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Combinatorial Strategies to find New Catalysts for Asymmetric Hydrogenation Based on the Versatile Coordination Chemistry of METAMORPhos Ligands

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To extend the toolbox and find improved catalysts, anionic METAMORPhos ligands and neutral amino-acid-based ligands were used separately and in mixtures to form Rh complexes used in the asymmetric hydrogenation of eight industrially relevant substrates. Spectroscopic studies showed that under the catalytic conditions, the mononuclear complex with two different ligands (the heterocombination) is the main complex in solution if both the anionic and neutral ligands have the same chirality. If the neutral ligand and the anionic ligand have the opposite chirality at the P atom, monometallic and bimetallic heterocomplexes were detected by NMR spectroscopy and MS. For the majority of substrates evaluated in this study, higher enantioselectivities were obtained if the complexes used were based on the heterocombination of an anionic and a neutral ligand compared to respective homocombinations. After we found the initial leads, higher turnover numbers and enantioselectivities could be obtained easily by further exploring focused ligand libraries. The superior activity of the complexes based on the different ligands is highlighted by their robustness: significant divergence from a 1:1 ratio between the ligands does not lower the selectivity of the catalyst, although more of the competing homocomplexes are formed under these conditions.

Introduction

Biologically active compounds often contain one or more stereocenters, and the fragrance, pharmaceutical, and crop protection industries rely heavily on synthetic strategies that lead to single-enantiomer compounds.[1,2] Following the pioneering work of Horner, Kagan, Knowles, and Noyori on asymmetric hydrogenation, the first industrial-scale synthesis of an optically enriched drug (L-dopa) was implemented in the early 1970s.[3] Many other commercial successes were achieved subsequently, and today homogeneous asymmetric hydrogenation is one of most proven methodologies to obtain enantiomerically pure molecules on a multiton scale as exemplified by the recent launch of a new L-menthol production unit of BASF (20 000 tons/year).[1b,4] Despite the multitude of publications on asymmetric hydrogenation,[3f] we are far from able to design the best catalyst for a given substrate rationally. Besides the general issue of small energy differences in the enantiodiscriminating reaction step, the particular reaction mechanism that a hydrogenation catalyst follows (Halpern,[5a] anti-Halpern,[5b] dinuclear,[5c] ligand assisted,[5d] etc.) cannot be predicted in advance, which introduces yet another uncertainty in the prediction of catalytic outcomes. For these reasons, high-throughput screening is often the method of choice to find a catalyst system that will yield the product in a sufficiently high enantiomeric excess (*ee*) with a sufficient turnover number (TON) and rate for industrial application.[6] Cationic Rh complexes that bear one bidentate or two monodentate neutral phosphorus ligands are often the most efficient for the asymmetric hydrogenation of C=C bonds. Bidentate ligands generally form more rigid, well-defined complexes, and it was, therefore, long thought that these complexes were superior to their monodentate counterparts. However, monodentate ligands are often easier and more cost-effective to synthesize.[7] In addition, they are particularly suitable for high-throughput combinatorial catalysis: n monodentate ligands can give rise to $n(n+1)/2$ unique combinations that consist of n "homocomplexes" (complexes with two of the same ligands) and $n(n-1)/2$ "heterocomplexes" (complexes with two different ligands). If two different ligands (L1 and L2) are combined with a metal precursor, a mixture of three complexes can be formed: two homocomplexes $[(L1)_2Rh]$ and $[(L2)_2Rh]$ and one heterocomplex [(L1)(L2)Rh], which are often obtained in a 1:1:2 statistical ratio.[7b] As these systems are (usually) in a thermodynamic equilibrium, the product is only produced in higher selectivity if the heterocomplex is more active and selective than the corresponding homocomplexes.[7c]

The concept of supramolecular ligands is based on the self-assembly of ligand building blocks to form supramolecular bi-

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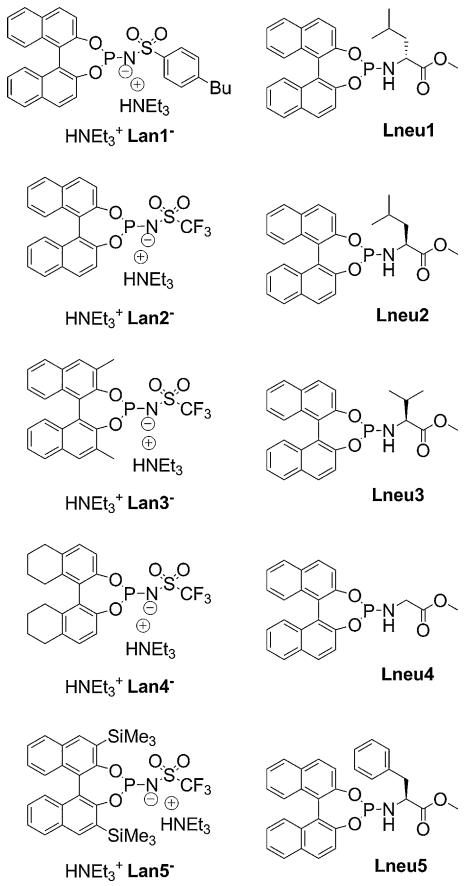
dentate ligands. Such systems combine the advantage of an easy synthesis of the building blocks and the rigidity of bidentate ligands. If sufficiently strong interactions between the ligand building blocks are present, selective heterobidentate ligands are formed if the two building blocks and the metal precursor are mixed in solution. To form such supramolecular bidentate ligands, different interactions[8] have been employed, such as hydrogen bonding,[9] metal–ligand interaction,[10] and ionic interactions.[11] Strategies based on hydrogen bonding have shown that a single hydrogen bond can be sufficient to achieve efficient self-assemblies,[12b] and hydrogen-bonded systems have even been used in solvents that compete for hydrogen bonding.[9f] Metal–ligand interactions have also been applied successfully as a tool to form rigid well-defined self-assemblies that result in selective catalysts. Ionic interactions have been used frequently to construct supramolecular host–guest structures,[13] but there are only a few examples in which such interactions are used for the assembly of supramolecular bidentate ligands.[11] Gennari and co-workers combined anionic (which have a carboxylate moiety) and cationic ligands (which have an ammonium moiety) with a cationic Rh center for the asymmetric hydrogenation of methyl 2-acetamidoacrylate. The formation of heterocomplexes was favored moderately as indicated by ^{31}P NMR spectra, and a slightly higher level of enantioselectivity was obtained if a mixture of ligands was applied compared to the corresponding homocombinations.[11a] More recently, Pfaltz et al. made a small library of phosphites and phosphoramidites equipped covalently with noninteracting anion moieties that were used in combination with neutral ligands and a cationic Rh precursor for asymmetric hydrogenation.[11e] They showed that the formation of the neutral heterocomplexes was favored over that of the anionic or the cationic homocomplexes and that in some cases, the neutral complexes were more stereoselective. This approach is particularly interesting as only one ligand needs to be functionalized with an anionic moiety; the second ligand can be virtually any neutral monodentate ligand.

In 2008, our group introduced METAMORPhos ligands based on 1,1′-bi-2-naphthol (BINOL) as efficient anionic ligands for asymmetric hydrogenation.[5c,14a–b] METAMORPhos ligands are effectively phosphorus ligands equipped covalently with weakly interacting sulfonamide anions (Scheme 1). Recently, it was shown that dinuclear Rh complexes based on anionic ligands **Lan2**$^-$ and **Lan1**$^-$ are dianionic in the resting state, that is, four negative charges are located on ligands, two positive charges are located on the metal centers, and the overall charge is balanced by two positive charges of the triethylammonium counterions (Scheme 2 a).[14c] These complexes display a high efficiency for a number a substrates such as methyl-2-acetamidoacrylate, but also for the challenging cyclic enamides. They show unrivalled selectivity for the hydrogenation of difficult tetrasubstituted cyclic enamides.[5c] Herein, we expand the scope of the application of METAMORPhos ligands (**Lan**$^-$) by using them in combination with neutral amino-acid-based ligands[12] (**Lneu**; Scheme 1), which are modular derivatives of MONOPhos-type ligands.[15] Depending on the characteristics of the METAMORPhos ligands and phosphoramidite ligands



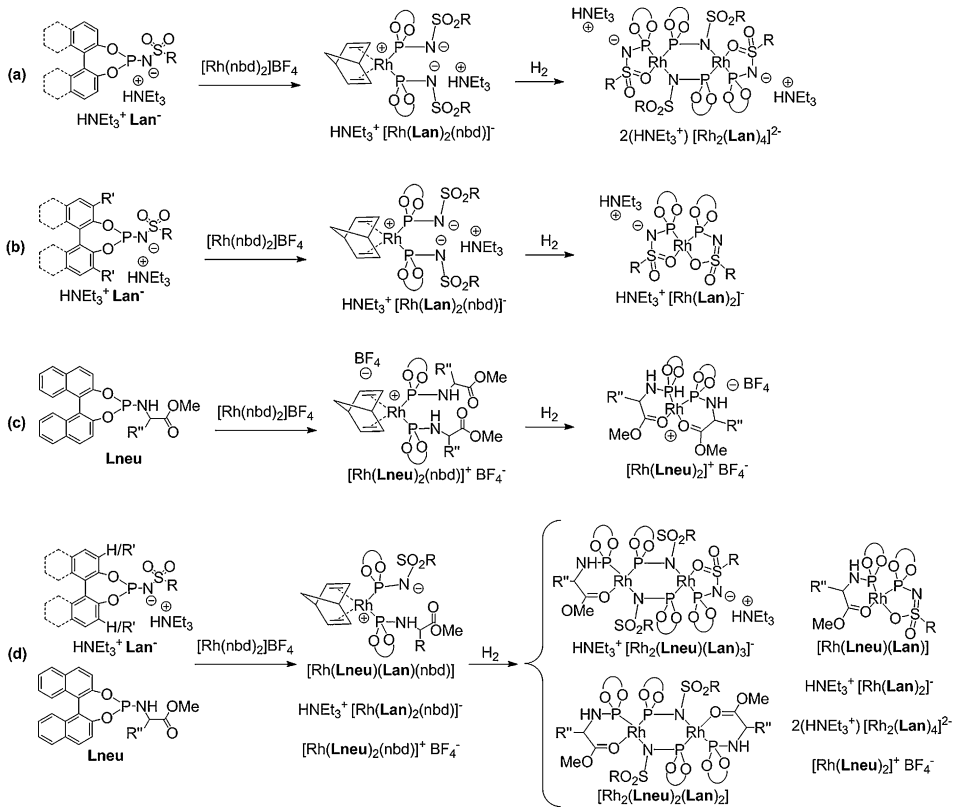
Scheme 1. Anionic METAMORPhos ligands **Lan**$^-$ and neutral ligands **Lneu** used in this study. The BINOL moiety of **Lan1**$^-$, **Lan4**$^-$, **Lneu1**, **Lneu2**, and **Lneu3** is in the *R* form. The other ligands were used in both enantiomeric forms.

used, various mono- and dinuclear complexes can form in solution, which represents an additional diversity factor for combinatorial catalysis. In the current study, the catalytic properties of the new complexes are compared with the pure mono- and dinuclear analogues for the hydrogenation of industrially relevant substrates. We demonstrate that for most substrates, the heterocombinations display improved catalytic performance compared to the homoligated counterparts. This work provides a new system to access diverse sets of catalysts easily and broadens the toolbox for asymmetric hydrogenation.

Results and Discussion

Choice of ligands

Triethylammonium salts of METAMORPhos ligands **Lan1**$^-$–**Lan5**$^-$ were synthesized in both enantiomeric forms by the simple condensation of 1,1′-binaphthyl-2,2′-diyl phosphorochloridate (BINOL P-Cl) with sulfonamide in the presence of triethylamine according to reported procedures.[5c,16a] The electronic properties of the ligand were varied by changing the substituent on the S atom (from weakly electron-withdrawing 4-butylphenyl to strongly electron-withdrawing trifluorometh-



Scheme 2. a) Negatively charged dinuclear complexes that arise from the coordination of METAMORPhos ligands **Lan**$^-$ to $[Rh(nbd)_2]BF_4$; b) negatively charged mononuclear complexes that arise from the coordination of bulky METAMORPhos ligands **Lan**$^-$ to $[Rh(nbd)_2]BF_4$; c) cationic complexes that arise from the coordination of amino-acid-based phosphoramidite ligands **Lneu** to $[Rh(nbd)_2]BF_4$; d) complexes that can be formed if $[Rh(nbd)_2]BF_4$ is exposed to a mixture of **Lan**$^-$ and **Lneu**.

yl) and the steric properties were tuned by introducing different groups on the 3,3′-position of the BINOL moiety.

The neutral ligands **Lneu1**–**Lneu5** were synthesized from BINOL P-Cl and commercially available amino acids [(*R*)- and (*S*)-leucine, -valine, -glycine, and -phenylalanine] according to reported procedures.[12]

Spectroscopic studies

Before we applied mixtures of these ligands in catalysis, we first explored their coordination chemistry under various conditions. The coordination behavior of unfunctionalized BINOL-METAMORPhos ligands (**Lan1**$^-$ and **Lan2**$^-$) has been well established (Scheme 2a).[5c,14a,c] If **Lan1**$^-$ (or **Lan2**$^-$) is mixed with $[Rh(nbd)_2]BF_4$ (nbd = norbornadiene) under a hydrogen atmosphere, a dianionic dinuclear complex is formed selectively. The ^{31}P NMR spectrum of such a complex displays characteristic signals that consist of a doublet-of-doublets at $\delta \approx 135$ ppm (chelating ligand) and an AA′BB′XX′ pattern at $\delta \approx 115$ ppm (bridging ligand). The crystal structures of these dinuclear complexes exhibit very short distances between the BINOL moieties connected to geminal P atoms:[14c,17a] the distance between the O atom from the BINOL moiety of the bridging ligand and the C atom from the BINOL moiety of the chelating ligand is less than 3.1 Å, which is significantly lower than the sum of the van der Waals radii (3.22 Å) and suggests the presence of lone pair–π interactions.[17] This interaction is difficult to observe in solution, but it is expected to also give additional stabilization to the bimetallic structure if the complex is dissolved. As a result of the anticipated stabilization effect of the close proximity of these ligands in the dinuclear structure, we expect that the functionalization of the BINOL moieties should disturb the formation of such complexes. Indeed, steric bulk on the 3,3′-positions of the BINOL unit (**Lan3**$^-$) leads to the formation of a mononuclear complex (Scheme 2b) as indicated by the doublet as the only signal that can be observed in the ^{31}P NMR spectrum (Figure S5). The use of octahydro-BINOL (**Lan4**$^-$), which has a similar bulk to the parent BINOL, again results in a dinuclear complex (Scheme 2a) as evidenced by the pattern in the ^{31}P NMR spectrum (Figure 1a). The coordination of **Lneu** ligands to $[Rh(nbd)_2]BF_4$ yields mononuclear cationic complexes, as expected for phosphoramidite ligands (Scheme 2c) and as evidenced by the doublets observed in the ^{31}P NMR spectra (see Figure S4 for the spectrum of $[Rh(\mathbf{Lneu3})_2(nbd)]^+$ or Figure 1b for the spectrum of $[Rh(\mathbf{Lneu3})_2]^+$).

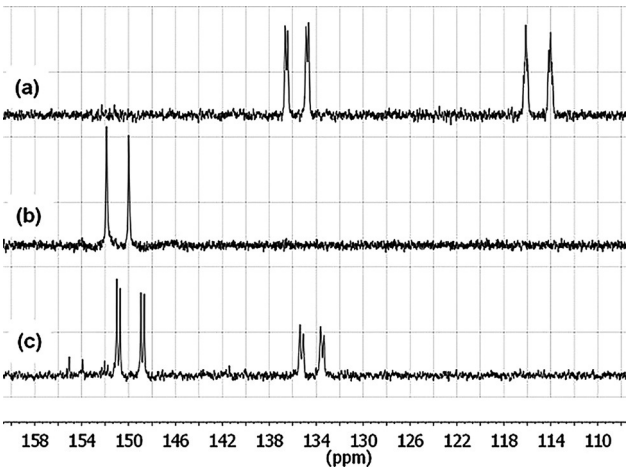


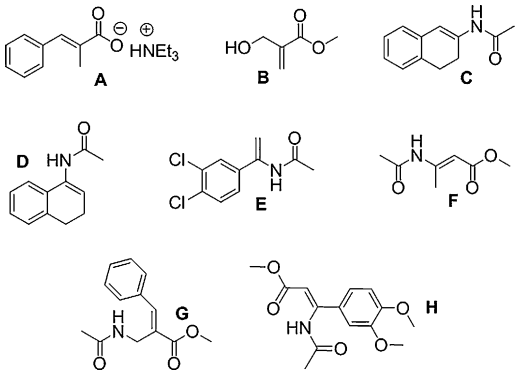
Figure 1. $^{31}P\{^1H\}$ NMR spectra (recorded under 10 bar of hydrogen) of a) the dinuclear homocomplex $(HNEt_3)_2[Rh_2((\mathbf{R})\text{-}\mathbf{Lan4})_4]$, b) the homocomplex $[(Rh(\mathbf{R})\text{-}\mathbf{Lneu3})_2]BF_4$, and c) the mononuclear heterocomplex [Rh((***R***)-**Lneu3**)((***R***)-**Lan4**)].

Next, we studied the complexes formed if a 1:1 mixture of various **Lneu** and **Lan**$^-$ ligands are mixed with the Rh(nbd) precursor under a nitrogen atmosphere. The ^{31}P NMR spectrum of the precatalyst made from a mixture of **(*R*)-Lan4**$^-$ and **(*R*)-Lneu3** shows two doublet-of-doublets, which indicates the formation of the neutral heterocomplex [Rh(**Lan4**)(**Lneu3**)(nbd)]. These signals integrate to approximately 75%, and the signals of [Rh(**Lan4**)$_2$(nbd)]$^-$ and [Rh(**Lneu3**)$_2$(nbd)]$^+$ integrate to only 1.5 and 3%, respectively. Three unassigned doublets, which do not appear in the spectra of the solutions that only contain homocomplexes, are also present (Figure S4). Next, we investigated the complexes that form if the nbd complexes are submitted to 10 bar of H_2. Under these conditions, a mononuclear heterocomplex is the major species, as indicated by the two doublet-of-doublets at $\delta = 149.8$ and 134.4 ppm (Figure 1). The spectrum displays a typical J_{P-P} coupling of 45.5 Hz, in line with a complex in which the P atoms are *cis* to each other. MS confirms the formation of a mononuclear heterocomplex, and the triethylammonium adduct HNEt$_3$[Rh(**Lan4**)(**Lneu3**)] is clearly visible in the spectrum ($m/z = 1120.2$). In addition, a dinuclear species can be identified by MS, that is, (H)$_2$[Rh$_2$(**Lan4**)$_3$-(**Lneu3**)] $^+$ and its acetonitrile adduct (eluent used for MS measurements). This species may be present in a small amount in solution as barely noticeable signals can be seen in the ^{31}P NMR spectrum ($\delta \approx 140$ and 155 ppm; Figure 1c). In the ^{1}H NMR spectrum of the heterocombination, hydride signals that do not appear in the spectra of the homocombinations are observed. A well-defined hydride signal at $\delta = -21.8$ ppm (ddd, $J_{Rh-H} = 26.1$ Hz) can be assigned tentatively to HNEt$_3^+$[HRh(**Lan4**)(**Lneu3**)]$^-$ or [HRh(**Lan4**)(**Lneu3**)] (Figure S7). These hydrides are present in a very small amount (~1%) according to the relative integration.

We performed the analogous NMR spectroscopy of complexes made from a 1:1 mixture of **Lan**$^-$ and **Lneu** ligands that bear the opposite chirality at their BINOL moieties (**(*S*)-Lan3**$^-$ and **(*R*)-Lneu3**). Under a nitrogen atmosphere, the homocomplex [Rh(**Lan**)$_2$(nbd)]$^-$ is present in a small amount (4%) and [Rh(**Lneu**)$_2$(nbd)]$^+$ cannot be detected. Six other signals that correspond to three different heterocomplexes are present in the ^{31}P NMR spectrum: three doublet-of-doublets, a doublet, and a doublet-of-triplets. This doublet (assigned to J_{Rh-P}) of a triplet (assigned to J_{P-P}) indicates a complex with three (or four) P ligands on one Rh atom: the nbd ligand is displaced even in the absence of hydrogen; this has not been observed for the homocombinations and reflects the difference in the steric properties of the heterocomplexes compared to the homocomplexes. If 10 bar of hydrogen is applied to this mixture, both homocomplexes [Rh(**Lan**)$_2$]$^-$ and [Rh(**Lneu**)$_2$]$^+$ are formed together with the heterocomplexes. The broadness of the signals and the fact that they are partially superimposed prevents a proper interpretation of the spectrum. According to the relative integrations, the homocomplexes/heterocomplexes ratio is roughly 1:1. Notably, two broad doublets are present at $\delta =$ 118.7 and 113.3 ppm ($J_{P-Rh} = 231$ and 201 Hz, respectively), which are typical shifts for bridging METAMORPhos ligands of dinuclear complexes (e.g., Figure 1a).[5c,14b–f] The existence of mononuclear [Rh(**Lneu**)(**Lan**)] complexes and dinuclear [Rh$_2$(**Lan**)$_2$(**Lneu**)$_2$] heterocomplexes complexes was confirmed by MS (see Supporting Information). These coordination experiments show that the use of mixture of ligands results in the formation of different complexes, and the type of complex formed (mono-/dinuclear, neutral/cationic) depends on the ligand structures. This suggests that the use of ligand mixtures gives rise to diverse sets of complexes that expand the library of complexes for combinatorial catalysis.

Choice of substrates

To explore the potential in asymmetric hydrogenation of the ligand mixtures based on METAMORPhos ligands, we chose a diverse library of industrially relevant substrates with various functional groups and coordination abilities (Scheme 3). **A** is



Scheme 3. Industrially relevant substrates subjected to asymmetric hydrogenation.

a trisubstituted anionic substrate that is a precursor for chiral carboxylic acid derivatives reported as building blocks for the synthesis of an antitumoral prodrug[18a] and several adenosine antagonists.[18b] The hydrogenation product of **B** (known as the Roche ester) is a broadly applicable synthon used, for example, to make the antitumoral drugs tedanolide[18c] and discodermolide.[18d] Cyclic enamides **C** and **D** belong to the important class of aminotetralin precursors. They can be used for the synthesis of many drugs such as Sertraline (antidepressant) and Rotigotine (used to treat Parkinson's disease). Enamide **E** is a precursor for the synthesis of CGP-55845, a GABA-B antagonist.[18e] **F**, **G**, and **H** are precursors of β-amino acids. **H** is also precursor in the synthesis of the VLA-4 antagonist S9059 (used in the treatment of relapsing multiple sclerosis).[3f]

Initial ligand screening

For the initial evaluation of the combinatorial approach that involves the METAMORphos ligands, we performed experiments in which six ligand combinations based on two different anionic ligands and one neutral ligand were applied. The anionic ligand **Lan2**$^-$ was used in its two enantiomeric forms. A relatively high catalyst concentration (2 mM) and low substrate-to-catalyst ratio were used as initial screening was focused on the determination of the enantioselectivity induced by the various

catalyst mixtures. The preparation of the reaction mixtures, the hydrogenation reaction (20 bar), and sampling for analysis were performed by using an Accelerator SLT workstation from Chemspeed Technologies (48 experiments in total). As expected, the substrates are produced in variable enantioselectivities, which depends strongly on the type of ligand employed. The most selective ligand mixture changes with the substrate (Table 1).

Substrate **A** is converted with the highest *ee* if a mixture of **(*S*)-Lan2**$^-$ and **(*R*)-Lneu1** is applied. The enantiomeric form of the product is determined by the chirality of the BINOL unit of **Lan2**$^-$ as the mixture **(*S*)-Lan2**$^-$**/(*R*)-Lneu1** leads to 21% *ee* and the mixture **(*R*)-Lan2**$^-$**/(*R*)-Lneu1** leads to 43% *ee* of the opposite enantiomer. The use of the neutral ligand leads to the lowest conversion in which the racemic product is formed. The homocomplex of **(*R*)-Lan1**$^-$ is as selective as the homocomplex of **(*R*)-Lan2**$^-$, but it is much less active: the conversion is 20% lower with **(*R*)-Lan1**$^-$.

For substrate **B**, all combinations give full conversion. The homocomplexes give poor *ee* values (<10%). Interestingly, the heterocombination of **(*S*)-Lan2**$^-$ and **(*R*)-Lneu1** leads to the highest *ee* (52%), whereas the combination of **(*R*)-Lan2**$^-$ and **(*R*)-Lneu1** leads to a racemic product.

For the hydrogenation of **C**, the combination of **(*R*)-Lan2**$^-$ and **(*R*)-Lneu1** leads to the highest *ee* (64%) with full conversion. The other combinations show good conversions and low *ee* values (25% or less).

For the hydrogenation of substrate **D**, the homocombination of the neutral ligand leads to the highest *ee* by far (−88%). The anionic complexes give very low *ee* values, and the heterocombinations lead to intermediate results.

In the case of substrate **E**, the three homocomplexes give similar *ee* values (43%), and all the heterocombinations lead to poor *ee* values, which indicates more active but less enantioselective heterocomplexes.

For substrate **F**, the highest selectivity is obtained with heterocombination of anionic and neutral ligands in which the BINOL moieties have the same enantiomeric form (**(*R*)-Lan2**$^-$**/(*R*)-Lneu1**; 76%). The application of the homocomplex of **Lneu1** also leads to a good *ee*, whereas the complex based on the anionic ligands gave a low *ee*.

Substrate **G** is hydrogenated with the highest conversion (89%) and the highest *ee* (76%) by the homocomplexes of the neutral ligand. The use of pure anionic ligands leads to much lower *ee* values and conversions.

For the hydrogenation of substrate **H**, the highest *ee* (50%) is obtained with a mixture of **(*R*)-Lneu1** and **(*R*)-Lan2**$^-$, and the highest conversion is achieved with a mixture of **(*R*)-Lneu1** and **(*S*)-Lan2**$^-$. Homocombinations of the anionic ligands lead to racemic products, and homocombinations of the neutral ligand lead to the product with a modest *ee* and low conversion.

Focused ligand optimization

Iterative procedures in combinatorial catalysis are typically used to converge rapidly to an active and selective catalyst.[6a,9e,16] We were curious to know if our system could be employed in such an evolutionary approach. We extended the ligand library by structural changes on the BINOL moiety for the anionic METAMORPhos ligand. The neutral ligands were varied systematically at their amino acid moiety. The robotic workstation was used to perform 94 hydrogenations in parallel, but the preparation of the catalyst solutions was performed in a glovebox to minimize catalyst decomposition by air. For this second run, the catalyst concentration was decreased to 1 mM, the substrate concentration was increased to 100 mM, and the other parameters were kept constant. Neutral and anionic ligands of opposite chirality at the BINOL unit were used for the hydrogenation of substrates **A** and **B**, and ligands with the same chirality at the BINOL were used for the reaction of **C**, **F**, and **H**. As substrates **D**, **E**, and **G** were hydrogenated more efficiently with homocombinations of ligands for the first run, they were not considered for this optimization run.

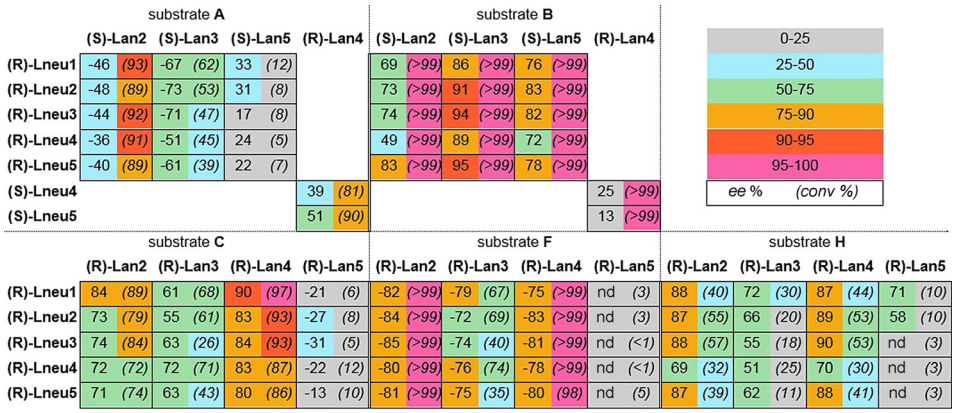
The results presented in Figure 2 establish that varying the amino acid moiety allows the fine-tuning of the catalytic system (minor contribution), whereas changing the BINOL unit of the METAMORPhos ligand has the biggest influence (major contribution) on the catalytic outcome. The effect of these contributions on the asymmetric hydrogenation of substrates **A**–**H** will be discussed below.

For substrate **A**, if the unfunctionalized BINOL unit of METAMORPhos is replaced with the methylated version **Lan3**$^-$, the *ee* is improved (from <50 to 73%), however, the conversion decreases (from >89 to <62%). If the bigger trimethylsilyl functionalized ligand **Lan5**$^-$ is used, the conversion decreases

Table 1. Initial hydrogenation results.

		A		B		C		D		E		F		G		H	
		ee[a] [%]	Conv.[a] [%]	*ee*[b] [%]	Conv.[b] [%]	*ee*[b] [%]	Conv.[b] [%]	*ee*[b] [%]	Conv.[b] [%]	*ee*[b] [%]	Conv.[b] [%]	*ee*[b] [%]	Conv.[b] [%]	*ee*[c] [%]	Conv.[b] [%]	*ee*[c] [%]	Conv.[b] [%]
(*R*)-Lan1$^-$		18	80	−7	>99	3	85	2	>99	**−43**	**>99**	−8	97	1	29	−2	73
(*R*)-Lan1$^-$	**(*R*)-Lneu1**	20	98	20	>99	13	91	−26	>99	−4	>99	−43	>99	−5	51	20	7
(*R*)-Lan2$^-$		17	>99	−10	>99	18	90	7	>99	**−43**	**>99**	−4	98	−5	12	<1	49
(*R*)-Lan2$^-$	**(*R*)-Lneu1**	21	>99	2	>99	**64**	**>99**	−33	>99	6	>99	**−76**	**96**	−58	56	**50**	**49**
(*S*)-Lan2$^-$	**(*R*)-Lneu1**	**−43**	**>99**	**52**	**>99**	<1	94	−33	>99	24	>99	−57	96	−37	43	29	78
(*R*)-Lneu1		1	50	−6	>99	25	99	**−88**	**>99**	**−43**	**>99**	−72	93	**−76**	**89**	10	4

Conditions: [Rh] = 2 mM, $[L]_{total}$ = 4.4 mM, [S] = 50 mM, reaction time = 18 h, pressure = 20 bar, solvent = CH_2Cl_2. [a] Determined by chiral GC after methylation (see Supporting Information). [b] Determined by chiral GC. [c] Determined by chiral HPLC.



substrate A

	(S)-Lan2		(S)-Lan3		(S)-Lan5		(R)-Lan4	
(R)-Lneu1	-46	(93)	-67	(62)	33	(12)		
(R)-Lneu2	-48	(89)	-73	(53)	31	(8)		
(R)-Lneu3	-44	(92)	-71	(47)	17	(8)		
(R)-Lneu4	-36	(91)	-51	(45)	24	(5)		
(R)-Lneu5	-40	(89)	-61	(39)	22	(7)		
(S)-Lneu4							39	(81)
(S)-Lneu5							51	(90)

substrate B

	(S)-Lan2		(S)-Lan3		(S)-Lan5		(R)-Lan4	
(R)-Lneu1	69	(>99)	86	(>99)	76	(>99)		
(R)-Lneu2	73	(>99)	91	(>99)	83	(>99)		
(R)-Lneu3	74	(>99)	94	(>99)	82	(>99)		
(R)-Lneu4	49	(>99)	89	(>99)	72	(>99)		
(R)-Lneu5	83	(>99)	95	(>99)	78	(>99)		
(S)-Lneu4							25	(>99)
(S)-Lneu5							13	(>99)

substrate C

	(R)-Lan2		(R)-Lan3		(R)-Lan4		(R)-Lan5	
(R)-Lneu1	84	(89)	61	(68)	90	(97)	-21	(6)
(R)-Lneu2	73	(79)	55	(61)	83	(93)	-27	(8)
(R)-Lneu3	74	(84)	63	(26)	84	(93)	-31	(5)
(R)-Lneu4	72	(72)	72	(71)	83	(87)	-22	(12)
(R)-Lneu5	71	(74)	63	(43)	80	(86)	-13	(10)

substrate F

	(R)-Lan2		(R)-Lan3		(R)-Lan4		(R)-Lan5	
(R)-Lneu1	-82	(>99)	-79	(67)	-75	(>99)	nd	(3)
(R)-Lneu2	-84	(>99)	-72	(69)	-83	(>99)	nd	(3)
(R)-Lneu3	-85	(>99)	-74	(40)	-81	(>99)	nd	(<1)
(R)-Lneu4	-80	(>99)	-76	(74)	-78	(>99)	nd	(<1)
(R)-Lneu5	-81	(>99)	-75	(35)	-80	(98)	nd	(5)

substrate H

	(R)-Lan2		(R)-Lan3		(R)-Lan4		(R)-Lan5	
(R)-Lneu1	88	(40)	72	(30)	87	(44)	71	(10)
(R)-Lneu2	87	(55)	66	(20)	89	(53)	58	(10)
(R)-Lneu3	88	(57)	55	(18)	90	(53)	nd	(3)
(R)-Lneu4	69	(32)	51	(25)	70	(30)	nd	(3)
(R)-Lneu5	87	(39)	62	(11)	88	(41)	nd	(3)

Figure 2. Results of focused ligand optimization. For each ligand combination, the *ee* [%] is given on the left and the conversion [%] is given on the right in brackets; [Rh] = 1 mM, [L] = 2.2 mM, [S] = 100 mM, reaction time = 18 h, pressure = 20 bar, solvent = CH_2Cl_2.

to less than 12%. For the neutral ligands, **Lneu4** gives the lowest *ee*, **Lneu5** gives the lowest conversion, **Lneu2** leads to the highest *ee*, and **Lneu1** shows the highest conversion (combined with **Lan2**$^-$ or **Lan3**$^-$). In the case of substrate **B**, **Lan3**$^-$ also gives better results in terms of enantioselectivity, and for this substrate the conversion remains high. Bulky **Lan5**$^-$ also gives a reasonable *ee* and full conversion, which is because **B** is a geminally disubstituted alkene with low hindrance. In combination with **Lan2**$^-$, **Lneu5** gives good results. In combination with **Lan3**$^-$, **Lneu5** and **Lneu3** lead to the highest *ee* (94–95%). **Lneu4** leads to the lowest *ee* if combined with **Lan2**$^-$. For the hydrogenation of **C**, the use of METAMORPhos with an octahydro-BINOL backbone **Lan4**$^-$ leads to the highest enantioselectivity and conversion (90% *ee* and 97% conversion if combined with **Lneu1**); the enantioselectivity with this ligand is on average 10% higher than that of the parent BINOL ligand (**Lan2**$^-$) at a similar conversion. Surprisingly, **Lan5**$^-$ gives the product of opposite chirality (−13 to −31% *ee*). This result cannot be because of the homocomplex of the amino-acid-based ligand, as the homocomplex of **Lneu1** leads to the product with +25% *ee* (Table 1). For the hydrogenation of **C**, the best neutral ligand is **Lneu1**, both in combination with **Lan2**$^-$ and **Lan4**$^-$. Both **Lan2**$^-$ and **Lan4**$^-$ in combination with any neutral ligand, give full conversion for the hydrogenation of substrate **F**. The use of **Lan2**$^-$ leads to the highest *ee* (−80 to −85%), followed by **Lan4**$^-$ (−75 to −83%). **Lan3**$^-$ is slightly less selective (72–79% *ee*) and significantly less active. The strong influence of the bulkiness of the BINOL moiety on the conversion of this substrate is further illustrated by the poor conversion obtained with the trimethylsilyl-BINOL-based ligand. Again, changing the neutral ligand only has a minor influence on the *ee* if **Lan2**$^-$ is used as the anionic ligand. If it is used in combination with **Lan4**$^-$, the choice of the neutral ligand shows a more profound effect: **Lneu1** gives −75% *ee* and **Lneu2** gives −83% *ee*.

The use of **Lan2**$^-$ and **Lan4**$^-$ gives the highest *ee* values and conversions for the hydrogenation of substrate **H**. The amino acid moiety has a strong influence on the activity of the catalyst: in combination with **Lan2**$^-$ and **Lan4**$^-$, the use of **Lneu2** and **Lneu3** lead to the highest conversion (>53%), the use of **Lneu1** and **Lneu5** lead to intermediate results (≈40% conversion), and the use of **Lneu4** leads to the lowest conversion (30–32%). Except for **Lneu4**, which leads to a lower *ee* (by ~20%), the choice of the neutral ligand does not have a major impact on the *ee* in combination with **Lan2**$^-$ and **Lan4**$^-$: 87 or 88% *ee* are obtained with **Lan2**$^-$ and 87–90% *ee* are obtained with **Lan4**$^-$.

Ligand ratio study

If mixtures of monodentate phosphorus ligands are used, a mixture of complexes is expected to be formed. As such, the optimal ratio to favor the presence of complex with two different ligands (heterocombination) is 1:1. For this reason, in most combinatorial studies, a ligand ratio of 1:1 is used. However, if the mixture of complexes is not statistical or if one homocomplex is significantly more active than the heterocomplex, the optimal ratio to obtain the highest selectivity can be far from this 1:1 ratio.[6a,7] To gain an insight into these aspects, we performed catalytic experiments in which the ligand ratios were varied. For each substrate, we used the ligand combination that gave the optimal *ee* and conversion (Figure 2): (***R***)-**Lneu1**/(***S***)-**Lan3**$^-$ for **A**, (***R***)-**Lneu3**/(***S***)-**Lan3**$^-$ for **B**, (***R***)-**Lneu1**/(***R***)-**Lan4**$^-$ for **C**, (***R***)-**Lneu3**$^-$/(***R***)-**Lan2**$^-$ for **F**, and (***R***)-**Lneu3**/(***R***)-**Lan4**$^-$ for **H**.

For each substrate, the *ee* and the conversion as a function of the mole fraction of ligand **Lan**$^-$ (the total concentration of ligand [**Lan**$^-$]+[**Lneu**] was kept constant) is shown in Figure 3. The plot obtained for substrate **A** shows a maximum *ee* if the fraction of **Lan**$^-$ was between 20 and 70%. The conversion shows a broad maximum around the 1:1 ratio of **Lan**$^-$ and **Lneu**.

These results indicate clearly that for this catalytic system, the heterocombination is significantly more active and selective as the results are relatively insensitive to the ligand ratio used. The plot obtained for substrate **B** is substantially different: although the *ee* is high between 40 and 70% of **Lan**$^-$, below 40% the *ee* decreases rapidly. This suggests that the homocomplex of **Lneu**, which forms the product of opposite enantioselectivity, shows significant activity compared to the heterocomplex. In the case of substrate **C**, the plot shows that the homocomplex of **Lneu** has a poor selectivity and a negligible activity compared to the heterocomplex.[19] Already with 10% of **Lan**$^-$, the *ee* reaches a plateau of ~90% *ee*. The heterocombination is more active than the homocomplex of **Lan**$^-$ as the maximum conversion was obtained between 50 and 70% **Lan**$^-$.

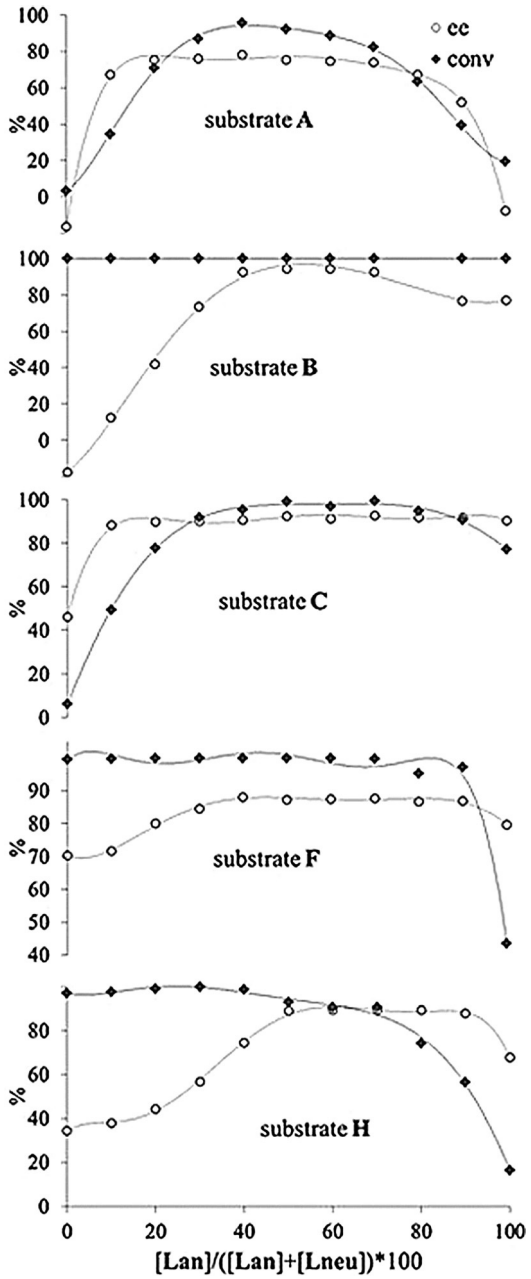


Figure 3. Results of the ligand ratio optimization. [Rh] = 0.5 mM, $[L]_{total}$ = 2.2[Rh], [S] = 200*[Rh], reaction time = 18 h, pressure = 20 bar, solvent = CH_2Cl_2.

The plot obtained for substrate **F** shows full conversion for all experiments, except if the homocomplex of **Lan**$^-$ is employed. The maximum *ee* is obtained as a plateau at a proportion of **Lan**$^-$ between 40 and 90%, which indicates that the heterocomplex is more active and selective. For the hydrogenation of **H**, the homocomplex of **Lneu** is significantly more active than the heterocombination, and the homocomplex of **Lan**$^-$ is almost inactive. As the homocomplex of **Lneu** gives poor enantioselectivity, the highest *ee* is obtained if $[Rh(\mathbf{Lneu})_2]^+$ is virtually absent in the mixture (this already occurs if the **Lan**$^-$/**Lneu** ratio is 1).

Conclusions

The potential of METAMORPhos ligands in combinatorial catalysis has been demonstrated. These ligands can form both mononuclear [ML_2] and dinuclear [M_2L_4] complexes that are active in asymmetric hydrogenation. Here we expanded the application of METAMORPhos ligands by using mixtures of ligands in combination with neutral phosphoramidite ligands as a new combinatorial strategy to arrive at a diverse set of catalysts. In situ spectroscopic studies show the formation of various mononuclear and dinuclear heterocomplexes. If the anionic ligand (**Lan**) and neutral ligand (**Lneu**) have the same chirality, mononuclear neutral heterocomplexes are by far the major species, although monoanionic dinuclear heterocomplexes have also been detected. If **Lan** and **Lneu** have the opposite chirality, mixtures of complexes are obtained. As a result of their modularity, METAMORPhos ligands are highly suitable for iterative procedures, which are commonly used in high-throughput screening. For most substrates hydrogenated in this study, the application of the mixture of ligands resulted in a more enantioselective formation of the product compared to the use of the pure homocomplexes.

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