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Asymmetric Catalysis

Enantioselectivity Induced by Stereoselective Interlocking: A Novel Core Motif for *Tropos* Ligands

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Abstract: Well-defined supramolecular interactions are a powerful tool to control the stereochemistry of a catalytic reaction. In this paper, we report a novel core motif for fluxional 2,2′-biphenyl ligands carrying (*S*)-amino acid-derived interaction sites in 5,5′-position that cause spontaneous enrichment of the R_{ax} rotamer. The process is based on strong non-covalent interlocking between interaction sites, which causes diastereoselective formation of a supramolecular ligand dimer, in which the axial chirality of the two subunits is dictated by the stereochemical information in the amino acid residues. The detailed structure of the dimer was elucidated by NMR spectroscopy and single-crystal X-ray analysis. Three different phosphorus-based ligand types, namely a bisphosphine, a bisphosphinite and a phosphoramidite were synthesized and characterized. Whereas the first one was found to exist in a strongly weighted equilibrium, the two others each exhibited stereoconvergent behavior transforming into the diastereopure R_{ax} rotamer. Enriched ligands were used in rhodium-mediated asymmetric hydrogenation reactions of prochiral olefins in which very high enantioselectivities of up to 96:4 were achieved.

Introduction

Transition-metal-catalyzed asymmetric hydrogenations are among the most versatile and broadly applied organometallic catalytic reactions for the preparation of enantioenriched compounds.[1] One of the most established ligands used to prepare catalysts for these reactions is BINAP,[2] whose rigid, atropisomeric axis stores the chiral information to be transferred onto a given substrate.[3] Stereolabile, biphenyl-based *tropos*[4] ligands offer a substantially different approach to enantioselectivity as a stereochemical bias on the dynamic chiral axis is needed to trigger the diastereomeric enrichment of one ligand rotamer. Pioneered by the groups of Gagné, Mikami and Noyori, enantiopure diamines and amino alcohols were employed as co-ligands to generate diastereomerically enriched 2,2′-bis(diphenylphosphino)biphenyl (BIPHEP) transition-metal complexes.[5] Similarly, Brown and Faller devised chiral diene ligands, whereas Klankermayer, Franciò and Leitner used proline-based ionic liquids that coordinate to a metal center across from the *tropos* ligand to have a similar effect.[6] A general drawback of metal-binding co-ligands is the loss of free coordination sites or the necessity for suitable conditions to preserve an imprinted stereochemical information after the chirality-inducing co-ligand has been displaced, for example, upon dissociation in the course of a catalytic reaction. To circumvent this problem, our group, as well as RajanBabu and co-workers, showed that chiral auxiliaries, covalently bound to the ligand core, induce diastereomeric enrichment through central-to-axial chirality transfer and provide a pathway in which chirality induction is orthogonal to the subsequent catalysis.[7]

In a similar way, non-covalent interactions have been used to induce stereochemical bias. Supramolecular ligands offer vast potential to control the stereoselectivity in catalysis, especially because nature provides templates for well-defined interaction patterns. Some of these have been mimicked, such as hydrogen bonding in DNA[8] or in proteins,[9] to generate self-assembling ligands for enantioselective catalysts. In other examples, non-covalent bonding of chiral molecules was employed to control the stereodynamic element of the catalyst such as a helix[10] or a chiral axis.[11] In our group, *tropos* biphenyl ligands were modified with selector units for non-covalent interactions and utilized their ability of hydrogen bond formation to design systems in which the transmission of chiral information solely relies on non-covalent bonding between the ligand and a chiral additive in solution.[12] Conceptionally, chirality can also be induced in this manner by the interaction with reaction products,[13] as demonstrated in a "by-design" self-amplifying hydrogenation reaction published by our group.[14]

With these concepts in mind, we envisioned a strategy that combines some of the approaches. By introducing strongly binding amino acid-based selector sites for a highly enantiose-

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lective interaction[15] into the backbone of stereodynamic biaryl ligands, we expected intermolecular interactions between ligands that would induce a stereodirecting effect on the ligand's rotamer distribution. We anticipated that, while adopting a substitution pattern compatible with the desired *tropos* nature, very short linking groups between selector units and ligand backbone would enhance rigidity and, consequently, improve the chirality transfer onto the ligand. Accordingly, a synthetic approach for a set of biphenol-based phosphorous ligands bearing (*S*)-amino acid derived diamide moieties in the 5,5′-positions was devised (see Figure 1). Methoxy groups in 3,3′-position facilitated coupling to the biphenyl and were also thought to act as bulky stereodirecting groups to enhance selectivity of the ligands during later use in asymmetric reactions.[16] Three different ligand types were to be compared: a bisphosphine, a bisphosphinite and a phosphoramidite ligand. All three classes are typical representatives of stereodynamic ligands with a falling inversion barrier within the series.

Results and Discussion

The synthesis of BIPHEP-based ligand **5** was achieved by initial Fischer esterification of 3-bromo-5-hydroxybenzoate **1** and subsequent reaction with chlorodiphenylphosphine oxide to give phosphinate **2**. Treatment with LDA induced an anionic phosphorous Fries rearrangement,[17] in which the diphenylphosphine oxide moiety selectively migrated to the desired position adjacent to the bromine substituent. Subsequent methylation of the free phenolic hydroxy group and Ullmann coupling[18] of the resulting phosphine oxide **3** was used to construct the biphenyl backbone. Final reduction of the bis(diphenylphosphine oxide) afforded bisphosphine **4**. Following saponification of the methyl esters, *t*BuNH-(*S*)-Val selector groups were attached in 5,5′-position employing standard peptide coupling reagents EDCI·HCl/HOBt under inert conditions to give the targeted bisphosphine **5**.

Except for the anionic Fries rearrangement, high yields were obtained for most of the transformations, especially at the end of the sequence, in which compound value increases.

The syntheses of the corresponding bisphosphinite ligands **9a** and **9b** has been reported by us in an earlier contribution.[19] Commercially available methyl vanillate **6** was dimerized to give compound **7**. Subsequent ester cleavage and introduction of the selector units by two-fold amide formation yielded selector-modified biphenols **8a**,**b**, which were treated with chlorodiphenylphosphine in the final step of the reaction sequence to afford ligands **9a**,**b**.

Finally, phosphoramidites **10a**,**b** could be conveniently synthesized from the same precursor molecule. For valine-based ligand **10a**, diol **8a** was refluxed with an excess of tris(diethylamino)phosphine to give the desired selector-modified phosphoramidite in good yield. Phenylalanine derivative **10b** was synthesized by treating the corresponding diol **8b** with diethylphosphoramidous dichloride in presence of trimethylamine.

Subsequent investigations revealed that the given substitution pattern indeed has a far-reaching influence on the properties of the ligands. The selector units' capacity to form a multitude of hydrogen bonds induces a strong and well-defined interlocking among two ligands forming supramolecular dimers (see Figure 2). The diastereoselective nature of these intermolecular interactions between selector units induces a process of cooperative chiral induction leading to spontaneous enrichment of one rotamer.

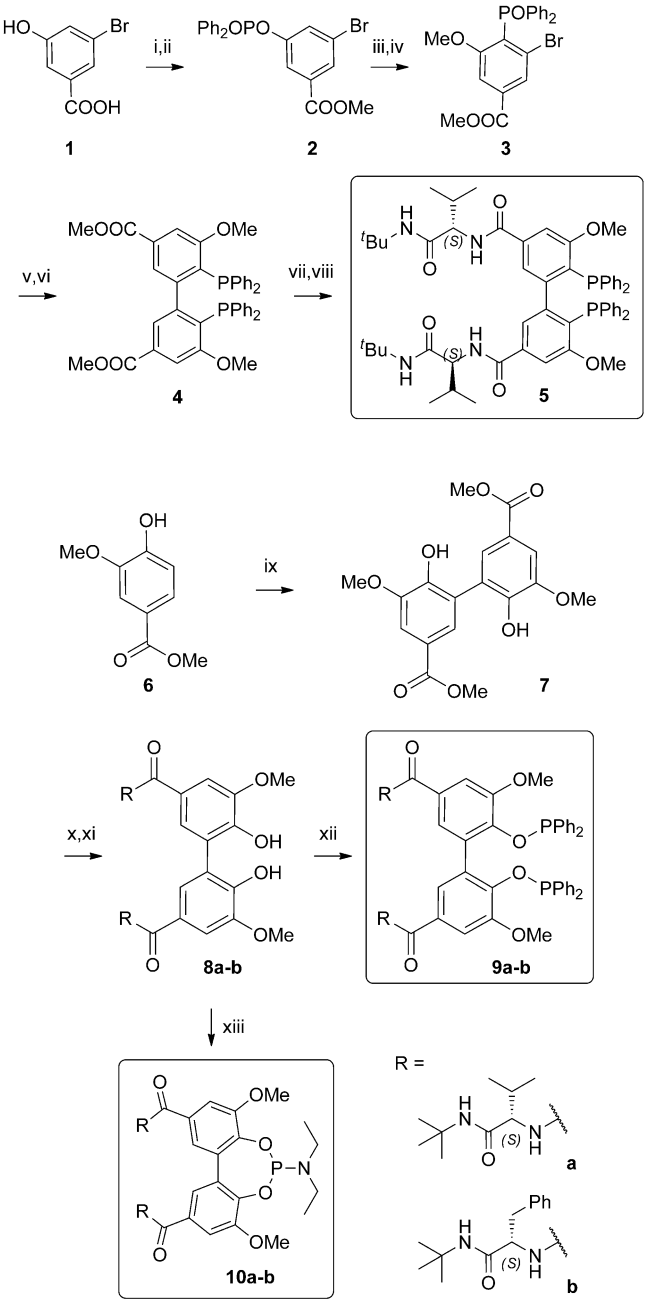


Figure 1. Bisphosphine synthesis of **5**: i) MeOH, H_2SO_4, 84%, ii) $POPh_2Cl$, 4-dimethylaminopyridine, NEt_3, 83%, iii) lithium diisopropylamine, 29%, iv) MeI, 98%, v) Cu, 91%, vi) $PhSiH_3$, 95%, vii) KOH, 99%, viii) *t*BuNH-(*S*)-Val-NH_3Cl, EDCI·HCl, HOBt, DIPEA(*N*,*N*-diisopropylethylamine), 63%. Bisphosphinite synthesis of **9**: ix) $PhI(OAc)_2$, 51%, x) KOH, 97%, xi) amide hydrochloride, EDCI·HCl, HOBt, DIPEA, then excess $Me_2NCH_2CH_2NH_2$; **8a**: *t*BuNH-(*S*)-Val-NH_3Cl, 89%; **8b**: *t*BuNH-(*S*)-Phe-NH_3Cl, 90% xii) PPh_2Cl, 1,4-diazabicyclo[2.2.2]octane; **9a**: 49%; **9b**: 83%. Phosphoramidite synthesis of **10** ix to xi, xiii) **a**: $P(NEt_2)_3$, 56%; **b**: NEt_2PCl_2, NEt_3, 74%.

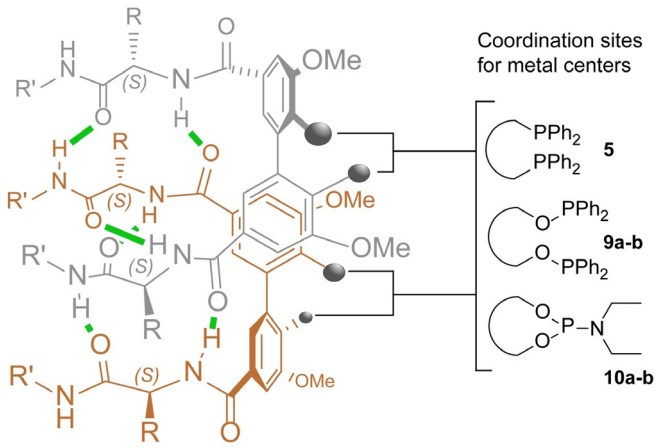


Figure 2. Stereodynamic biphenyl ligands interlock to form supramolecular dimers when equipped with amino acid-derived sites for non-covalent interaction in 5,5′-position. The diastereoselective nature of interactions induces stereoconvergent ligand behavior during dimerization and enrichment of the R_{ax} rotamer is observed. Ligand subunits are depicted in beige and grey and hydrogen bonds are indicated as green lines. The different ligand types that were investigated are shown on the right.

We recently published preceding results of this phenomenon with a set of corresponding bisphosphinites, ligands **9a** and **9b** among them, and their respective biphenol precursors.[19] Herein, we expand by reporting a series of different phosphorous ligands with valine- and phenylalanine-based diamide selectors. Their self-assembling behavior was investigated, and the structure of the dimer was elucidated using single-crystal X-ray structure analysis and NMR spectroscopy. The properties of the different ligands were examined and compared.

Finally, they were tested for their suitability as ligands in the enantioselective hydrogenation of prochiral olefins to ensure that the observed rotamer enrichment is accompanied by a corresponding increase in selectivity. Initial investigations of bisphosphine **5** revealed two interconverting ligand species with a ratio of 16:84 after equilibrating the compound in $CDCl_3$ at 60 °C. In the $^{31}P\{^1H\}$ NMR spectrum, the minor species was represented by a singlet and the major one represented by two sets of doublets in which the coupling of two diastereotopic phosphorus atoms indicated that both signals belong to the same C_1-symmetric molecular scaffold. The two species could be separated by selective precipitation and were individually characterized. Both showed identical HR-ESI-MS spectra with the desired product peak at $m/z = 979.4666$. Single crystals of the major compound, suitable for X-ray analysis, were obtained. The structure showed a C_2-symmetric ligand dimer comprising two R_{ax} rotamers of **5** (see Figure 3a). The complex can be divided into an inner sphere part, in which two selectors align in a Herrick conformation[20] ([β^2]-turn) forming two hydrogen bonds, and an outer sphere part in which the remaining two selectors engage in a "pincer"-like interaction mode forming two additional hydrogen bonds with the backside of the inner sphere selector of the respective other ligand molecule. The free electron pairs of the phosphorus atoms

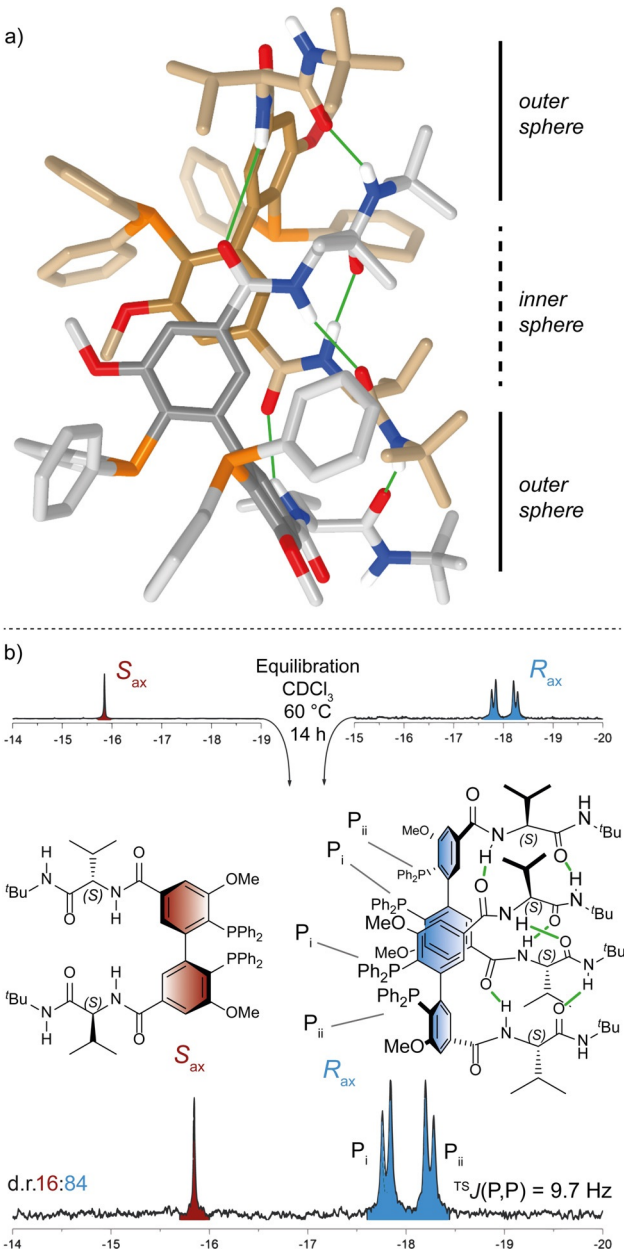


Figure 3. a) Representation of the single-crystal X-ray structure of (R_{ax})-**5**.Two molecules form a supramolecular C_2-symmetric dimer of C_1-symmetric subunits (indicated in beige and grey, biphenyl core atoms are colored darker). Nitrogen = blue, oxygen = red, phosphorus = orange. Hydrogen bonds are indicated as green lines. Non-relevant hydrogen atoms and solvent molecules are omitted for clarity. Images were produced using UCSF Chimera.[22] b) $^{31}P\{^1H\}$ NMR spectra of the two separated rotamers of **5** before (*top*) and after (*bottom*) re-equilibration.

point toward the aromatic backbone on the respective other side of the same molecule.

NMR analysis of the major compound exhibited a twofold set of signals with identical intensity in each ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectrum, indicating reduced symmetry within the ligand. This phenomenon is in line with the molecular arrangement of **5** in the crystalline state and suggests its persistence in solution. Arrangement of the ligand subunits in the dimeric complex lowers their symmetry rendering both halves of each

molecule chemically inequivalent. Also, the orientation of the phosphorus atoms provides a coupling pathway through π* orbital interaction (through space coupling) with the adjacent backbone phenyl ring. This is a known phenomenon for bidentate ligands with diastereotopic phosphorus atoms.[21] Heating a pure sample of either species to 60 °C in $CDCl_3$ for 14 hours resulted in complete re-equilibration to the same, previously observed mixture with a diastereomeric ratio (d.r.) of 16:84 (see Figure 3b). This result indicates their conformational relationship, that is, interconversion of the axial rotamers by rotation. We consequently concluded that a major rotamer (S,S,R_{ax})-**5** exists as a supramolecular dimer in equilibrium with a minor rotamer (S,S,S_{ax})-**5**. Analysis of ^{1}H NMR signals for amide protons of (R_{ax})-**5** (9.05, 8.34, 6.96 and 5.75 ppm) shows high downfield shifts for three protons found to engage in non-covalent interactions according to structural data from single-crystal X-ray analysis. Even though it is likely that the minor rotamer (S_{ax})-**5** engages in some sort of non-covalent interaction as well, these bonds seem to be much less stable and more transient with amide protons showing a comparably high field value for ^{1}H NMR shifts (6.38 and 5.84 ppm). In retaining the original C_2-symmetry, (S_{ax})-**5** does not seem to form a similar supramolecular structure compared to (R_{ax})-**5**. Moreover, no heterodimeric species is observed. This is indicative for a high level of diastereoselectivity during the hydrogen bond formation that is governed by the chirality of the selector units.

We proceeded by examining the interconversion barrier of the bisphosphines. Ligand precursor **4** was investigated for comparison using dynamic HPLC[23] and was found to have a barrier of interconversion of $\Delta G_{298K}^{\neq} = 97.8\ kJ\,mol^{-1}$. Assuming an opposing reaction of first order, NMR spectroscopic measurements of the isomerization kinetics of ligand **5** at 60 °C gave rate constants for the epimerization of $k(R_{ax} \rightarrow S_{ax}) = 1.3692 \times 10^{-5}\ s^{-1}$ and $k(S_{ax} \rightarrow R_{ax}) = 6.9798 \times 10^{-5}\ s^{-1}$, yielding thermodynamic parameters of $\Delta G(R_{ax} \rightarrow S_{ax})_{333K}^{\neq} = 112.9\ kJ\,mol^{-1}$ and $\Delta G(S_{ax} \rightarrow R_{ax})_{333K}^{\neq} = 108.4\ kJ\,mol^{-1}$, respectively (correlation factor $R^2 = 0.978$, see the Supporting Information for details). Comparing the two bisphosphines, steric hindrance as well as the latter's strong hydrogen bond stabilization of the ground state that needs to be overcome for an epimerization clearly explains the observed difference in the transition state energy.

As noted above, a full account on investigations concerning 2,2′-bisphosphinite ligands **9a** and **9b** has been presented elsewhere.[19a] For this ligand type, it was found that introduction of selector sites in the 5,5′-position causes spontaneous interlocking of two ligand molecules, inducing stereoconvergent behavior, that is, the rotamer ratio of the ligand was found to completely shift to one side, yielding exclusively the R_{ax} isomer (see Figure 4). In close resemblance to ligand dimer (R_{ax})-**5**, reduced ligand symmetry and amide protons with very low field shifts between 10.22 and 7.44 ppm were NMR-spectroscopically observed, which indicates strong engagement in hydrogen bonding, however, no coupling of phosphorus atoms was observed. The supramolecular ligand structure could be further verified by X-ray structure analysis and by

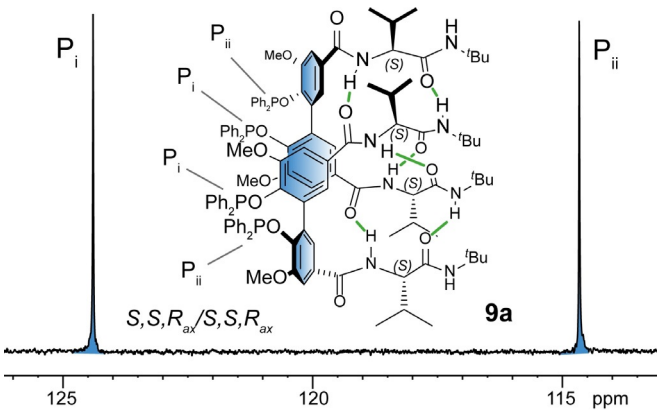


Figure 4. $^{31}P\{^1H\}$ NMR spectrum of bisphosphinite **9a**, which transforms into a diastereomerically pure R_{ax} rotamer. Two singlet signals represent the C_1-symmetric subunits of the C_2-symmetric, supramolecular dimer.

two-dimensional HMBC and NOE-based NMR spectroscopy in which an identical molecular arrangement to that of (R_{ax})-**5** was found. Moreover, the intermolecular nature of hydrogen bonding was verified in a crossover experiment, in which two differently substituted ligands were mixed, and instant formation of a heterodimeric species was observed.

The synthesized phosphoramidite ligands **10a** and **10b** bear strong resemblance to their bisphosphinite counterparts. Full diastereomeric enrichment of one ligand species was observed, which, in analogy to the previous cases, is assigned to the R_{ax} rotamer. With low field ^{1}H NMR shifts between 10.64 and 7.63 ppm (**10a**) and between 10.72 and 7.32 ppm (**10b**), all amide protons prove to be strongly engaged in hydrogen bonding and the expected reduction of the ligand symmetry due to its arrangement in the self-assembled dimer could be confirmed by the appearance of an additional set of ^{1}H and $^{13}C\{^1H\}$ NMR signals. Intriguingly, the reduction of symmetry for ligands **10a**,**b** has additional implications. Due to the non-equivalence of both molecular halves of each ligand subunit within the interlinked dimer, the phosphorus atoms become chiral. As a result, dimerization produces a mixture of diastereomeric adducts with different chirality at the phosphorus atom: two homomers (S,S,R_{ax},P^*_R)/(S,S,R_{ax},P^*_R) and (S,S,R_{ax},P^*_S)/(S,S,R_{ax},P^*_S) and the heteromer (S,S,R_{ax},P^*_R)/(S,S,R_{ax},P^*_S) give four signals in the respective $^{31}P\{^1H\}$ NMR spectrum as well as additional signals in ^{1}H and $^{13}C\{^1H\}$ NMR spectra (see Figure 5).

Since the stereoselective formation of hydrogen bonds is evidently the driving force behind the rotameric enrichment of these compounds, we subsequently investigated the effects of achiral and chiral hydrogen bond donors and acceptors on the equilibrium of the ligands. Additives were added in excess to a solution of the equilibrated ligand **5** (d.r. 14:86 S_{ax}:R_{ax}) in $CDCl_3$. The resulting mixtures were heated to 60 °C and monitored by $^{31}P\{^1H\}$ NMR until equilibrium was reached. Chiral amino acid derivatives **11**–**13** with different steric and electronic properties were employed. These were thought to match the selector's interaction pattern and thus be effective competitors for the ligand's self-interaction. As achiral additives, dicyclohexyl urea (**14**) and [D_6]DMSO (as solvent instead of $CDCl_3$) were used. In-

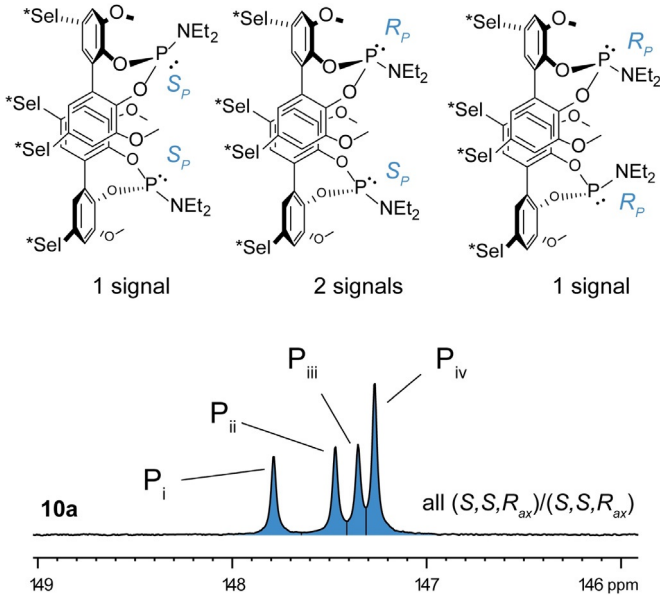


Figure 5. Reduction of symmetry during dimerization renders phosphorus atoms in phosphoramidite ligands **10a**,**b** chiral. Three different diastereomeric adducts form that can be distinguished by NMR. For annotation of stereogenic phosphorus atoms, each *inner sphere* ligand half was given priority over the *outer sphere* half.

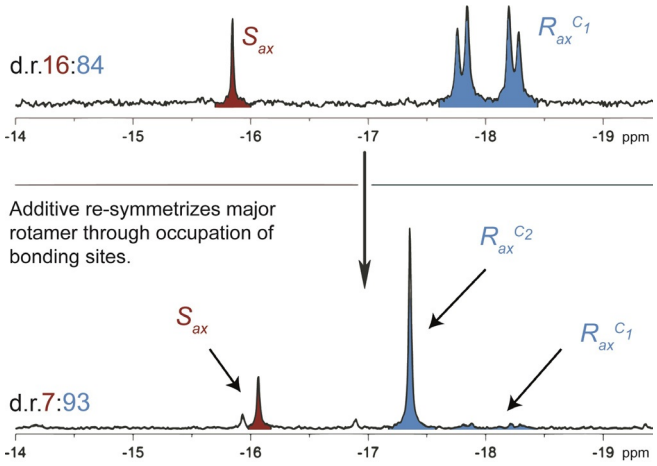
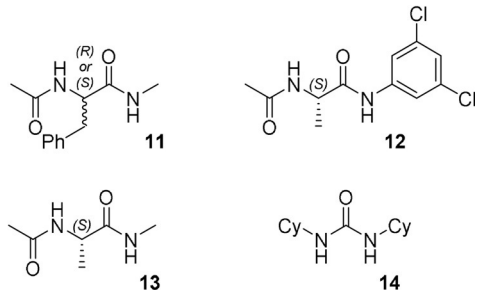


Figure 6. $^{31}P\{^{1}H\}$ NMR spectra of bisphosphine **5** before (*top*) and after (*bottom*) addition of a chiral additive in excess, which interferes with the hydrogen bond network and breaks up the supramolecular dimer (R_{ax}^{C1})-**5**, presumably into a monomeric (R_{ax}^{C2})-**5**, by occupying the ligand binding sites. Upon re-equilibration, a new equilibrium distribution of the rotameric species is reached.

triguingly, addition of (*S*)-amino acid-based additives immediately gave rise to a new, "re-symmetrized" singlet species (R_{ax}^{C2})-**5** at the expense of the two doublets of (R_{ax}^{C1})-**5** (see Table 1 and Figure 6). It was concluded that the interlocked dimer is split by interfering additive molecules that occupy hydrogen bonding sites instead, thus yielding a labile C_2-symmetric additive–ligand hydrogen bond adduct of unknown stoichiometry.[24] The extent of re-symmetrization was found to depend on the substitution pattern of the diamide additive. Apart from hydrogen bond donor and acceptor sites, aromatic moieties seem indispensable for maximum interaction. Re-equilibration of all samples led to an increased diastereomeric excess of **5** with best results for phenylalanine derivative (*S*)-**11** (d.r. 7:93 S_{ax}:R_{ax}, entry 2). When (*R*)-**11** was employed, no re-symmetrization was observed (entry 3), which is yet another indicator for the stereoselectivity that governs interactions between the ligand selector sites and its chiral environment. Equilibration of this sample slightly decreased the excess of the major rotamer (d.r. 24:76 S_{ax}:R_{ax}). Both achiral additives dicyclohexylurea (**14**) and [D_6]DMSO were found to reduce the diastereomeric excess of the ligand even more significantly (entries 5 and 6). These results are in line with earlier observations linking the rotameric enrichment of bisphosphine **5** to stereoselective non-covalent interactions as opposed to mere central-to-axial chirality transfer.

Table 1. Distribution of ligand species of bisphosphine **5** in presence of different chiral and achiral compounds.



Entry[a]	Solvent/Additive	Ligand species of **5** [%] S_{ax}	R_{ax}^{C2}	R_{ax}^{C1}	d.r.[e]
1	$CDCl_3$/ no additive	16	–	84	16:84
2	$CDCl_3$/(*S*)-**11**	7	82	11	7:93
3	$CDCl_3$/(*R*)-**11**	24	5	71	24:76
4	$CDCl_3$/(*S*)-**12**[b]	9	59	32	9:91
5	$CDCl_3$/(*S*)-**13**	11	38	51	11:89
6	[D_6]DMSO[c]	35	ND	65	35:65
7	$CDCl_3$/**14**[d]	33	–	67	33:67

ND = not determined. [a] Detailed experimental protocol can be found in the Supporting Information. [b] Additive did not fully dissolve and only 5 equivalents were used. [c] Measured in $CDCl_3$ after equilibration to circumvent heavy line broadening. [d] Additive did not fully dissolve. [e] d.r. = $S_{ax}/(R_{ax}^{C1}+R_{ax}^{C2})$

Attempts to interfere with the dimer structure of ligands **9** and **10** using diamide (*S*)-**11** failed. No re-symmetrization was observed, which leads to the conclusion that the energetic stabilization associated with their dimerization is significantly larger compared to bisphosphine **5**. This coincides with the observation that, in contrast to the latter, full transformation into more stable R_{ax} isomer is observed for both ligand types.

All ligands were employed in rhodium-catalyzed hydrogenation experiments to test if the observed diastereomeric enrichment translates into stereoselectivity during subsequent catalysis. Starting with the bisphosphines, ligand precursor **4** was initially studied to assess the ligand core's potential for chiral induction in the asymmetric hydrogenation of methyl 2-acetamidoacrylate **15**. Isolation of (S_{ax})-**4** by preparative HPLC gave the desired ligand with an enantiomeric ratio (*er*) of 96:4 (S_{ax}:R_{ax}),

which, after in situ reaction with $[Rh(COD)_2]BF_4$, afforded a catalyst that converted substrate **15** with 95:5 *er* (*S*:*R*). Having ensured that the given ligand core structure induces very high stereoselectivity, equilibrated ligand **5** (d.r. 16:84 S_{ax}:R_{ax}) was employed under identical conditions and converted the same substrate into the corresponding *R* product enantiomer with an *er* of 17.4:82.6 (*S*:*R*). This shows the direct correlation between the diastereomeric equilibrium distribution of the ligand and the *er* of the hydrogenation product. It also corroborates the assignment of the ligand rotamers to be correct when comparing the results to ligand selectivities of similar *atropos* systems.[16a] Hydrogenation experiments in which the ligand sample was pre-conditioned in presence of a chiral diamide gave product enantiomer distributions that also corresponded to the newly adjusted equilibria (see Figure 7). The best selectivity was achieved when AcNH-(*S*)-Ala-NH(3,5-dichlorophenyl) (*S*)-**12** was used, yielding methyl *N*-acetamidoalanine methyl ester in a ratio of 8.6:91.4 (*S*:*R*).

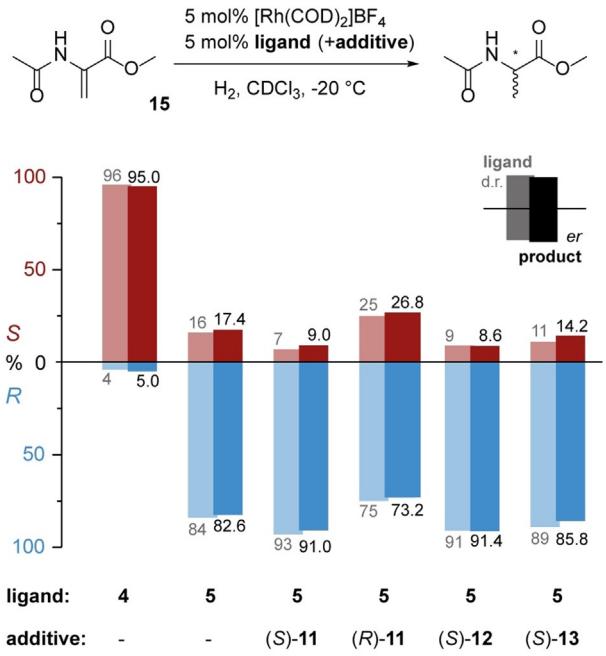


Figure 7. Hydrogenation experiments using bisphosphine ligands **4** and **5**. Additives were added to ligand **5** in a tenfold excess and the mixture was equilibrated at 60 °C prior to complexation. In case of (*S*)-**12**, only a fivefold excess was used and not all solids dissolved. Detailed experimental procedures can be found in the Supporting Information.

We subsequently compared the diastereomerically pure phosphinite and phosphoramidite ligands for their performance during the hydrogenation of prochiral olefins **15**–**18** (see Figure 8). Employment of bisphosphinite ligands **9a**,**b** consistently gave very good results.[19a] All olefins were converted with very high selectivities and phenylalanine-based ligand **9b** slightly outperformed valine-based counterpart **9a**. Selectivities ranged from 8.0:92.0 (*S*:*R*), when methyl 2-acetamidoacrylate **15** was hydrogenated using ligand **9a**, to 4.0:96.0 (*S*:*R*), when the same substrate was converted with

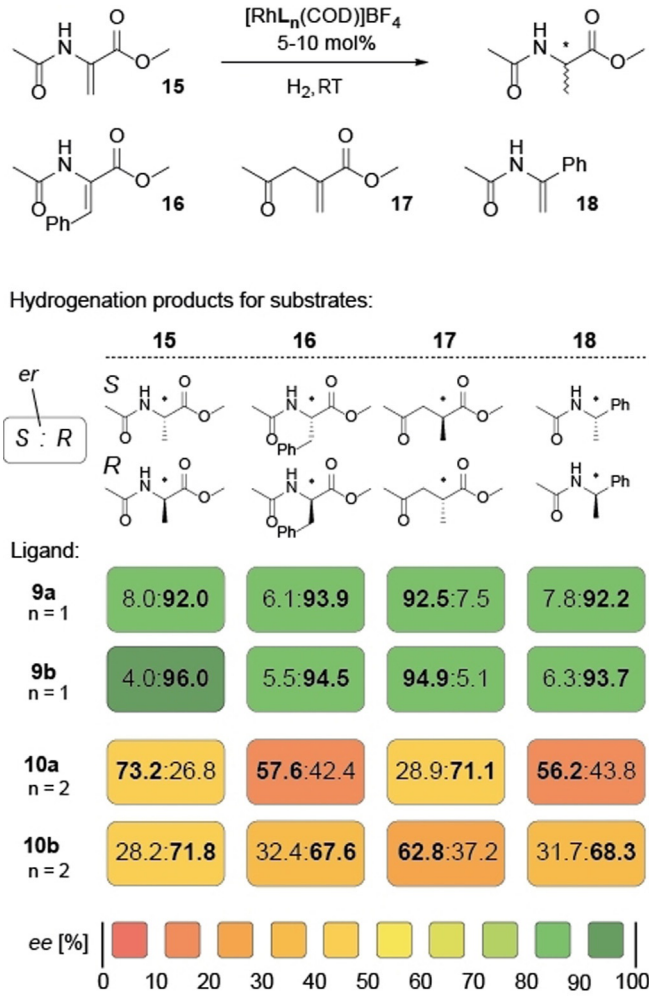


Figure 8. Results for Rh-mediated hydrogenation experiments using diastereomerically pure phosphinite ligands **9a**,**b** ([Rh**L**$_1$(COD)]BF_4) and phosphoramidite ligands **10a**,**b** ([Rh**L**$_2$(COD)]BF_4) on a series of prochiral olefins. Results for ligands **9a**,**b** were taken from ref. [19]. Detailed experimental procedures can be found in the Supporting Information.

ligand **9b**. These results are particularly promising as the selectivities are comparable to those obtained with classical, enantiopure phosphinite ligands of *atropos* nature.[16b]

Phosphoramidite ligands **10a** and **10b** were generally found to be less selective with enantiomeric ratios for products ranging from 57.6:42.4 (*S*:*R*) for the hydrogenation of 1-phenyl-1-acetamidoethylene **18** with ligand **10a** to 73.2:26.8 (*S*:*R*) when the same ligand was employed to reduce of olefin **15**. When comparing the two phosphoramidites, it was interestingly observed that a change of the amino acid moiety in the selector units was accompanied by a change of selectivity during later catalysis. Although ligand **10a** showed selectivity for the generation of the *S* enantiomer during the hydrogenation of substrates **15**, **16** and **18** and for the *R* enantiomer in case of substrate **17**, ligand **10b** proved to be selective for the opposite enantiomer for every single olefin. This clearly indicates that for this ligand type, enantioselectivity is not solely determined by the axial chirality of the two coordinating ligands. It is known, that phosphoramidite metal complexes exist as a mix-

ture of different P-Rh rotamers.[14] The supramolecular nature of the ligands investigated here potentially allows formation of oligomeric clusters, which might influence this rotation, thus altering the catalyst's selectivity. Yet, further investigations are necessary to ascertain, how an inversion of enantioselectivity can be evoked by altering the substituents on the selector moieties, whereas in both cases selector units were derived from the respective (*S*)-amino acid with the same point chirality.

Conclusions

We have investigated a new core motif of *tropos* 2,2′-biphenol ligands decorated with (*S*)-amino acid-based sites for non-covalent interaction in the 5,5′-position. Based on this motif, the synthesis of a bisphosphine, a bisphosphinite and a phosphoramidite ligand was realized. It was found that such a substitution induces intermolecular interlocking of selector groups, which leads to the formation of well-ordered ligand dimers. The self-assembly concurrently initiates a process of spontaneous diastereomeric enrichment of the R_{ax} rotamer, which is directed by the stereochemical information of the selector units. The structure of the hydrogen bond complexes was elucidated by NMR spectroscopy and single-crystal X-ray structure analysis. The degree of binding strength and the associated enrichment widely depends on the type of ligand. Bisphosphine **5** exists as a mixture of the monomeric S_{ax} rotamer and the dimeric R_{ax} rotamer in a strongly shifted equilibrium (16:84 S_{ax}:R_{ax}), whereas bisphosphinites **9a**,**b** and phosphoramidites **10a**,**b** are completely transformed into the more stabilized dimer. Therefore, attempts to manipulate the supramolecular structures by adding chiral and achiral hydrogen bond donors and acceptors were only successful with bisphosphine **5**, in which additives occupied binding sites and partial monomerization of the R_{ax} rotamer occurred. Re-equilibration of ligand-additive mixtures allowed for the rotamer distribution to be selectively shifted toward the S_{ax} or R_{ax} rotamer by either inhibiting the ligand's self-interaction or by employing amino acid-derived additives of the same chirality as selector sites.

All ligands were employed in rhodium-catalyzed hydrogenation experiments. Enantioselective reduction of methyl 2-acetamidoacrylate **15** using ligand **5** gave enantiomer distributions of 17.4:82.6 (*S*:*R*) for the corresponding product, which correlated to the determined rotamer distribution of the ligand (16:84 S_{ax}:R_{ax}). Selectivity of the reaction could be further altered in both directions by employing mixtures in which ligand **5** was re-equilibrated in the presence of chiral additives. The highest selectivity was obtained with AcNH-(*S*)-Ala-NH(3,5-dichlorophenyl) (*S*)-**12** as additive, which allowed for the subsequent hydrogenation of compound **15** to proceed with a selectivity of 8.6:91.4 (*S*:*R*). Diastereomerically pure phosphinite ligands **9a**,**b** were previously tested for their performance in the reduction of prochiral substrates **15**–**18**.[19a] Very good results were obtained for both selector types and all olefins were converted with very high selectivities ranging from 8.0:92.0 (*S*:*R*) for the reduction of methyl 2-acetamidoacrylate **15** with ligand **9a** to 4.0:96.0 (*S*:*R*) when the same substrate was converted using ligand **9b**. Employment of the respective phosphoramidite ligands **10a**,**b** gave lower selectivities and best performance was achieved with compound **10a** which allowed conversion of olefin **15** with an *er* of 73.2:26.8 (*S*:*R*). Most surprisingly, ligands **10a** and **10b** exhibited opposing selectivities for all four substrates, despite both of them bearing selector moieties with same chiral information.

To the best of our knowledge, these are the first examples in which the concepts of *tropos* nature and supramolecular self-interaction are combined to induce stereoconvergent behavior in *tropos* ligands. Spontaneous alignment is caused by cooperative chiral induction of chiral interaction sites, which, in turn, translates into very high enantioselectivities in subsequent asymmetric transformations. Consequently, the presented examples exhibit how non-covalent interactions can become a strong driving force for the transmission of chiral information. They also yield promising starting points for the development of prospective catalyst systems due to their robust nature, their straightforward realization and simple modifiability.

Experimental Section

X-ray crystallographic data

CCDC 1904993 ((R_{ax})-**5**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Conflict of interest

The authors declare no conflict of interest.

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[24] Placing a sample of ligand and (poorly soluble) diamide (*S*)-**12** (Table 1, entry 4) in the fridge led to crystalization of the additive. As a result, (R_{ax}^{C2})-**5** vanished and (R_{ax}^{C1})-**5** reformed.

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