upon using (S)-*ortho* **3** as a monodentate ligand, we observed an unexpected high ee (85%, S), because only a few monodentate ligands are known to give high ee for this reaction.[2c] The (S)-*meta* **5** resulted in a much lower selectivity (20% ee, S). Interestingly, bidentate ligand assembly **3·b** gave the enantiomeric product (47% ee, R) opposite to that of monodentate **3**, probably because in this system the attack of the nucleophile is trans to the phosphine ligand,[12,13] while bidentate ligand assembly **5·b** gave a higher ee of the same product as **5** (59% ee, S). Another remarkable result is that obtained with bulky phosphite **6**, which preferentially gives an enantiomeric product other than **3** (48% ee, R). However, in the presence of co-ligand (**b, d, e, f, g, h**) forming a chelating bidentate, it does give the same enantiomer as do the analogue assemblies based on **3**. As expected, optically inactive **1** and **2** gave ee (up to 40%) only in combination with chiral building blocks **g−i**. It is interesting to note that all reactions in the presence of triphenyl-phospine (**a**) gave no ee, indicating that the catalysis is dominated by palladium triphenylphosphine species. This clearly shows the importance of the chelate effect induced by the binding motif.

From the initial screening experiments, some "hits" were identified, and these catalyst systems were subsequently studied at −20 °C. Under these conditions, the palladium catalyst based on **3** gave a very high enantioselectivity (97% (S)) (Table 2). The catalyst based on ligand assembly **3·b** gave under these conditions an enantiomeric excess of 60% (R).[14] The assembly **3·b** proved to be more active than the catalyst based on **3**, because the yield after 24 h was 100% as compared to 56%. The catalyst based on the bidentate assembly **3·d** resulted in the formation of the S-product with an enantiomeric excess of 44%. Similar to that previously found for covalently linked phosphine−phosphite ligands,[13] a small difference in the length of the bridge between the phosphine and phosphite resulted in a large difference in enantioselectivity (**3·b** 60% (R) and **3·d** 44% (S)). At −20 °C, ligand **5** resulted in a catalyst that produces 42% ee (S), whereas the bidentate assembly **5·b** resulted in 70% ee (S). In this case, the assembly **5·b** gave a slightly slower catalyst (40% yield as compared to 73% for **5**). Importantly, small changes in the assembly of the phosphite zinc(II) porphyrin and the phosphorus ligands **a−i** have a large influence on the enantioselectivity as well as the activity of the catalyst system. The

diversity of the relatively small supramolecular catalyst library is already sufficient to give catalysts with selectivities ranging from 70% (S) to 60% (R), and, unexpectedly, monomer ligand **3** resulted even in 97% ee.

In conclusion, a new strategy for the preparation of chelating bidentate ligands is presented. It involves mixing of two mono-dentate ligands functionalized with complementary binding sites. In the current example, the assembly process is based on selective metal−ligand interactions, using phosphite zinc(II) porphyrins **1−6** and the nitrogen donor ligands **b−i**. From only 16 monodentate ligands, a library of 60 palladium catalysts based on 48 bidentate ligand assemblies has been prepared. The relatively small catalyst library gave a large variety in the selectivity of the alkylation of *rac*-1,3-diphenyl-2-propenyl acetate. So far, we only used phosphite zinc(II) porphyrin **1−6** and monodentate ligands **a−i**, but many other (a)chiral building blocks can be used for the ligand assemblies including those based on hydrogen bonds.[15]

Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Chaloner, P. A.; Esteruelas, M. A.; Joo', F.; Oro, L. A. *Homogeneous Hydrogenation*; Kluwer: Dordrecht, 1994. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 5.1. (c) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*; Wiley: New York, 1992. (d) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.

(2) (a) Komarov, I. V.; Borner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197. (b) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539. (c) Hayashi T. *Acc. Chem. Res.* **2000**, *33*, 354.

(3) Hu, J.-B.; Zhao, G.; Ding, Z.-D. *Angew. Chem., Int. Ed.* **2001**, *40*, 1109.

(4) (a) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677. (b) Harris, R. F.; Natio, A. A. J.; Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 11270. (c) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123. (d) Yue, T.-Y.; Nugent, W. A. *J. Am. Chem. Soc.* **2002**, *124*, 13692. (e) Reetz, M. T.; Kuhling, K. M.; Deege, A.; Hinrichs, H.; Belder, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 3891. (f) Reetz, M. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1335. (g) Vries, de J. G.; Vries, de A. H. M. *Eur. J. Org. Chem.* **2003**, 799. (h) Stauffer, S. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 6977.

(5) (a) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790. (b) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284. (c) Reetz, M. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1335. (d) Taylor, S. J.; Morken, J. P. *Science* **1998**, *280*, 267. (e) Francis, M. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 937 (f) Crabtree, R. H. *Chem. Commun.* **1999**, 1611. (g) Francis, M. B.; Jamison, T. F.; Jacobsen, E. N. *Curr. Opin. Chem. Biol.* **1998**, *2*, 422.

(6) (a) Slagt, V. F.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4271. (b) Slagt, V. F.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5619. (c) Slagt, V. F.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Commun.* **2003**, 2474. (d) Slagt, V. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2004**, *126*, 1526.

(7) Phosphorus donor atoms do not coordinate to the zinc(II) porphyrin.

(8) Bidentate ligand assembly **2·b** gave similar results.

(9) In this competition experiment, the chelate effect appears as an increase in the binding constant in the presence of the rhodium complex; see Supporting Information.

(10) *Rhodium-catalyzed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C., Eds.; Kluwer Academic Publishers: Dordrecht, 2000.

(11) (a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (d) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(12) Prétot, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323.

(13) Deerenberg, S.; Schrekker, H. S.; van Strijdonck, G. P. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K. *J. Org. Chem.* **2000**, *65*, 4810.

(14) The enantioselectivity did not change in the presence of excess **b**.

(15) Breit, B.; Seiche, W. *J. Am. Chem. Soc.* **2003**, *125*, 6608.

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