Asymmetric Catalysis Using Self-Assembled Chiral Bidentate *P,P*-Ligands

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The need for advances in asymmetric catalysis fuels the search for new ligand and catalyst designs, especially those using combinatorial and modular approaches.[1] Recently, several reports have appeared wherein self-assembly is used to generate novel bidentate ligands[2−7] and catalyst systems.[8−10] We now report a remarkably effective strategy for modular catalyst development based upon self-assembly of bifunctional subunits around a structural metal to form a heteroleptic complex in which a second set of ligating groups are now suitably disposed to bind a second metal to form a catalytic site (Figure 1). Most modular approaches to ligand design attach ligating groups as substituents to a preformed backbone template. Here, metal-directed self-assembly generates the backbone as the final step and, as such, offers the opportunity to rapidly assemble a diverse set of backbones and more thoroughly explore and exploit the influence of template structure.

Mixing a "racemic mixture" of monosubstituted bisoxazoline (box) ligands (e.g., (*S*,*S*)- and (*R*,*R*)-**1**) with Zn(OAc)$_2$ results in the rapid formation of a neutral (box)$_2$Zn complex. While three 2:1 complexes are possible, two homoleptic and one heteroleptic, the tetrahedral coordination geometry of zinc(II) favors the heteroleptic complex **2**, and only the latter is observed in solution by NMR analysis or upon crystallization (Figure 2). These (box)$_2$Zn complexes are proving to be quite remarkable compounds and provide an extraordinarily simple, efficient method to prepare new chiral bidentate *P,P*-ligands.

A series of monosubstituted box derivatives were prepared, each member bearing a pendant TADDOL-derived monophosphite[11] (Figure 3, **3A−M**). The synthetic route is straightforward, the key step being mono-alkylation[12] of the box subunit with a substituted benzyl bromide bearing a pendant silyl-protected hydroxyl substituent. Deprotection of the silyl ether followed by phosphorylation with ((*R*,*R*)-TADDOL)PCl[13] affords the desired box-(TADDOL)-phosphite conjugate **3**.

Treating complementary combinations of the bifunctional ligands in Figure 3 with Zn(OAc)$_2$ provides a simple way to prepare a library of new heteroleptic (box)$_2$Zn complexes bearing two free chiral phosphite moieties.[14] For example, the combination of (*S*,*S*)-**3F** and (*R*,*R*)-**3F** affords the pseudo-*C*$_2$-symmetric diphosphite **4FF** (Figure 4). Mass spectral and NMR data support the structural assignment. The ^{31}P NMR spectrum of **4FF** shows a single resonance at 130.2 ppm, similar to that of the precursor (*S*,*S*)-**3F** (130.7 ppm). To test whether the pendant phosphites can coordinate a second metal, **4FF** was treated with an equivalent of [(cod)$_2$Rh]BF$_4$. The ^{31}P NMR signal at 130.2 ppm is lost and a new doublet appears at 112.7 ppm ($J_{Rh,P}$ = 248.6 Hz),[15] consistent with the formation of a chiral heterobimetallic complex with rhodium.[16]

Preferential formation of the heteroleptic (box)$_2$Zn complex is driven by the complementary chirality of the box subunits and is largely independent of the nature of the remote substituents on the box ligand. We prepared 50 combinations of SAL **4** from subunits
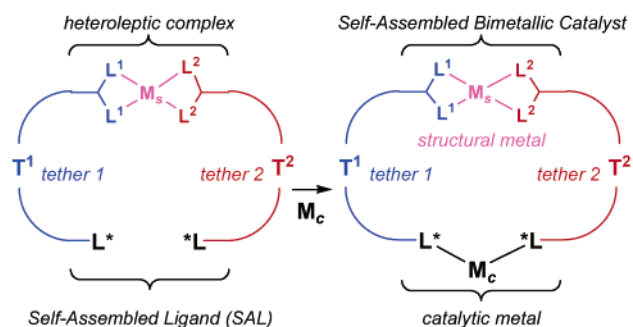

Figure 1. Metal-directed self-assembly of bimetallic catalysts incorporating structural (M$_s$) and catalytic metals (M$_c$).
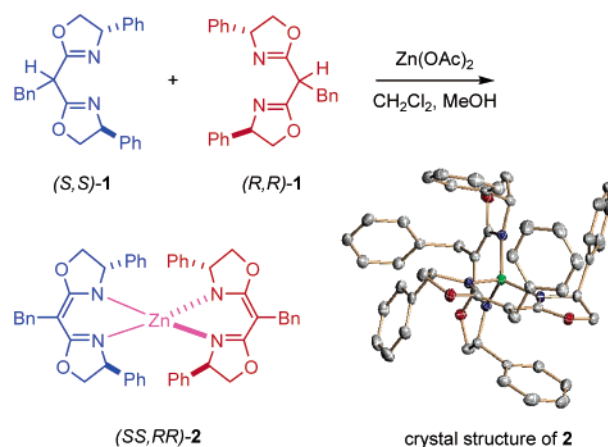

Figure 2. Preparation and crystal structure of (box)$_2$Zn complex **2**.

3A−M and screened them in the palladium-catalyzed asymmetric allylic amination[17−21] of racemic carbonate **5** with *N*-methyl-*p*-toluenesulfonamide. Chiral diphosphites have been employed in a wide range of asymmetric reactions, including palladium-catalyzed allylations;[22] the latter are frequently used as a testing ground for new chiral ligand motifs.

The chiral diphosphites screened differ only in the structure of the ligand backbone, and while each gives predominantly (*R*)-**6** (R = Me), the variation in enantioselectivity is striking. As Figure 5 illustrates, the enantiomeric excess varies quite smoothly over a wide range, 20−97% ee, as a function of the combination of subunits **A−M** employed. The striking variations in enantiomeric excess demonstrate the ability to employ very subtle changes in the structural backbone to manipulate the ligand topography around palladium. For reference, the corresponding amination using ((*R*,*R*)-TADDOL)POPh gives (*R*)-**6** (R = Me) in 48% ee.

Nine combinations of **4** effect the asymmetric allylation in 90% ee or higher (Table 1). Each contains one of two closely related subunits, **F** or **H**. The most successful ligand, **4FH**, contains both and affords **6** (R = Me) in 97% ee (entry 1). Surprisingly, the
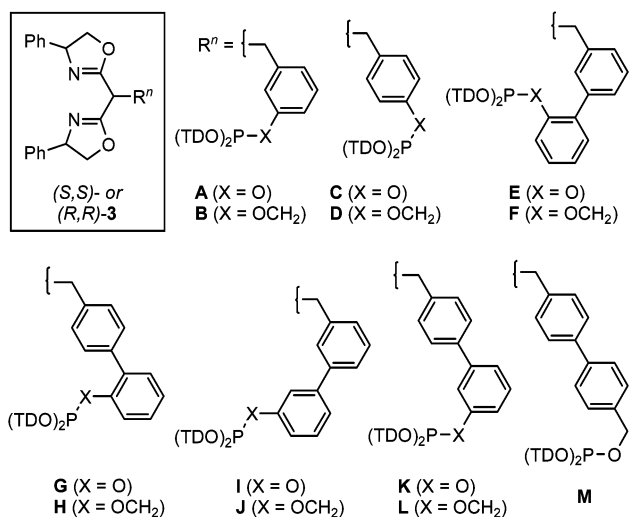
Figure 3. Series of bifunctional box-(TADDOL)phosphite conjugates, **3A−M** ((TDO)$_2$ = (R,R)-TADDOL), used to prepare chiral diphosphites.
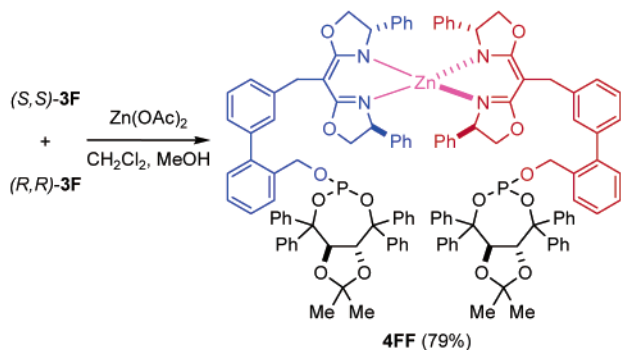

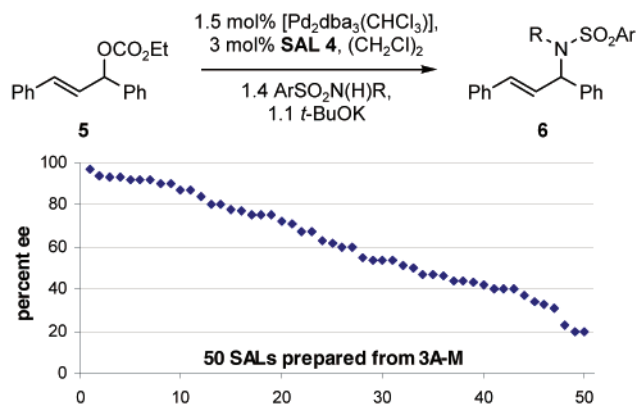**Figure 4.** Preparation of the chiral diphosphite **4FF**.

Figure 5. Remarkable variation in enantioselectivity from a series of 50 closely related SALs **4** in the allylic amination to form **6** (R = Me).

pseudo-C_2-symmetric derivatives, **4FF** and **4HH**, are less effective, giving 84 and 87% ee, respectively (entries 10 and 12). Chiral diphosphites **4FF**, **4FH**, and **4HH** were screened with a selection of other N-substituted sulfonamides, giving **6** in 88−95% ee (entries 15−18).

In summary, a library of chiral diphosphites was prepared via metal-directed self-assembly and used in a simple asymmetric allylation reaction. The chiral heterobimetallic catalysts employ zinc as an important structural element and palladium as a catalytic metal and offer a remarkably flexible and effective approach to catalyst design. Further studies are in progress.

Table 1. Partial Summary of Screening SALs **4** in the Palladium-Catalyzed Allylic Amination Reaction of **5** with TsN(H)R

entry	R in TsN(H)R	SAL 4	% yield	% ee
1	Me	**FH**	82	97
2	Me	**FM**	88	94
3	Me	**FJ**	74	93
4	Me	**HJ**	85	93
5	Me	**HL**	85	92
6	Me	**FL**	81	92
7	Me	**EH**	80	92
8	Me	**HM**	86	90
9	Me	**GH**	84	90
10	Me	**HH**	88	87
11	Me	**FG**	83	87
12	Me	**FF**	84	84
13	Me	**EF**	77	80
14	Me	**FI**	80	80
15	n-Bu	**FF**	83	90
16	Bn	**FH**	95	91
17	i-Pr	**HH**	74	95
18	Ph	**FF**	92	88

Supporting Information Available: Experimental details for **4FF**, **6**, and the crystal structure of **2** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Gennari, C.; Piarulli, U. *Chem. Rev.* **2003**, *103*, 3071−3100.
(2) Slagt, V. F.; Van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Commun. (Cambridge)* **2003**, 2474−2475.
(3) Braunstein, P.; Clerc, G.; Morise, X.; Welter, R.; Mantovani, G. *Dalton Trans.* **2003**, 1601−1605.
(4) Braunstein, P.; Clerc, G.; Morise, X. *New J. Chem.* **2003**, *27*, 68−72.
(5) Breit, B.; Seiche, W. *J. Am. Chem. Soc.* **2003**, *125*, 6608−6609.
(6) Jiang, H.; Hu, A.; Lin, W. *Chem. Commun. (Cambridge, U.K.)* **2003**, 96−97.
(7) Lee, S. J.; Hu, A.; Lin, W. *J. Am. Chem. Soc.* **2002**, *124*, 12948−12949.
(8) Gianneschi, N. C.; Bertin, P. A.; Nguyen, S. T.; Mirkin, C. A.; Zakharov, L. N.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 10508−10509.
(9) Mikami, K.; Matsukawa, S.; Volk, T.; Terada, M. *Angew. Chem., Int. Ed.* **1998**, *36*, 2768−2771.
(10) Mikami, K.; Tereda, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angeluad, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532−3556.
(11) Seebach, D.; Hayakawa, M.; Sakaki, J.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711−1724.
(12) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2001**, 1045−1048.
(13) Kranich, R.; Eis, K.; Geis, O.; Muhle, S.; Bats, J. W.; Schmalz, H.-G. *Chem.−Eur. J.* **2000**, *6*, 2874−2894.
(14) The mixture is stirred briefly (ca. 10 mn) and then concentrated to dryness, and the residue is triturated and washed with methanol.
(15) A set of partially resolved overlapping doublets separated by approximately 20 Hz can be discerned in the expanded spectrum.
(16) Pamies, O.; Net, G.; Ruiz, A.; Claver, C. *Eur. J. Inorg. Chem.* **2000**, 1287−1294.
(17) Hamada, Y.; Seto, N.; Takayanagi, Y.; Nakano, T.; Hara, O. *Tetrahedron Lett.* **1999**, *40*, 7791−7794.
(18) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905−7920.
(19) Pamies, O.; van Strijdonck, G. P. F.; Dieguez, M.; Deerenberg, S.; Net, G.; Ruiz, A.; Claver, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Org. Chem.* **2001**, *66*, 8867−8871.
(20) Agarkov, A.; Uffman, E. W.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 2091−2094.
(21) Vasse, J.-L.; Stranne, R.; Zalubovskis, R.; Gayet, C.; Moberg, C. *J. Org. Chem.* **2003**, *68*, 3258−3270.
(22) Ansell, J.; Wills, M. *Chem. Soc. Rev.* **2002**, *31*, 259−268.

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