Pure Appl. Chem., Vol. 80, No. 5, pp. 855–860, 2008.
doi:10.1351/pac200880050855

Catalysts through self-assembly for combinatorial homogeneous catalysis*

Bernhard Breit‡

Institute for Organic Chemistry and Biochemistry, Albert-Ludwigs-Universität Freiburg, Albertstrasse 21, 79104 Freiburg, Germany

Abstract: Inspired by the principle of DNA base-pairing, a new concept for the self-assembly of molecular catalysts is described herein. Thus, employing A–T analogous complementary hydrogen-bonding templates, self-assembly of monodentate to bidentate ligands in the coordination sphere of a transition-metal salt occurs to give defined self-assembly catalysts. This approach is intrinsically combinatorial and allows the facile generation of defined catalyst libraries through simple component mixing. From the study of these ligand libraries, excellent catalysts for linear-selective hydroformylation, asymmetric hydrogenation, and *anti*-Markovnikov hydration of terminal alkynes have emerged.

Keywords: homogeneous catalysis; supramolecular chemistry; self-assembly; hydroformylation; asymmetric hydrogenation.

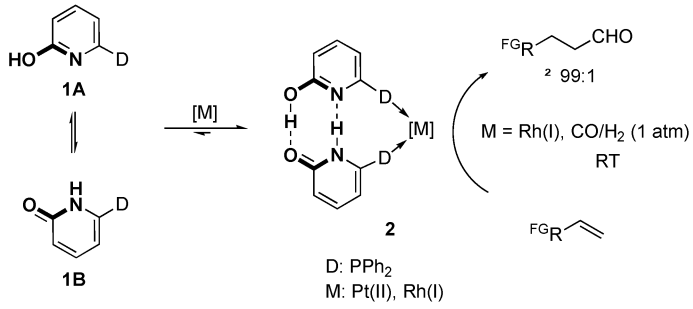
The evolution of modern homogeneous catalysis is driven by the quest for higher efficiency and selectivity. While enzymes are highly substrate-specific, their scope is limited. Synthetic catalysts are of particular interest because of their potential for a broader range of substrates and conditions. However, in both fields no general catalyst giving optimal results for all kinds of substrates is available. Hence, to achieve the desired selectivity for a catalytic reaction of interest, the catalyst must be optimized and adjusted to the particular problem. Especially in the field of metal-complex catalysis, the choice of the right ligand, which shapes the microenvironment at the catalytically active metal center, is crucial. However, despite significant progress in the field of theoretical and computational chemistry, there is no rational way to model from scratch the best ligand for a given reaction and selectivity problem. For this reason, combinatorial approaches have emerged in order to accelerate the catalyst discovery process [1]. However, this approach still suffers from the limited access toward structurally diverse and meaningful ligand libraries. The problem is particularly acute for the important class of bidentate ligands, for which ligand synthesis in many cases involves nontrivial synthetic operations which 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, and as an alternative to the classical bidentate ligand synthesis, the principle of self-assembly of monodentate to bidentate ligands relying on complementary noncovalent interligand interactions has been introduced by us [2] and others [3]. Our investigations have shown that systems which self-assemble through complementary hydrogen bonding are of particular use in homogeneous catalysis, and the results of these studies are summarized herein.

---

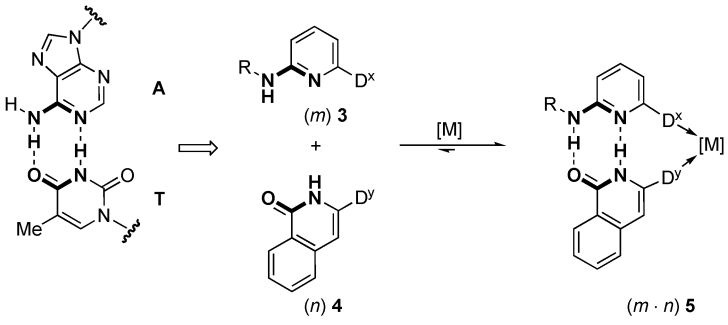
*Paper based on a presentation at the 14th International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-14), 2–6 August 2007, Nara, Japan. Other presentations are published in this issue, pp. 807–1194.
‡Fax: +49 761 203 8715; E-mail: bernhard.breit@organik.chemie.uni-freiburg.de

We recently showed that 6-diphenylphosphinopyridone **1B** self-assembles in the presence of a transition-metal salt with its tautomer **1A** to give complex **2** (Scheme 1) [2a]. The bidentate nature of **1** in these complexes has been proved in solution (NMR) as well as in the solid state (X-ray). Interestingly, Rh complexes derived from **1** displayed excellent regioselectivity and activity upon hydroformylation of terminal alkenes. Furthermore, these catalysts allowed the first room-temperature, ambient-pressure regioselective hydroformylation of a wide range of functionalized terminal alkenes, which is of particular use to synthetic organic chemistry [4].



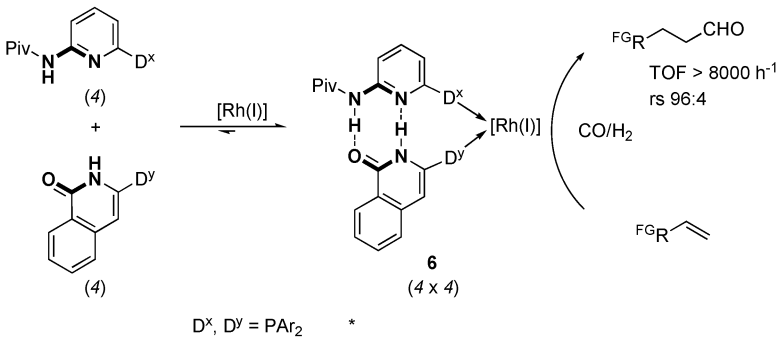
Scheme 1 Concept of self-assembly of monodentate to bidentate ligands through hydrogen bonding on the basis of the 6-diphenylphosphanyl-2(1*H*)-pyridone/2-hydroxypyridine (**1**) tautomer system.

The advantage of the self-assembly approach is its inherent possibility for combinatorial ligand library generation through mixing of two different ligands. However, since both tautomers of **1**—the hydroxypyridine **1A** and the pyridone **1B**—are energetically almost equivalent and show rapid equilibration, mixing of two different ligands **1** would furnish a mixture of the two homodimeric and the heterodimeric ligand complex. In order to generate selectively the unsymmetrical heterodimeric ligand, a complementary self-assembly platform based on the Watson–Crick base-pairing of A and T in DNA has been developed (Scheme 2) [5]. As an A–T base pair analog, the 2-aminopyridine (**3**)/isoquinolone (**4**) platform proved well suited. Thus, mixing of two monodentate ligands based on this platform in the presence of a transition-metal salt led to the selective formation of the heterodimeric complexes **5** featuring a bidentate coordination mode as proved by NMR and X-ray diffraction analysis [5].



Scheme 2 An A-T base pair model as a complementary platform for specific self-assembly of heterodimeric bidentate ligands.

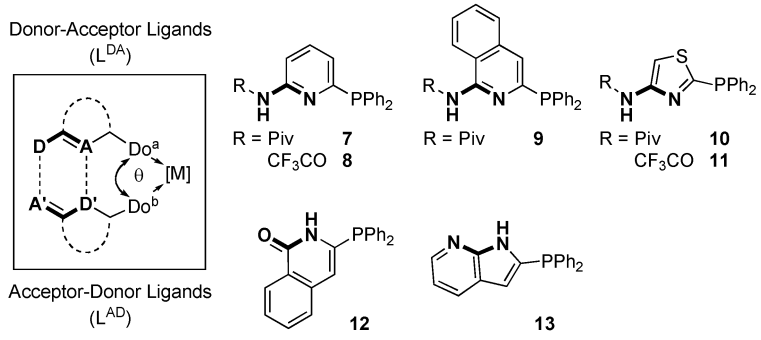
On the basis of this platform, the first 4 × 4 self-assembled ligand library relying on hydrogen bonding was generated and explored for regioselective hydroformylation of terminal alkenes (exem-



Scheme 3 Evaluation of a 4 × 4 ligand matrix of aminopyridine/isoquinolone-derived self-assembled bidentate ligands in the [Rh]-catalyzed hydroformylation of 1-octene.

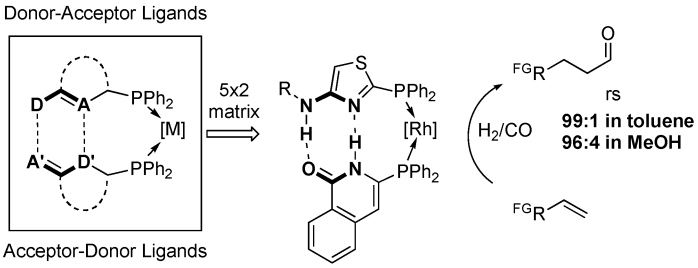
plarily for 1-octene). This study allowed us to identify a catalyst (**6**) which operated with truly outstanding activity (TOF > 8000 h^{-1}) and regioselectivity (96:4, Scheme 3) [5].

We next explored whether this approach is restricted to the aminopyridine/isoquinolone self-assembly system or whether indeed a second variation site could stem from variation of the A–T base pair analogous platform (Scheme 4) [6]. It was reasonable to expect that any change of platform geometry as well as the nature of the hydrogen-bonding system should have an immediate impact on the ligand bite angle (θ) and coordination geometry at the metal, and thus, should have an important influence on performance in catalysis.



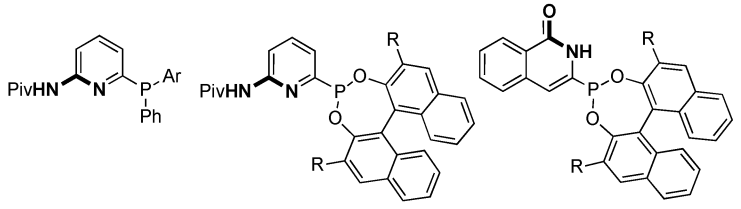
Scheme 4 Library of ligands with complementary hydrogen-bonding motifs.

Thus, heterocycle-functionalized phosphine ligands **7–13** were prepared and the coordinating properties were studied. In all possible combinations of donor–acceptor ligands (**7–11**) and acceptor–donor ligands (**12**, **13**), the formation of heterodimeric metal complexes via self-assembly through complementary hydrogen bonding was observed. The resulting Rh catalysts proved very active and regioselective in the course of the hydroformylation of alkenes. Most interestingly, the thiazole/isoquinolone system proved stable even in polar protic solvents such as methanol (Scheme 5) [6].



Scheme 5 Evaluation of a 5 × 2 ligand matrix of A–T-analogous self-assembly ligands in the [Rh]-catalyzed hydroformylation of 1-octene using toluene and MeOH as solvents.

In order to control enantioselectivity in a catalytic reaction, chirality information has to be installed into the catalyst. As such, we prepared a library of chiral ligands based on the aminopyridine/isoquinolone platform [7]. The chiral information was introduced at the donor sites employing either chiral phosphines **14a–c** or phosphonite systems **15a–c** and **16a**,**b** (Scheme 6).



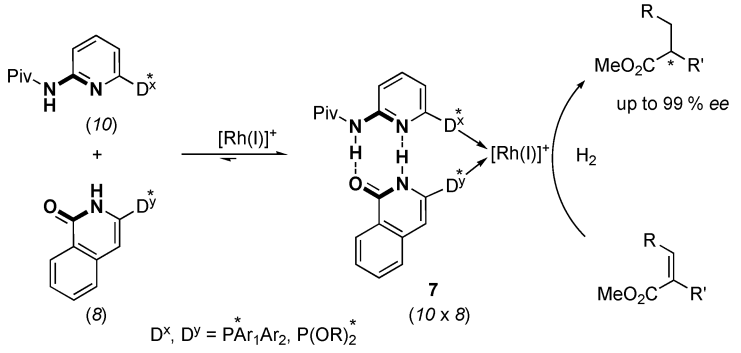
(–)-**14a**: Ar = *o*-Anisyl
(+)-**14a**: Ar = *o*-Anisyl
(–)-**14b**: Ar = 1-Naphthyl
(+)-**14b**: Ar = 1-Naphthyl
(–)-**14c**: Ar = *o*-Tol
(+)-**14c**: Ar = *o*-Tol

(*S*)-**15a**: R = H
(*S*)-**15b**: R = Me
(*S*)-**15c**: R = p-Tol

(*S*)-**16a**: R = H
(*R*)-**16a**: R = H
(*S*)-**16b**: R = Me

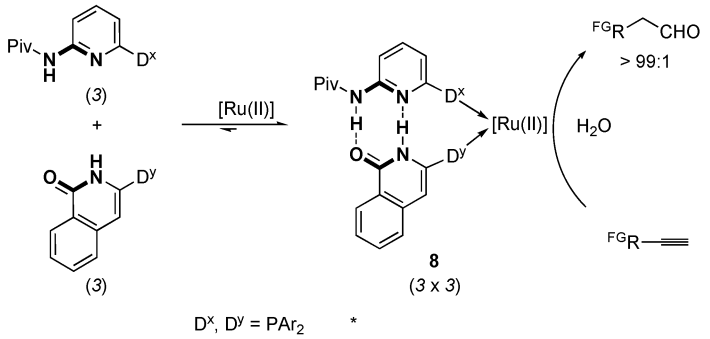
Scheme 6 Selected self-assembly phosphine and phosphonite ligands.

We evaluated a 10 × 8 chiral ligand library in the course of the Rh-catalyzed asymmetric hydrogenation of itaconate and *N*-acetacrylates. From these studies, bidentate ligand combinations of phosphine/phosphonites as well as diphosphonite systems were identified, which furnished excellent catalysts performing with enantioselectivities of up to 99 % ee and quantitative conversion at substrate/catalyst ratios as low as 1000:1 (Scheme 7) [7].



Scheme 7 Evaluation of a 10 × 8 ligand matrix of chiral self-assembly ligands in the Rh-catalyzed asymmetric hydrogenation.

In addition to a square planar coordination geometry, the A–T-analogous self-assembly platform can accomodate a piano stool arrangment as found in the corresponding cationic diphosphine ruthenium phosphine complexes [8]. Such complexes have been recently identified to be good catalysts for an unusual *anti*-Markovnikov hydration of terminal alkynes. Interestingly, the self-assembly ruthenium catalyst turned out to be an efficient catalyst for this reaction. A wide range of functionalized terminal alkynes could be transformed into the corresponding aldehydes in good yield and excellent chemoselectivity (Scheme 8) [8].



Scheme 8 Evaluation of a 3 × 3 ligand matrix of self-assembly phosphine ligands in the Ru-catalyzed *anti*-Markovnikov hydration of terminal alkynes.

Preliminary, theoretical investigations indicate that the hydrogen-bonding network of the ligand might be involved in water binding and activation toward a nucleophilic attack. Further investigations to clarify this issue are underway.

In conclusion, the self-assembly concept of monodentate to bidentate ligands has become a very promising approach to the combinatorial generation of novel ligand libraries. From these studies, excellent catalysts for regioselective hydroformylation, enantioselective hydrogenation, as well as *anti*-Markovnikov hydration of terminal alkynes have emerged.

ACKNOWLEDGMENTS

This work has been supported by the Fonds der Chemischen Industrie, the DFG (International Graduate School *Catalysts and Catalytic Reactions for Organic Synthesis*, GRK 1038), the Alfried Krupp Award for young university teachers of the Krupp foundation (to BB), and BASF AG.

REFERENCES

1. C. Gennari, U. Piarulli. *Chem. Rev.* **103**, 3071 (2003).
2. (a) B. Breit, W. Seiche. *J. Am. Chem. Soc.* **125**, 6608 (2003); (b) B. Breit, W. Seiche. *Pure Appl. Chem.* **78**, 249 (2006).
3. For a review on alternative approaches to self-assembled ligand/catalyst libraries, see: (a) B. Breit. *Angew. Chem., Int. Ed.* **44**, 6816 (2005); see also (b) J. M. Takacs, D. S. Reddy, S. A. Moteki, D. Wu, H. Palencia. *J. Am. Chem. Soc.* **126**, 4494 (2004); (c) V. F. Slagt, M. Röder, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek. *J. Am. Chem. Soc.* **126**, 4056 (2004); (d) V. F. Slagt, P. W. N. M. van Leeuwen, J. N. H. Reek. *Angew. Chem., Int. Ed. Engl.* **42**, 5619 (2003); (e) V. F. Slagt, P. W. N. M. van Leeuwen, J. N. H. Reek. *Chem. Commun.* 2474 (2003); (f) K. Ding, H. Du, Y. Yuan, J. Long. *Chem.—Eur. J.* **10**, 2872 (2004); (g) A. J. Sandee, A. M. v. d.

Burg, J. N. H. Reek. *Chem. Commun.* 864 (2007); (h) H. Gulyás, J. Benet-Buchholz, E. C. Escudero-Adan, Z. Freixaa, P. W. N. M. van Leeuwen. *Chem.—Eur. J.* **13**, 3424 (2007).
4. W. Seiche, A. Schuschkowski, B. Breit. *Adv. Synth. Catal.* 1488 (2005).
5. B. Breit, W. Seiche. *Angew. Chem., Int. Ed.* **44**, 1640 (2005).
6. C. Waloch, J. Wieland, M. Keller, B. Breit. *Angew. Chem., Int. Ed.* **46**, 3037 (2007).
7. M. Weis, C. Waloch, W. Seiche, B. Breit. *J. Am. Chem. Soc.* **128**, 4188 (2006).
8. F. Chevallier, B. Breit. *Angew. Chem., Int. Ed.* **45**, 1599 (2006).