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Inducing Enantioselectivity in a Dynamic Catalyst by Supramolecular Interlocking

Jan Felix Scholtes[a,b] and Oliver Trapp*[a,b]

Abstract: *Supramolecular ligands offer a variety of possibilities to control selectivity in catalysis due to their non-covalent interactions with other molecules. Conceptionally, enantioselectivity can be induced by interaction of chiral additives or products with the interaction sites of a supramolecular catalyst. However, the design of such catalysts is very challenging due to the complex fusion of recognition sites and catalytically active center. Here, we report the design of a new class of fluxional biphenyl bisphosphinite (BIBIPHOS) ligands decorated with amino acid-based diamide interaction sites that undergo spontaneous desymmetrization. Hydrogenation of prochiral alkenes using Rh-BIBIPHOS results in enantiomeric ratios of up to 96:4 (R/S). This stereoconvergent behavior of the fluxional BIBIPHOS ligand is triggered by pronounced intermolecular interlocking of the recognition sites, leading to the formation of a supramolecular assembly, where the axial orientation of the biphenyl ligand backbone is governed by the chirality of the amino acid moieties. Stereoinduction during catalysis is decoupled from this process and occurs as an immediate consequence of the ligands' emergent behavior. This supramolecular system is very robust and has the potential be adopted for other ligand designs in enantioselective catalysis.*

Enantioselective interactions between molecules play a pivotal role in a wide range of natural processes. While this interaction is of non-covalent nature, it is the basis for molecular recognition and chirality transfer, processes believed to be deeply rooted in natural chiral replication.[1] Understanding how non-covalent interactions can be used to exert enantiocontrol over chemical reactions promises far-reaching possibilities for the future design of chiral catalysts. Therefore, great efforts have been made to find ways to enable enantiocontrol at the molecular level.

The classical supramolecular approach aims at the stabilization of a molecular skeleton by non-covalent interaction, which ideally results in catalysts with a certain selectivity.[2] Much less prevalent are examples where the nature of the chiral element is determined by the interaction itself. Inspired by nature, nucleobase-derived ligands[3] as well as ligands bearing amino acid-derived interaction site[4] have been reported, that mimic naturally occurring hydrogen bonding patterns in DNA or in proteins to enantioselectively generate self-assembled ligands with chiral axes. Other examples were reported where chiral molecules were capable of controlling the stereodynamic element of a catalyst[5] such as its helicity[6] or a chiral axis[7] through non-covalent bonding.

A more elaborate feature that results from intermolecular interactions between different components of a catalytic system, i.e. different catalyst molecules, ligands or reagents, is that formation of aggregates can cause the emergence of nonlinear effects such as the amplification of asymmetric processes.[8] Particularly intriguing are autocatalytic reactions[9] where this is induced by the product of the catalysis, as most impressively demonstrated by Soai *et al*. during their investigations of the Zn-mediated alkylation of 5-pyrimidinecarbaldehydes[10]. Similarly, non-covalent interactions of a catalyst with the targeted reaction product can control selectivity in an autoinductive way to amplify a sense of chirality.[11] This has been demonstrated by Wynberg and Feringa in oxidative couplings of phenols and camphor to obtain homochiral dimers.[12] Other examples include enantioselective hydrocyanation reactions reported by Danda *et al*.[13] and Shvo *et al*.[14] as well as a self-amplifying hydrogenation reaction by our own group.[15]

Another form of chiral amplification, referred to as the "sergeant-soldier principle" relies on the self-organizational ability of supramolecular systems.[16] Most commonly found in larger self-assembling structures[17] or helical polymers,[18] it is based on chirality transfer along a chain of subunits where only few chiral "sergeants" are needed to align a much greater number of achiral "soldiers" in order to build structures with a high degree of stereoselectivity.

Combining some of these approaches, we developed a strategy to introduce a highly selective receptor group[19] for enantioselective recognition into the backbone of a stereodynamic biphenyl ligand.[20] Because of the C_2-symmetry of the ligand core, we expected a homochiral alignment of the ligands that would have a stereodirecting effect on the ligand's rotamer distribution and would allow to reinforce stereo-alignment through cooperative interaction.

We synthesized a set of biphenyl bisphosphinite ligands (BIBIPHOS) with low rotational barriers resulting in high stereodynamic flexibility (see Figure 1). Interestingly, all ligands (and their phenol precursors) were found to adapt a single well-defined structure in solution, that rendered both molecular halves unsymmetrical as apparent by two sets of signals of equal intensity in all ^{1}H, ^{13}C and ^{31}P NMR spectra. Furthermore, no interconverting ligand rotamers were observed which indicates a full diastereomeric enrichment of one ligand rotamer. This intriguing behavior prompted a comprehensive investigation of the ligand structure.

The ^{31}P NMR spectrum of each compound showed two distinct singlet peaks. Similarly, both ^{1}H and ^{13}C NMR spectra contain two sets of signals with identical intensity which were assigned by 2D NMR spectroscopy to the same molecular scaffold. Analysis of ^{1}H NMR signals of amide protons revealed a very strong downfield shift as found in peptide bonds that engage in strong and steady hydrogen bonding.[21]

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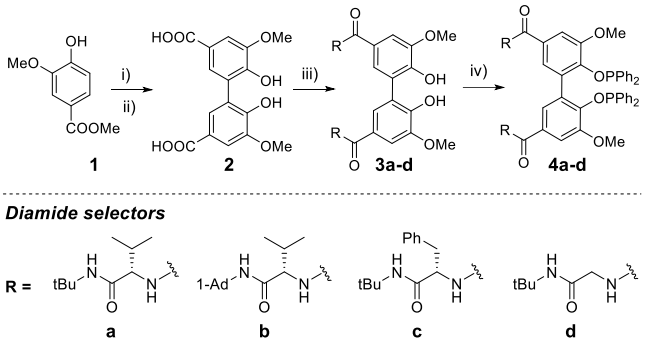

Figure 1: Biphenyl bisphosphinite (BIBIPHOS) synthesis i) $PhI(OAc)_2$, 51%, ii) KOH, 97%, iii) amide selector hydrochloride, EDCI·HCl, HOBt, DIPEA, then excess $Me_2NCH_2CH_2NH_2$, 89% **a**; 51% **b**, 91% **c**, 80% **d,** iv) PPh_2Cl, 1,4-diazabicyclo[2.2.2]octane, 49% **a**, 53% **b**, 83% **c**, 53% **d**.

Signals for compound **4a** were observed at 9.43, 9.12, 8.11 and 7.56 ppm and those for ligands **4b**, **c** and **d** were found between 10.22 and 7.44 ppm. When ^{31}P NMR spectra of **4a** were collected at various temperatures between -40 and 100 °C, significant line broadening was observed at 80 °C. At 40 °C, new singlet species appeared, which was only stable at elevated temperatures and vanished again when returning to room temperature (see SI for spectral data). These findings indicate that ligand behavior is governed by strong hydrogen bonding of the compound's selector moieties with supramolecular interactions fading at elevated temperatures. It also signifies that the dimeric complex retains enough dynamic to disengage and to undergo chemical exchange with other complexes.

We obtained an X-ray structure of ligand **4d** with glycine-derived selectors. The structure shows a C_2-symmetric dimer comprising two R_{ax} rotamers (see Figure 2).

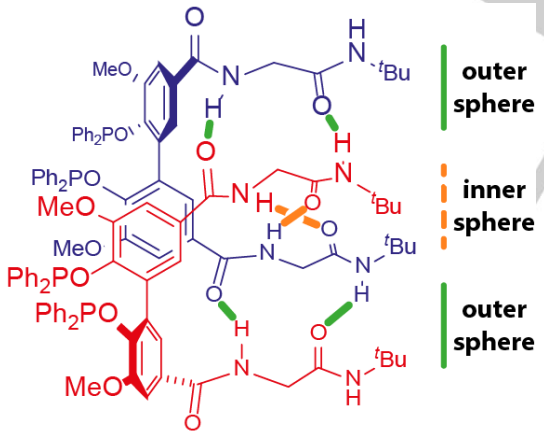

Figure 2: Representation of the supramolecular arrangement of **4d**, which is based on the single crystal X-ray structure obtained for this compound. Two molecules form a supramolecular C_2-symmetric dimer of C_1-symmetric subunits. One selector of each subunit engages in β-turn-like, two-fold hydrogen bonding in the center (*inner sphere*), while the two remaining selector moieties form two more hydrogen bonds each with the *inner sphere* selector of the respective other molecule (*outer sphere*).

The complex is divided into an *inner sphere* part, where two selectors align in a [b²]-turn forming two hydrogen bonds and an *outer sphere* part where the remaining two selectors engage in a "tweezer"-like assembly by forming two additional hydrogen bonds with the back-side of the *inner sphere* selector of the respective other ligand molecule. This results in desymmetrization of the two subunits. This is in line with the aforementioned observation of an additional signal set for each of these compounds. It also becomes apparent that the spatial arrangement of the glycine moieties does not allow the formation of dimers with different axial chirality. For ligands **4a**-**c** with chiral selectors, only one of two possible isomers $S,S,R_{ax}/S,S,R_{ax}$ or $S,S,S_{ax}/S,S,S_{ax}$ is observed, which leads to the conclusion that the chiral information in the amide linker determines the axial chirality of the biphenyl backbone in the dimer and only one rotamer is present in solution. By conducting hydrogenation experiments (see below) and comparing the obtained selectivities to those of similar ligand structures with known chirality, we established that all ligands transform into their respective R_{ax} isomers.

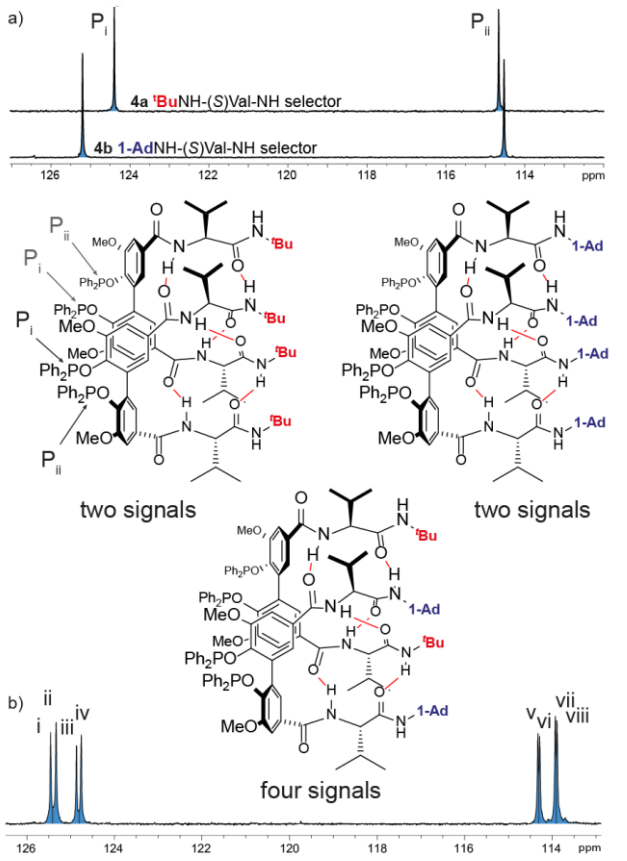

Figure 3: ^{31}P NMR spectra (a) of individual ligands **4a** and 4**b** and (b) of an equimolar mixture of **4a** and **4b**, where four additional signals of equal intensity arise. With a total of eight peaks, four of them represent the original two ligand dimers. Remaining signals display formation of a supramolecular heterodimer comprising both ligands, which contains four diastereotopic phosphorus atoms.

To corroborate that the supramolecular structure is still conserved in solution, crossover experiments were conducted. When mixing

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ligands **4a** and **4b**, which differ with respect to the terminal amide substituent, formation of an additional species was observed. While the phosphorus atoms of the individual compounds show two signals each (see Figure 3a), the ^{31}P NMR spectrum of a 1:1 mixture comprised eight different peaks of identical intensity (see Figure 3b). We conclude from preceding experiments that the four additional signals belong to a heterodimeric species where all four phosphorus atoms are diastereotopic. A 2:1 mixture of the two ligands resulted in a similar spectrum with a 4:4:1 distribution of the three species, indicating a statistical distribution of dimers (for spectral data and kinetic considerations see SI). It should be stressed that the ligand mixture exhibits identical behavior compared to the pure ligand. All amide protons show low-field NMR shifts in the same range as the individual pure ligands. ^{31}P NMR spectra measured at elevated temperatures exhibit line broadening along with formation symmetric species like those found for the pure ligand, which also vanish again when the spectrum is re-measured at room temperature afterwards. These findings provide the definite proof for dimer formation in solution and demonstrate intermolecular nature of the hydrogen bonding that cause the C_1-symmetric appearance of the ligands and the energetic differences among rotamers.

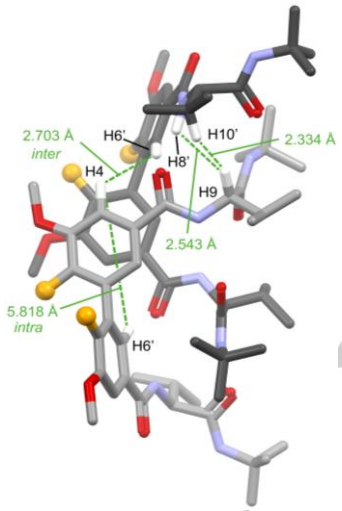

Figure 4: Model of the calculated structure of ligand R_{ax}/R_{ax}-**4a** with annotated atomic distances for protons what show strong NOE-based cross peaks. The initial structure for optimization was based on the crystal structure of **4d** and was optimized at the B3LYP/(aug)-cc-pvdz level of theory. To improve clarity, only annotated hydrogen atoms are shown and $OPPh_2$ moieties are abstracted as orange placeholder atoms. The two molecular subunits of the dimer are colored in light and dark grey. Nitrogen = blue, oxygen = red, $OPPh_2$ moiety = orange.

To corroborate the structure of the supramolecular complex, NOESY spectra of compound **4a** were collected. The most prominent signals are illustrated in Figure 4. The structure of **4a** is based on the crystal structure of glycine derivative **4d** and was optimized using DFT calculations on the B3LYP/(aug)-cc-pvdz level of theory. Cross peaks indicate proximity between protons H4 and H6'. Comparing atomic distances in the model structure suggests that corresponding atoms within the same molecule are too far away to give a strong coupling signal. Intermolecular coupling, however, seems likely. Coupling was also observed for H9 and H8', and for H9 and H10', which both accounts for the interaction between *inner* and *outer sphere* selector protons.

This remarkable stereoconvergent behavior of the fluxional BIBIPHOS ligands, triggered by pronounced intermolecular interlocking of the recognition sites, leading to the formation of a defined supramolecular assembly is a promising approach to generate selectivity in asymmetric catalysis. Consequently, BIBIPHOS ligands **4a-c** were employed in Rh-catalyzed hydrogenation experiments (see Figure 5). All three ligands exhibited high to very high enantioselectivities with phenyl alanine ligand **4c** performing slightly better than the valine-based ligands **4a** and **b**. The former was found to convert methyl 2-acetamidoacrylate **5** with the best enantiomeric ratio observed (96.0:4.0 *R*:*S*), followed by dimethyl-2-methyl succinate **7** with a ratio of 94.9:5.1 (*S*:*R*) and *N*-acetylphenylalanine methyl ester **6** with 94.5:5.5 (*R*:*S*).

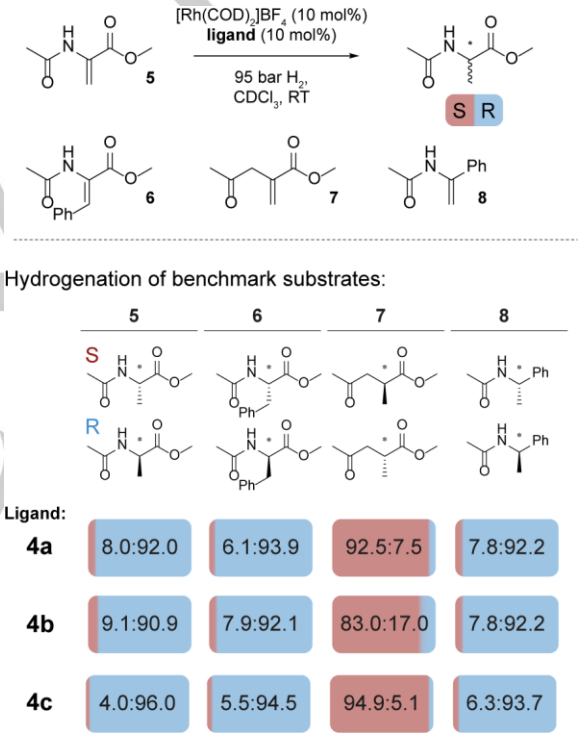

Figure 5: Results for the enantioselective hydrogenation of substrates **5**-**8** using BIBIPHOS ligands **4a**-**c**. Detailed experimental procedures can be found in the SI.

For enamide **8**, a selectivity of 93.7:6.3 (*R*:*S*) was obtained. These results also allowed us to corroborate our assumption of all ligands being diastereomerically pure R_{ax} isomers by comparing obtained selectivities to those of similar, earlier reported systems.[22] We also conducted experiments with various catalyst loadings and und lower hydrogen pressure (see SI) yielding identical outcomes. These experiments were designed to show that the selectivity is independent of the turnover number thus excluding selective catalyst activation or temporal change of the catalyst as a source of selectivity. The catalysis was also performed in THF and MeOH to evaluate solvent effects. While THF, a weakly

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coordinating solvent, gave comparable results for hydrogenation of methyl 2-acetamidoacrylate **5** using ligand **4c** (95.2:4.8 *R:S*) compared to those in $CDCl_3$, employment of methanol as reaction solvent led to a significant drop in selectivity (80.8:19.2 *R:S*), most likely attributed to the solvent inhibiting ligand-ligand interaction that drive the rotameric enrichment.

In summary, we have shown that the fluxional ligands **4a-c**, all of which contain chiral (*S*)-amino acid derived 5,5'–diamide selector moieties, form well-defined supramolecular dimers by intermolecular interlocking. Due to the bias of the chiral selectors, a complete transformation into a single R_{ax} rotamer is achieved. The diastereomeric enrichment is based on a process of supramolecular, cooperative self-recognition, where diamide moieties diastereoselectively lock the rotamers through a "tweezer"-like network of hydrogen bonds into a preferential axial conformation. The ligands were employed in Rh-catalyzed, enantioselective hydrogenation experiments. All ligands showed high to very high enantioselectivities with various prochiral olefins. The best performance was observed with phenylalanine-based ligand **4c** which converted methyl 2-acetamido acrylate **5** with an *er* of 96.0:4.0 (*R*:*S*). The catalytic experiments could also be used to ascertain the axial chirality of the ligands and to verify the diastereomeric purity of the ligand and the stereomeric integrity of the catalyst over the course of the reaction.

To the best of our knowledge, this is the first example where the concepts of stereodynamic ligands and supramolecular assemblies are combined to generate a diastereomerically pure compound that can convey very high enantioselectivity in an asymmetric transformation. It is important to point out, that chiral induction during catalysis is conceptually decoupled from the alignment of the ligands. Cooperative chiral induction that results from the self-recognition properties of the selector units evokes a stereoconvergent response from the dynamic ligand core, a bias which is further relayed during catalysis. The presented system yields a predictable core structure that has the potential to be combined with other biaryl-based ligand types to yield self-recognizing enantioselective catalysts for a number of different transformations.

Experimental Section

Supporting information for this article is available on the WWW under XXX

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Keywords: supramolecular chemistry • self-recognition • stereodynamics • asymmetric catalysis • ligand design

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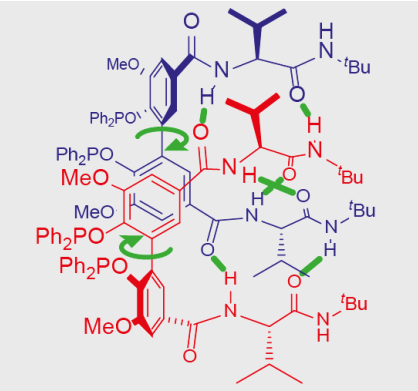
Emergence in Chiral Induction: *Intermolecular interaction of fluxional biphenyl bisphosphinite (BIBIPHOS) ligands decorated with amino acid-based diamide selectors undergo spontaneous deracemization. Hydrogenation of prochiral alkenes using Rh-BIBIPHOS results in enantiomeric ratios of up to 96:4 (R/S).*



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