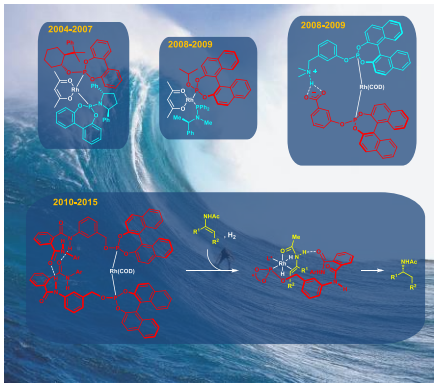
Catch the wave. The re-discovery of chiral monodentate ligands which was made around 2000 triggered new trends in enantioselective transition metal catalysis, such as the use of ligand mixtures and an increasing interest for supramolecular ligands. This account summarizes the most important contributions provided by our group within this area between 2004 and 2015.



*Luca Pignataro, Cesare Gennari**

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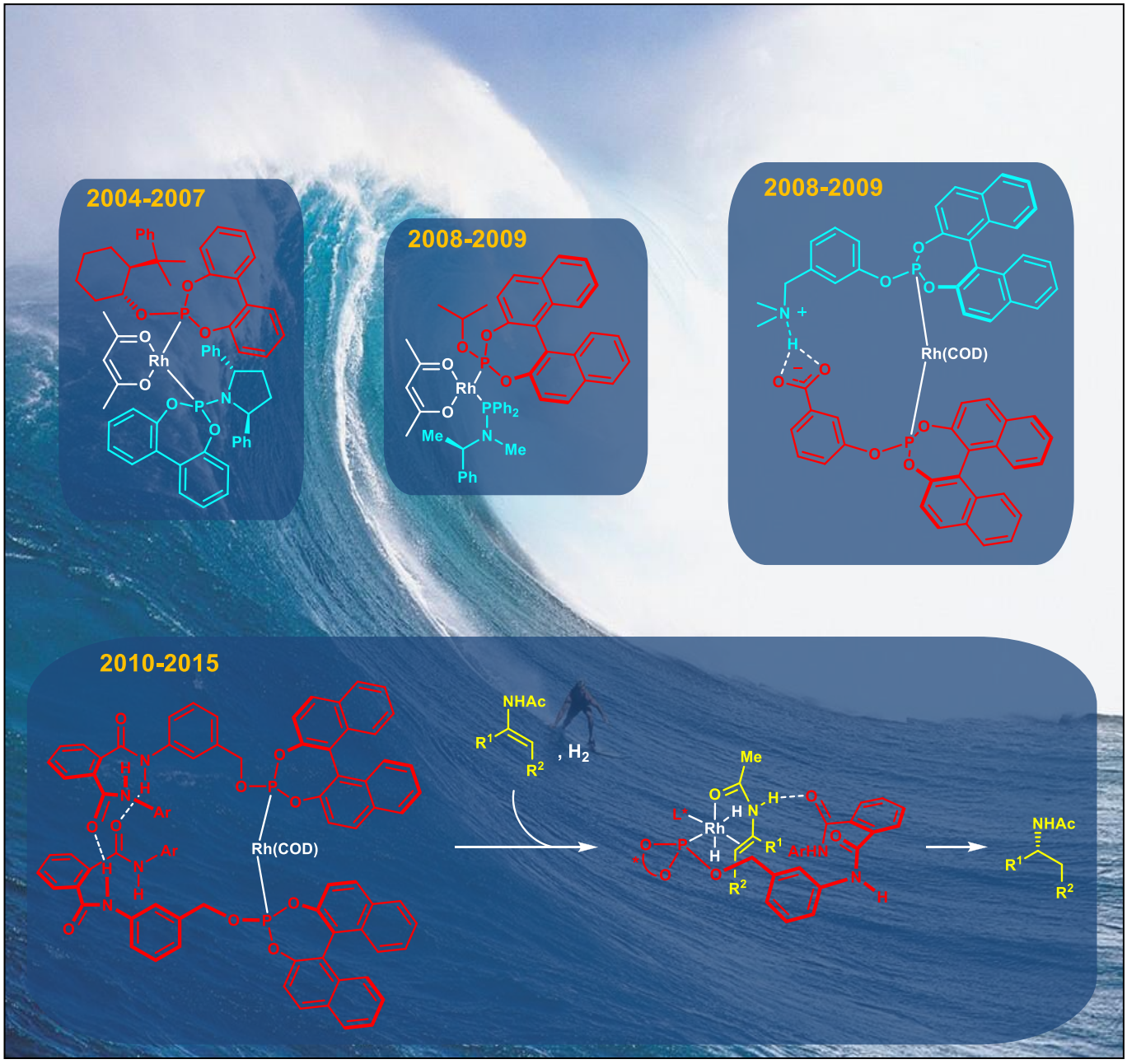
Riding the wave of monodentate ligand revival: from the A/B concept to non-covalent interactions

Riding the wave of monodentate ligand revival: from the A/B concept to non-covalent interactions

Luca Pignataro,[a] and Cesare Gennari*[a]

Dedicated to Prof. Ryoji Noyori on the occasion of the 15th anniversary of his Nobel Prize in Chemistry



Abstract: The re-discovery of chiral monodentate ligands that was made in the 1999-2003 period had important consequences in enantioselective transition metal catalysis, such as the introduction of the A/B concept (i.e., use of monodentate ligand mixtures) and, later, a renewed interest in supramolecular ligands capable of ligand-ligand and ligand-substrate interactions. This Personal Account summarizes the contributions made by our research group in this area in the period 2004-2015, which reflect quite well the above-mentioned developments. Within this area, we introduced some original concepts, such as: i) use of chiral *tropos* ligand mixtures; ii) development of new strategies to maximize the heterocomplex formation from combinations of simple monodentate ligands; iii) investigation of new ligand-ligand interactions to achieve selective heterocomplex formation; iv) development of highly efficient and synthetically accessible supramolecular ligands.

1. Introduction

It all started some twenty years ago when, at the end of a "Human Capital and Mobility" EC Network (1993-1996) where I served as the scientific coordinator, I passed the lead to Reinhard Hoffmann (Philipps-Universität Marburg), who successfully applied for a “Training and Mobility of Researchers” EC Network (1996-2000) called "Combinatorial Approaches to Molecular Catalysts". In 2000, we renewed a successful application for an “Improving Human Potential” EC Network (2000-2004) called "The Discovery of New Catalysts through Combinatorial Chemistry: Activity and Selectivity from Diversity", with Albrecht Berkessel (Universität zu Köln) as coordinator. Under the strong leadership of Reinhard first and then Albrecht, we made the first steps in the Combicat field, which included combinatorial catalysis, parallel synthesis of libraries of chiral ligands, and high-throughput screening of the catalyst libraries. It was the time when Combinatorial Chemistry was being developed in the pharmaceutical world, and we investigated alternative aspects. Our first paper in this field, entitled “Combinatorial Libraries: Studies in Molecular Recognition and the Quest for New Catalysts”, was published in *Liebigs Ann./Recueil* in 1997,[1] the year before merging into the *European Journal of Organic Chemistry*. In that period, our main focus was the investigation of new chiral ligands for enantioselective catalysis via parallel synthesis and high throughput screening of the ligand library.[2,3]

New libraries containing hundreds of chiral ligands were designed and synthesized in parallel. A multisubstrate high-throughput screening of the ligand library was realized by performing the reactions on an equimolar mixture of substrates and directly analyzing the reaction crudes for conversion and enantiomeric excess by gas chromatography with a chiral capillary column, under conditions where the 2n peaks of the n enantiomeric products showed baseline separation.[2e-j] From the screening of the ligand library, the best ligand was identified for a particular substrate. The results confirmed the value of the combinatorial approach: it would have been very difficult to identify the best ligand for a particular substrate if a “rational” or a “positional scanning” approach were followed for the ligand synthesis.[2]

The field was reviewed in 2003 with a highly cited article “Combinatorial libraries of chiral ligands for enantioselective catalysis” in Chemical Reviews.[3] I like to mention the collaborations of that period, with Richard Jackson (The University of Newcastle and then the University of Sheffield from 2001), Adriaan Minnaard and Ben Feringa (University of Groningen), Sergio Cenini and his group (University of Milan). I also like to mention a number of students and postdocs of that period, who later on embarked in an academic career: Umberto Piarulli (University of Insubria at Como), Isabelle Chataigner (Université de Rouen, Mont-Saint-Aignan), Sandrine Ongeri (Université Paris-Sud).

At the end of this first decade, we shifted our focus towards the use of dynamic libraries of monodentate ligands in catalysis and of heteroleptic catalysts (i.e., obtained from mixtures of two ligands). This work – which was supported by another EC Research Training Network (2006-2010) called "(R)evolutionary Catalysis" and coordinated by Joost Reek (University of Amsterdam) – is described in the first part of this account (Paragraph 2).[4,5,6,7,8] During these studies, we became interested in supramolecular catalysis, and our contributions in this field – produced within the frame of the European Industrial Doctorate-Initial Training Network “REDUCTO” (2012-2016), coordinated by myself – are described in Paragraph 3.[9,10,11,12,13,14]

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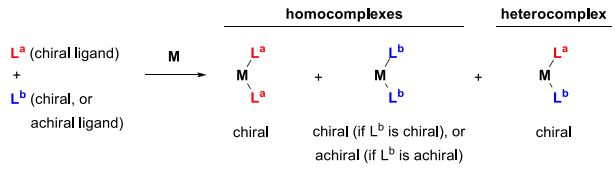
Cesare Gennari was born in Milan (Italy) in 1952. He graduated as “doctor in chemistry” cum laude from Milan University in 1975. After becoming an assistant professor at the same University in 1978 in the group of professor Scolastico, he joined professor Clark Still's group at Columbia University (New York) as a research associate in 1982-83. In 1985 he became an associate professor, and in 1994 a full professor of organic chemistry at Milan University. In the period 2008-2012 he served as director of the Department of Organic and Industrial Chemistry and from 2012 he is a member of the Academic Senate. He is presently (2013-) chairman of the Editorial Board of the European Journal of Organic Chemistry, and a member of the consulting board of editors of Tetrahedron:Asymmetry since 1990. In the period 1998-2001 he has been a member of the IUPAC Organic Chemistry Division Committee, and he is presently a IUPAC fellow since 2004. From 2015 he is a ChemPubSoc Europe Fellow. His research interests include the design and development of new enantioselective methods, and their application to the synthesis of natural and unnatural targets with interesting biological and chemical properties.

Luca Pignataro was born in Gallarate, Italy, in 1978. After graduating at the University of Milan (2003), he got his PhD in 2006 at the same university, under the supervision of Prof. F. Cozzi, with a thesis work in asymmetric organocatalysis. He spent postdoc periods in the groups of Prof. D. Leigh (University of Edinburgh), Prof. C. Gennari (University of Milan) and Prof. U. Piarulli (University of Insubria), before becoming assistant professor at the Department of Chemistry of the University of Milan. His current research interests include synthetic methodologies, enantioselective catalysis and medicinal chemistry.

2. Mixtures of monodentate ligands

2.1. The A/B concept

The "A/B concept" (Scheme 1) was independently proposed by Reetz and co-workers[15] and by Feringa, de Vries and co-workers[16] in the early 2000s: it was shown that use of binary monodentate ligand mixtures (L^a and L^b) in the presence of a metal source (M = Rh in most cases) can lead to better catalytic activity and/or enantioselectivity than when the single ligands are employed. This outcome is observed when the heterocomplex [ML^aL^b] is more active and/or enantioselective than the corresponding homocomplexes [ML^aL^a] and [ML^bL^b]. Interestingly, in some cases, heterocomplexes in which one of the ligands is achiral ([ML*L]) are more enantioselective than the chiral ligand homocomplexes ([ML^*_2]).[15c,17]

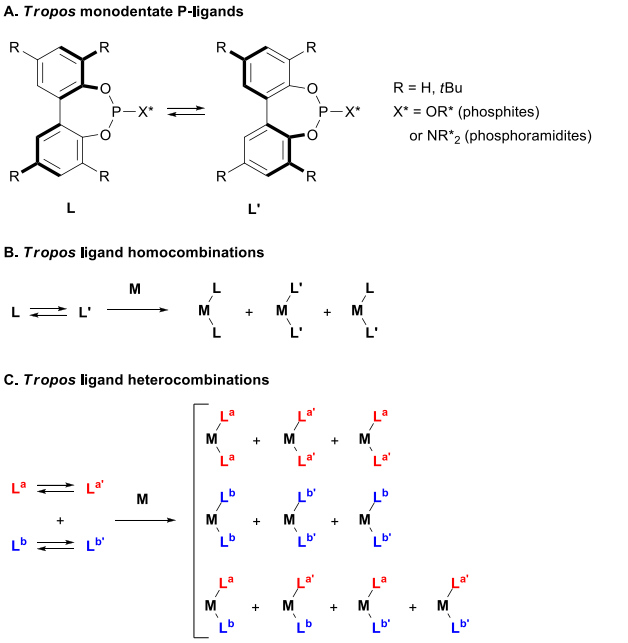


Scheme 1. The "A/B concept": use of binary mixtures of monodentate ligands.

The ligand mixture approach made a strong impact in the field of homogeneous catalysis, whose adepts were generally accustomed to deal with single and well-defined complexes. Moreover, the potential of this approach for combinatorial, high-throughput catalyst screening became immediately evident. Indeed, using a relatively small pool of chiral ligands (*n*), a much bigger number of catalysts could be screened, spreading from *n* ligand homocombinations and [$n \cdot (n + 1) / 2$] - *n* heterocombinations. The A/B concept rapidly found numerous applications in important reactions such as Rh-catalyzed asymmetric hydrogenation and conjugate addition, which were extensively reviewed by M. Reetz in 2008.[18]

2.2. Mixtures of *tropos* ligands

Our main contribution in this field consisted in applying the A/B concept to chiral *tropos* P-ligands, in which the substituents at the phosphorus atom are a chiral alkoxy or amino moiety and a 'flexible' biphenol unit (Scheme 2 A).[19] *Tropos* P-ligands possessing the biphenol motif had been already employed by others in Cu-catalyzed reactions (enantioselective conjugate addition[20] and allylic substitution[21]), Rh-catalyzed transformations (olefin asymmetric hydrogenation[22] and hydroformylation [23]), but we were the first to use *combinations* of monodentate ligands belonging to this family. As a consequence of the free stereoaxis rotation, these ligands exist as mixtures of the rapidly interconverting diastereoisomers L and L' (Scheme 2 B) and, in the presence of a metal with two free coordination sites, each ligand can form up to three complexes: [ML_2], [ML'_2] and [MLL']. When two *tropos* monodentate ligands L^a and L^b are mixed in the presence of a metal, a sort of 'dynamic library' of up to 10 complexes may be formed *in situ* (Scheme 2 C): [ML^aL^a], [$ML^aL^{a'}$], [$ML^{a'}L^{a'}$], [ML^bL^b], [$ML^bL^{b'}$], [$ML^{b'}L^{b'}$], [ML^aL^b], [$ML^aL^{b'}$], [$ML^{a'}L^b$], [$ML^{a'}L^{b'}$].



Scheme 2. Stereoaxis rotation in biphenol-derived *tropos* ligands (A); homocombinations (B) and heterocombinations (C) of *tropos* monodentate ligands in the presence of a metal.

In principle, each of these species can catalyze a given reaction with a different level of stereoselectivity and stereochemical preference (*R* or *S* product). As a consequence, the overall observed stereochemical outcome is a sort of average weighted by the catalytic activity of each complex, with the most active complex(es) overriding the less active ones. We thus synthesized a library of nineteen biphenol-derived chiral *tropos* P-ligands (11 phosphites and 8 phosphoramidites), shown in Figure 1.

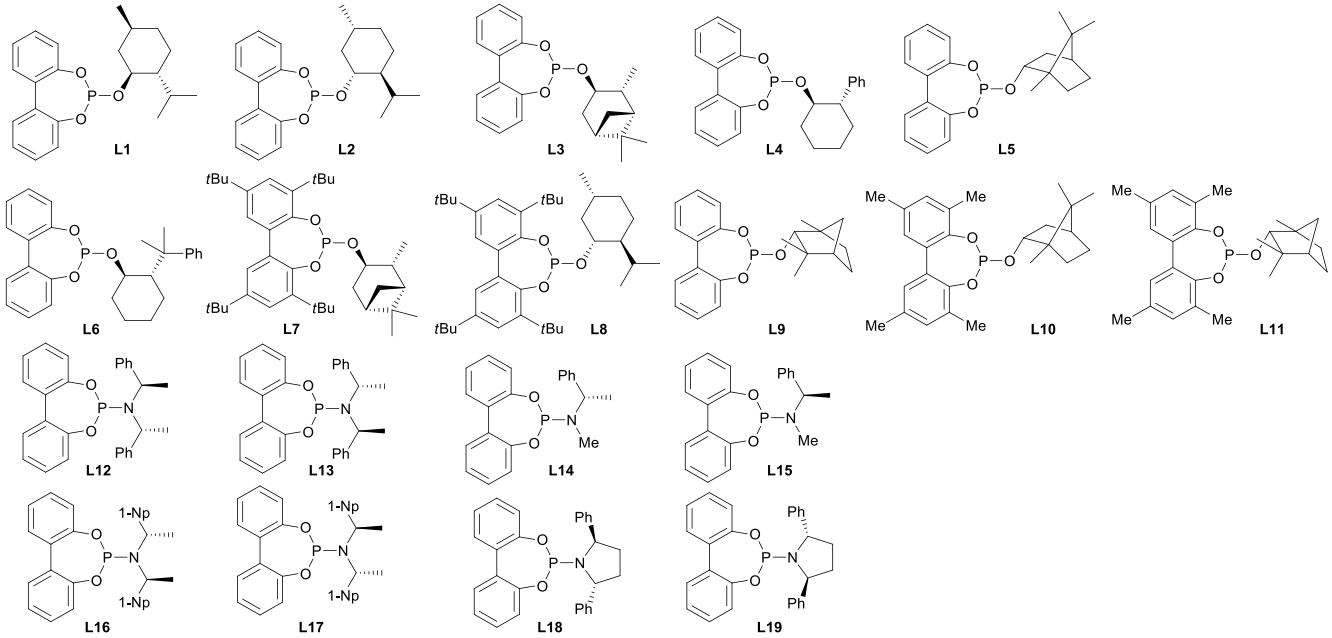
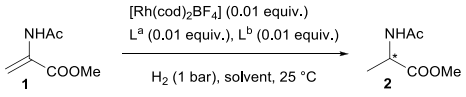


Figure 1. Library of *tropos* phosphites (**L1**-**L11**) and phosphoramidites (**L12**-**L19**) employed by our research group in Rh-catalyzed reactions.

Ligands **L1-L19** and their combinations were screened in two different Rh-catalyzed reactions:[6] (i) the asymmetric hydrogenation of olefins[4] and (ii) the asymmetric conjugate addition of phenylboronic acids to cyclic enones.[5]

The first hydrogenation screening was carried out using methyl 2-acetamidoacrylate (**S1**) as a substrate (selected results in Table 1).[4]

Table 1. Selected results in Rh-catalyzed hydrogenation of methyl 2-acetamidoacrylate (**1**) using ligands **L1**-**L19**.[a]



Entry	L^a	L^b	Solv.	Yield (%)[b]	*ee* (%),[b] abs. config.
1	**L3**	**L3**	DCM	100	25, *R*
2	**L4**	**L4**	DCM	80	53, *S*
3	**L5**	**L5**	DCM	100	55, *R*
4	**L12**	**L12**	DCM	7	52, *R*
5	**L13**	**L13**	DCM	7	52, *S*
6	**L3**	**L13**	DCM	40	73, *S*
7	**L4**	**L12**	DCM	100	35, *R*
8	**L4**	**L13**	DCM	100	87, *S*
9	**L4**	**L13**	MeOH	100	88, *S*
10	**L4**	**L13**	*i*PrOH	100	94, *S*
11	**L4**	**L13**	AcOEt	100	91, *S*

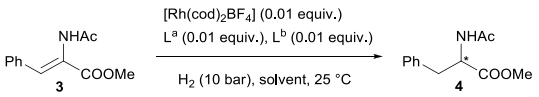
[a] Reaction conditions: ligands (0.002 mmol L^a and 0.002 mmol L^b), $[Rh(cod)_2BF_4]$ (0.002 mmol), **1** (0.2 mmol), solvent (2 mL), H_2 (1 bar), r.t., 60 h. [b] Yields and *ee*s determined by GC equipped with a chiral column.[4a]

Before using ligand mixtures ('heterocombinations'), the ligands were screened individually ('homocombinations'). As a general trend, phosphites (Table 1, entries 1-3) showed much higher catalytic activity than phosphoramidites (Table 1, entries 4-5), and both types of ligand gave moderate enantioselectivity (up to 55% *ee*). No benefit derived from the use of phosphite/phosphite and phosphoramidite/phosphoramidite heterocombinations: the former gave full conversions and low enantioselectivity, and the latter gave low conversion and lower enantioselectivity than the corresponding single ligands. On the contrary, the phosphite/phosphoramidite combinations (Table 1, entries 6-11) led in several cases to a remarkable improvement of the enantioselectivity, while substantially retaining the high activity of the phosphite complexes. The best combination **L4**/**L13** allowed to obtain (*S*)-*N*-acetylalanine methyl ester **2** with 100% yield and 87% *ee* (Table 1, entry 8). The corresponding mismatched combination **L4**/**L12** gave the (*R*)-product with only 35% *ee* (Table 1, entry 7), thus showing that the sense of stereocontrol is determined by the configuration of the phosphoramidite ligand. Use of polar solvents allowed to improve the enantioselectivity (Table 1, entries 9-11), and the best *ee* (94%) was obtained in *i*PrOH (Table 1, entry 10). Under these optimized conditions (*i*PrOH, 1 bar H_2, r.t.), also *N*-acetamidoacrylic acid was hydrogenated with full conversion and 94% *ee* using the combination **L4**/**L13**.

In collaboration with Prof. J. G. de Vries, Dr. A. H. M. de Vries, and Dr. L. Lefort (DSM Pharma Chemicals – Advanced Synthesis, Catalysis, and Development), we could carry out high-throughput ligand screening in hydrogenation using a Premex-96 multireactor.[4a]

In the hydrogenation of methyl 2-acetamidocinnamate **3** (selected results in Table 2) the scenario was quite similar to that observed with substrate **1**: phosphites formed more active catalysts than phosphoramidites and the phosphite/phosphoramidite heterocombinations led to a remarkable improvement of the enantioselectivity (Table 2, entry 3 vs. entries 1-2).

Table 2. Selected results in Rh-catalyzed hydrogenation of methyl 2-acetamidocinnamate (**3**) using ligands **L1**-**L19**.[a]



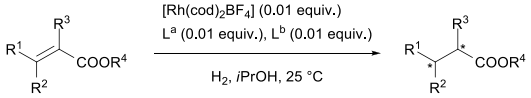
Entry	L^a	L^b	Solv.	Yield (%)[b]	*ee* (%),[b] abs. config.
1	**L4**	**L4**	DCM	100	64, *S*
2	**L13**	**L13**	DCM	2	6, *S*
3	**L4**	**L13**	DCM	82	85, *S*
4[c]	**L4**	**L13**	*i*PrOH	100	95, *S*
5	**L5**	**L19**	DCM	100	69, *R*
6	**L6**	**L19**	DCM	100	64, *R*

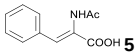
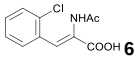
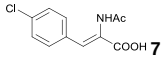
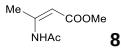
[a] Reaction conditions: ligands (0.0035 mmol L^a and 0.0035 mmol L^b), $[Rh(cod)_2BF_4]$ (0.0035 mmol), **3** (0.175 mmol), solvent (2.5 mL), H_2 (10 bar), r.t., 16 h. [b] Yields and *ee*s determined by GC equipped with a chiral column.[4a] [c] H_2 (5 bar).

Also with **3**, the combination **L4**/**L13** gave the best results (Table 2, entry 3). A solvent screening carried out in an autoclave multireactor (Agonaut Endeavor™) led to identify *i*PrOH as the best solvent (100% yield, 95% *ee*, Table 2, entry 4). Switching to 2-acetamidocinnamic acid (**5**) under optimized conditions (*i*PrOH, 10 bar H_2, r.t.) led to similar results (Table 3, entry 1), **L4**/**L13** being again the best ligand combination. However, improved enantioselectivity was obtained with substrates **6** and **7**, chloro-substituted derivatives of 2-acetamidocinnamic acid (Table 3, entries 2-3).

Another ligand screening was carried out with methyl (*Z*)-3-acetamidocrotonate (**8**), precursor of chiral β-aminoacids, which are pharmaceutical building blocks. With this substrate, **L3**/**L19** was identified as the best ligand combination, forming the (*R*)-product with 71% *ee* (Table 3, entry 4).

Table 3. Selected results in Rh-catalyzed hydrogenation of 2-acetamidocinnamic derivatives (**4**-**6**) and methyl (*Z*)-3-acetamidocrotonate (**7**) using ligands **L1**-**L19**.[a]



Entry	Substrate	L^a	L^b	Yield (%)[b]	*ee* (%),[b] abs. conf.
1	 **5**	**L4**	**L13**	100	93, *S*
2	 **6**	**L4**	**L13**	100	98, *S*
3	 **7**	**L4**	**L13**	100	97, *S*
4[c]	 **8**	**L3**	**L19**	100	71, *R*

[a] Reaction conditions: ligands (0.01 mmol L^a and 0.01 mmol L^b), $[Rh(cod)_2BF_4]$ (0.01 mmol), substrate (0.5 mmol), solvent (5 mL), H_2 (10 bar), r.t., 16 h. [b] Yields and *ee*s determined by GC equipped with a chiral column.[4a] [c] Ligands (0.0035 mmol L^a and 0.0035 mmol L^b), $[Rh(cod)_2BF_4]$ (0.0035 mmol), substrate (0.175 mmol), solvent (2.5 mL), H_2 (25 bar).

Kinetic studies were carried by monitoring the H_2 uptake of hydrogenation of substrates **1**, **3** and **8** in the presence of the most efficient ligand heterocombination (**L4**/**L13** for **1** and **3**; **L3**/**L19** for **8**) and of the corresponding homocombinations (Figure 2).[4a] For substrate **1** (Figure 2 A), it was found that phosphite **L4** forms a very fast Rh-catalyst, achieving full conversion (with 61% *ee*) in 12 minutes. On the contrary, the homocomplex of phosphoramidite **L13** proved very sluggish, giving only 2% conversion (with 89% *ee*) after a few hours. The **L4**/**L13** heterocombination – yet slightly less active than the **L4**-homocomplex – showed good catalytic activity, giving full conversion and 94% *ee* in 20 minutes. This result clearly indicates that a Rh-complex containing both **L4** and **L13** was the most enantioselective species present in solution. As a consequence, maximizing the extent of heterocomplex formation was expected to lead to an increase of the enantioselectivity.

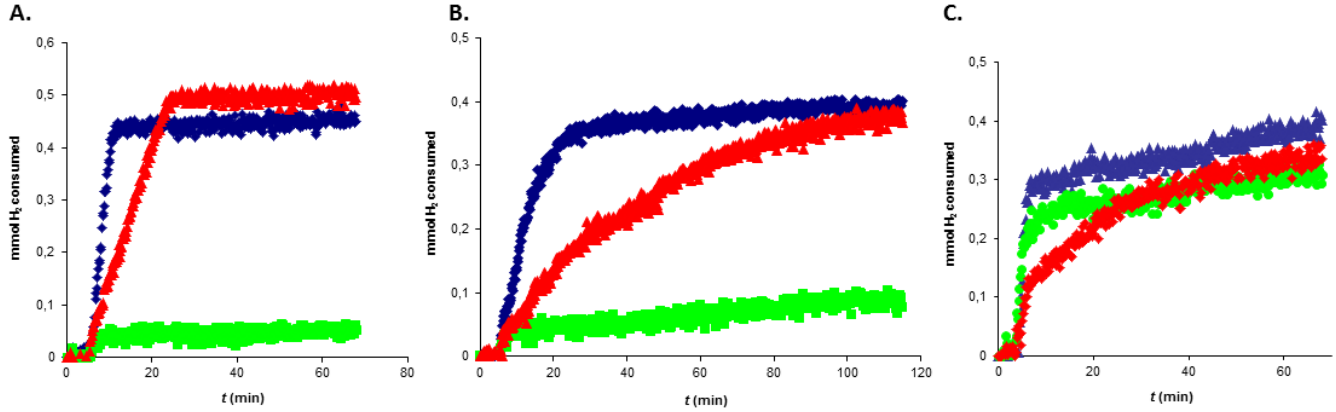


Figure 2. Hydrogen uptake experiments (P_{H2} = 5 bar; solvent: *i*PrOH). A: substrate = methyl 2-acetamidoacrylate (**1**), ligand(s) = **L4** (♦), **L13** (■) and 1:1 **L4**/**L13** (▲); B: substrate = methyl 2-acetamidocinnamate (**3**), ligand(s) = **L4** (♦), **L13** (■) and 1:1 **L4**/**L13** (▲); C: substrate = methyl (*Z*)-3-acetamidocrotonate (**7**), ligand(s) = **L3** (▲), **L19** (●) and 1:1 **L4**/**L19** (♦).

We reasoned that decreasing the **L4/L13** ratio (while keeping the 2:1 [**L4** + **L13**]/Rh ratio constant) would allow to enhance the amount of **L4**/**L13**-heterocomplex and **L13**-homocomplex formed, at the expense of the **L4**-homocomplex. As the **L13**-homocomplex is a very sluggish catalyst, it should not negatively affect the overall observed enantioselectivity, which instead would benefit from the enhanced amount of heterocomplex. Delightfully, when a 0.25:1.75 **L4/L13** ratio was used, the hydrogenation of **1** occurred with 100% yield and 98% *ee*. We carried out several other experiments varying the **L4/L13** ratio (Figure 3, curve A), which confirmed that 0.25:1.75 is the optimal ratio between the two ligands.

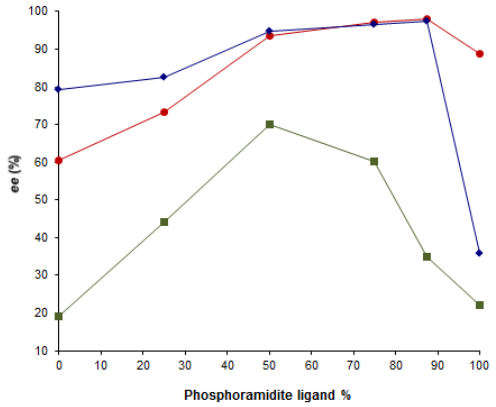
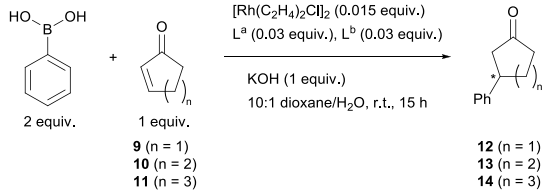


Figure 3. Dependence of the product *ee* on the phosphite/phosphoramidite ratio in the hydrogenation of: A (●): methyl 2-acetamidoacrylate **1** (P_{H2} = 5 bar, ligands = **L4/L13**); B (♦): methyl 2-acetamidocinnamate **3** (P_{H2} = 5 bar, ligands = **L4/L13**); C (■): methyl (*Z*)-3-acetamidocrotonate **7** (P_{H2} = 25 bar, ligands = **L3/L19**). Solvent = *i*PrOH.

The H_2 uptake profiles in the hydrogenation of methyl 2-acetamidocinnamate **3** (Figure 2 B) are analogous to those observed with substrate **1** (Figure 2 A): the **L4** homocomplex showed high catalytic activity (full conversion and 79% *ee* in 30 minutes) and the **L13** homocomplex was very sluggish (only 2% conversion and 36% *ee*), while the 1:1 **L4/L13** heterocombination gave full conversion and 95% *ee* in 2 h. Also in this case, experiments carried out with different ligand ratios (while keeping the 2:1 [**L4** + **L13**]/Rh ratio constant) showed that the highest *ee* (98%) is obtained with a 0.25:1.75 **L4/L13** ratio (Figure 3, curve B), although at the cost of a lower conversion (79%). Therefore, with these examples we demonstrated that *the ee obtained from binary ligand mixtures which are more enantioselective than the corresponding homocomplexes can be enhanced by carefully adjusting the L^a:L^b ratio, provided that at least one of the homocomplexes is remarkably less active than the heterocomplex*. As can be seen in Figure 2 C, the latter requirement was not satisfied in the case of the hydrogenation of methyl (*Z*)-3-acetamidocrotonate **8** with ligands **L3** and **L19**. Indeed, in this case the two Rh-homocomplexes were both more active than the heterocomplex (which was the most enantioselective species): as demonstrated by our experiments with different **L3/L19** ratios (Figure 3, curve C), in this case the optimal ligand ratio is 1:1, which statistically favors the formation of the heterocomplex over the homocomplexes.

We tested our *tropos* ligands **L1**-**L19** (Figure 1) also in the Rh-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic enones,[24] to which chiral monophosphoramidites had been recently applied with success by Feringa and co-workers.[25] The reaction of phenylboronic acid with 2-cyclohexenone **10** was carried out in the presence of 1.5 mol% of $[Rh(C_2H_4)_2Cl]_2$ and 6 mol% of ligand(s) (Rh/L = 1:2).[5,6] The reaction was carried out in a 10:1 dioxane/H_2O mixture at r.t. in the presence of KOH (1 equiv.) as base.[26] Selected results of this screening are shown in Table 4.

Table 4. Selected results from the screening of the **L1**-**L19** library (homo- and heterocombinations) in the Rh-catalyzed conjugate addition of phenylboronic acid to cyclic enones.[a]



9 (n = 1)
10 (n = 2)
11 (n = 3)

12 (n = 1)
13 (n = 2)
14 (n = 3)

Entry	Enone	L^a	L^b	Yield (%)[b]	*ee* (%),[b] abs. conf.
1	**10**	**L6**	**L6**	100	70, *R*
2	**10**	**L9**	**L9**	100	28, *R*
3	**10**	**L18**	**L18**	100	36, *S*
4	**10**	**L19**	**L19**	100	36, *R*
5	**10**	**L6**	**L19**	100	95, *R*
6	**10**	**L9**	**L19**	100	91, *R*
7	**10**	**L6**	**L18**	100	70, *S*
8	**10**	**L9**	**L18**	100	87, *S*
9	**11**	**L9**	**L18**	100	80, *S*
10	**11**	**L2**	**L18**	80	83, *S*
11	**11**	**L6**	**L19**	100	90, *R*
12	**11**	**L9**	**L19**	100	90, *R*
13	**9**	**L7**	**L7**	100	58, *S*
14	**9**	**L6**	**L19**	100	73, *R*
15	**9**	**L9**	**L19**	100	68, *R*

[a] Standard reaction conditions: (L^a + L^b)/$[Rh(C_2H_4)_2Cl]_2$/$PhB(OH)_2$/KOH/substrate = 0.06:0.015:2:1:1. [b] Yields and *ee*s determined by GC equipped with a chiral column.[5a]

As a general trend, when the ligands were used individually (homocombinations), phosphites (**L1**-**L11**) formed more active and enantioselective complexes than phosphoramidites (**L12**-**L19**). However, the enantioselectivities were moderate, the best *ee* (70%) being obtained with ligand **L6** (Table 4, entry 1). Most of the ligand mixtures screened formed catalysts less active and enantioselective compared to phosphite homocomplexes, with the remarkable exception of the phosphite/phosphoramidite combinations containing either **L18** or **L19** (Table 4, entries 5-15). These heterocombinations gave full conversion and remarkably higher enantioselectivities compared to the corresponding homocomplexes: the combinations **L6/L19** and **L9/L19** allowed to obtain (*R*)-3-phenylcyclohexanone (**13**) with 95% and 91% *ee*, respectively (Table 4, entries 5-6). As in the above-discussed hydrogenation, the corresponding mismatched

combinations **L6**/**L18** (Table 4, entry 7) and **L9**/**L18** (Table 4, entry 8) showed opposite stereochemical preference [(*S*)- instead of (*R*)-**13**], thus proving that it is the phosphoramidite which determines the absolute configuration of the reaction product. The effect of substrate's ring size was assessed by screening all the homocombinations and several heterocombinations with 2-cyclopentenone (**9**) and 2-cycloheptenone (**11**). Also with these substrates, the heterocombinations containing the 2,5-diphenylpyrrolidine phosphoramidites **L18** and **L19** gave the best results: in particular, the matched combination **L6**/**L19** afforded the products (*R*)-**12** and (*R*)-**14** with 90% and 73% *ee*, respectively (Table 4, entries 11 and 14).

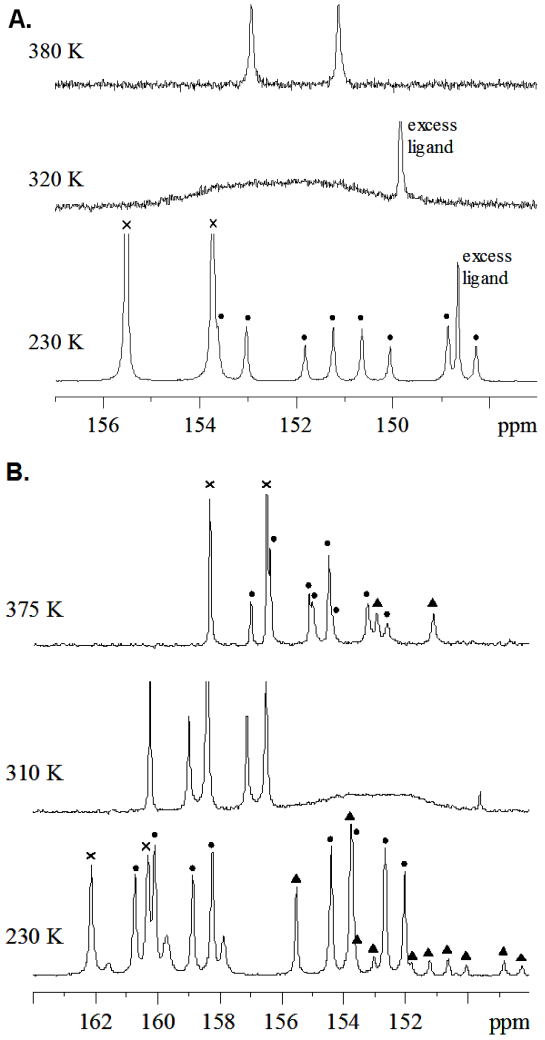
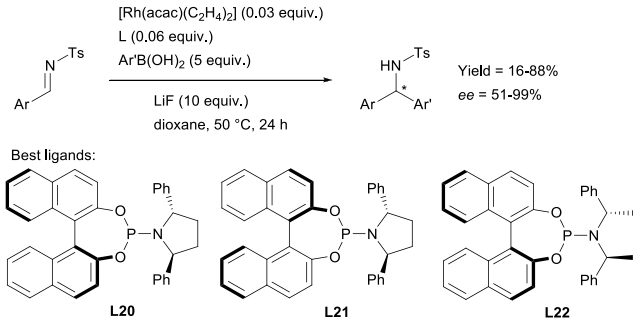


Figure 4. Variable-temperature ^{31}P NMR experiments. A: homocomplex **L19**/[Rh(acac)(C_2H_4)$_2$]; B: heterocombination **L6**/**L19**/[Rh(acac)(C_2H_4)$_2$]. Marks above the peaks allow the identification of the different complexes.

Although such terms as "induced atropoisomeric"[20b] and "fluxionally atropoisomeric"[17c] had been used for metal complexes of biphenolic *tropos* ligands, as of 2005 no in-depth study of their *tropos* or *atropos* behavior had been reported. Thus, we were among the first to carry out such investigation,[27] which was performed by variable-temperature ^{31}P NMR spectroscopy.[5] In particular, we studied the dynamic behavior of the two best performing ligands (phosphite **L6** and phosphoramidite **L19**) and of their homo- and heterocombinations in the presence of [Rh(acac)(C_2H_4)$_2$]. The free ligands were studied over the temperature range 380-180 K. Above 210 K, one singlet peak was always observed, indicating a free rotation of the biaryl bond (*tropos* behavior). Below this temperature, the signal broadened and eventually split in two signals with coalescence temperatures (T_C) between 200 K and 180 K. In the case of ligand **L6**, we observed T_C = 197 K, corresponding to a free energy barrier for biphenol rotation $\Delta G^{\ddagger}$ = 8.5 kcal mol^{-1}. The Rh-complexes were studied over the temperature range 380-230 K, as it was not possible to cool below 230 K due to solubility issues. Within this range, the **L6** homocomplex always gave a doublet signal, denoting a *tropos* behavior. On the contrary, the **L19** Rh-homocomplex displayed a typical coalescence behavior (T_C = 320 K in [D]$_8$toluene; T_C = 290 K in CD_2Cl_2). As shown in Figure 4 A, below the T_C, the originally observed doublet signal split in one doublet (×), corresponding to the complexes {Rh[(a*R*)-**L19**]$_2$} and {Rh[(a*S*)-**L19**]$_2$} – in which the P-ligands are homotopic – and two doublet doublets (•), corresponding to the complex {Rh[(a*R*)-**L19**][(a*S*)-**L19**]} – in which the P-ligands are diastereotopic. The **L6**/**L19** heterocombination treated with [Rh(acac)(C_2H_4)$_2$] (Figure 4 B), besides the above-described homocomplex signals (× and ▲, ca. 40% of total integration), showed other signals (•) which can be assigned to a heterocomplex [Rh(**L6**)(**L19**)] (ca. 60% of total integration): at 375 K, two doublet doublets were observed, corresponding to a *tropos* behavior of both **L6** and **L19**. These signals coalesced at 310 K and, by further cooling to 230 K, a new system of two doublet doublets appeared. The latter was assigned as one of the possible diastereoisomers that can be obtained when **L19** is *atropos* while the stereoaxis of **L6** is still free to rotate (*tropos*): {Rh(**L6**)][(a*R*)-**L19**]} or {Rh(**L6**)][(a*S*)-**L19**]}. The free energy barrier for phosphoramidite biphenol rotation in [D$_8$]toluene (T_C = 310 K) was calculated: $\Delta G^{\ddagger}$ = 14.5 kcal mol^{-1}. To guess the configuration of the **L19** stereoaxis in this complex, we synthesized ligands **L20** and **L21** (Scheme 3) – (*S*)- and (*R*)-BINOL-derived analog of **L19**, respectively – and we used them in combination with **L6** in our test reaction on 2-cyclohexenone. However, surprisingly these combinations were less effective than **L6**/**L19** [50% yield, 46% *ee* (*R*) with **L6**/**L20**; 70% yield, 72% *ee* (*R*) with **L6**/**L21**], thus emphasizing the peculiar properties of a *tropos*/*atropos* biphenol moiety near the coalescence temperature.



Scheme 3. Rh-catalyzed enantioselective addition of arylboronic acids to *N*-tosylarylimines.[7]

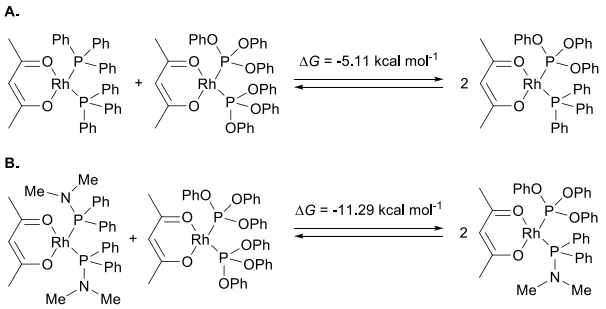
In the attempt to further expand the application scope of our chiral *tropos* ligands, we investigated the Rh-catalyzed addition

of arylboronic acids to *N*-tosylarylimines.[7] However, in this transformation the use of ligand mixtures did not bring any significant benefits, and the best results were obtained with the *atropos* phosphoramidites **L20**-**22** (Scheme 3).

Recently, in collaboration with Dr. L. Lefort and Prof. J. G. de Vries, we used a mixed ligand strategy in the asymmetric hydrogenation of 2-substituted *N*-benzylated pyridinium salts. A catalyst formed in situ from $[Ir(cod)Cl]_2$, a chiral monodentate phosphoramidite and an achiral phosphine, allowed to obtain the corresponding *N*-benzyl-2-aryl-piperidines with full conversion and good enantioselectivity (up to 82% *ee*).[17a]

2.3. Maximizing the amount of heterocomplex

Our interest in chiral monodentate ligands and their combinations led us to investigate new methods to maximize the formation of the heterocomplexes $[ML^aL^b]$ at the expense of the corresponding homocomplexes $[ML^aL^a]$ and $[ML^bL^b]$. Indeed, when the heterocomplex is more enantioselective than the homocomplexes, the statistical distribution 2:1:1 $[ML^aL^b]/[ML^aL^a]/[ML^bL^b]$ leads to erosion of the overall enantioselectivity, unless the catalytic activity of $[ML^aL^b]$ is much higher than that of $[ML^aL^a]$ and $[ML^bL^b]$. Whereas most of the strategies to achieve selective heterocomplex formation rely on supramolecular ligands (see Paragraph 3), we also pursued a different approach, which consists in combining simple monodentate ligands with complementary electronic properties.[8] We reasoned that electronically matching ligands, such as a π-acceptor phosphite and a σ-donor phosphine, could selectively form the heterocomplex owing to its higher stability compared to the homocomplexes. To test this hypothesis, we carried out a preliminary computational study (DFT calculations at the B3LYP/SDD level of theory), showing that the triphenylphosphite/triphenylphosphine Rh-heterocomplex is more stable than the corresponding homocomplexes by 5.11 kcal mol^{-1} (Scheme 4 A).



Scheme 4. DFT study on the relative stability of heterocomplexes vs. homocomplexes (B3LYP/SDD level of theory). A: a phosphite/phosphite heterocombination. B: a phosphite/phosphinamine heterocombination.

Consistent with this theoretical result, when $[Rh(acac)(C_2H_4)_2]$ was added to a 1:1 mixture of phosphite **L23** (Figure 5) and PPh_3, 94:6 heterocomplex/homocomplexes selectivity was observed by ^{31}P NMR spectroscopy, the heterocomplex giving a set of two doublet doublet signals (Figure 6 A). We aimed at applying this approach to chiral ligand mixtures, but chiral monophosphines are not readily available nor easy to make. Therefore we envisaged phosphinamines as a possible replacement for phosphines. Indeed, chiral phosphinamines can be easily prepared from readily available chiral amines, while retaining σ-donor properties similar to those of phosphines. DFT calculations showed that the triphenylphosphite/(*R*)-*N*,*N*-dimethyl-1,1-diphenylphosphinamine heterocomplex is more stable than the corresponding homocomplexes by 11.29 kcal mol^{-1} (Scheme 4 B).

We thus synthesized a small library of chiral phosphites (**L23**-**27**), derived from BINOL, and phosphinamines (**L28**-**34**), which are shown in Figure 5.

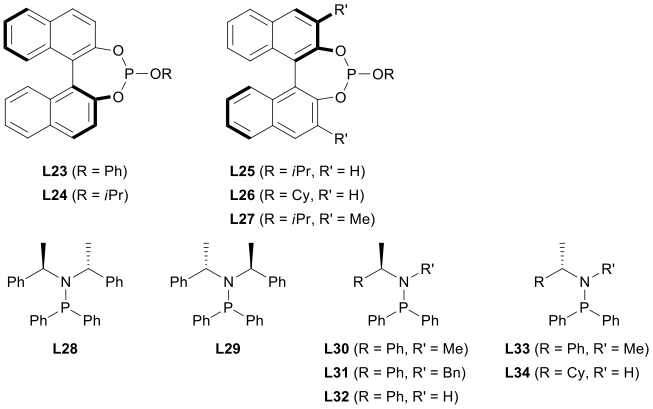


Figure 5. Chiral phosphites (**L23**-**27**) and phosphinamines (**L28**-**34**) used for π-acceptor/σ-donor heterocombinations.

The formation of phosphite/PPh_3 and of phosphite/phosphinamine heterocomplexes in the presence of $[Rh(acac)(C_2H_4)_2]$ was investigated by ^{31}P NMR spectroscopy. When either PPh_3 (Figure 6 A) or C_1-symmetric phosphinamines (**L30**-**34**) were combined with a BINOL-phosphite, the heterocomplexes were formed with selectivities ranging from 70% to ≥ 99%, as in the case of combination **L25**/**L30** (Figure 6 B).

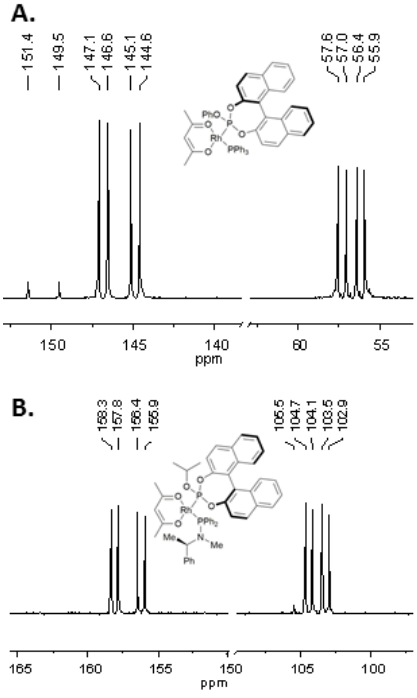
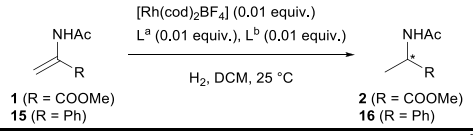


Figure 6. ^{31}P NMR study on the formation of Rh-heterocomplexes (CD_2Cl_2). A: 1:1:1 PPh_3/**L23**/$[Rh(acac)(C_2H_4)_2]$ (94:6 heterocomplex/homocomplexes). B: A: 1:1:1 **L30**/**L25**/$[Rh(acac)(C_2H_4)_2]$ (99:1 heterocomplex/homocomplexes).

Homo- and heterocombinations of ligands **L23**-**34** were tested in the asymmetric hydrogenation of methyl 2-acetamidoacrylate **1** and *N*-(1-phenylvinyl)acetamide **15** (selected results are shown in Table 5).

Table 5. Selected results in Rh-catalyzed hydrogenation of methyl 2-acetamidoacrylate (**1**) and *N*-(1-phenylvinyl)acetamide (**15**) using ligands **L23**-**L30**.[a]



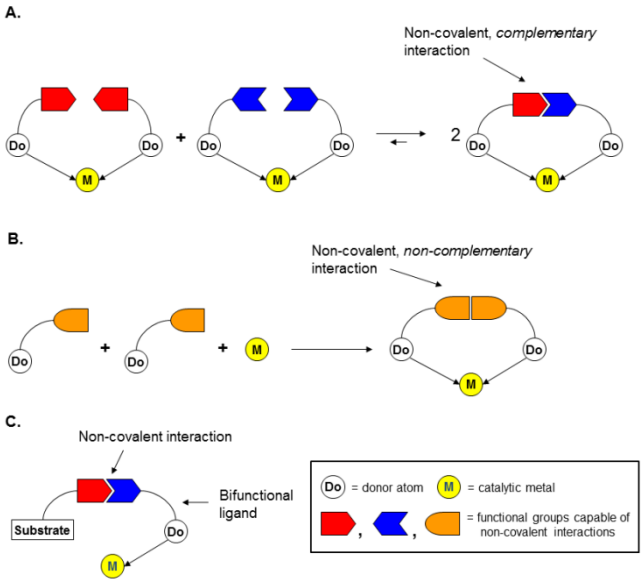
Entry	Substrate	L^a	L^b	Yield (%)[b]	*ee* (%),[b] abs. config.
1	**1**	**L25**	**L25**	100	96, *S*
2	**1**	**L30**	**L30**	52	12, *S*
3	**1**	**L33**	**L33**	57	12, *R*
4	**1**	**L25**	**L30**	87	60, *R*
5	**1**	**L25**	**L33**	48	40, *R*
6	**15**	**L25**	**L25**	100	92, *S*
7	**15**	**L30**	**L30**	83	7, *R*
8	**15**	**L33**	**L33**	74	7, *S*
9	**15**	**L25**	**L30**	99	57, *R*
10	**15**	**L25**	**L33**	96	38, *R*

[a] Reaction conditions: ligands (0.0077 mmol L^a and 0.0077 mmol L^b), $[Rh(cod)_2BF_4]$ (0.007 mmol), substrate (0.7 mmol), DCM (8 mL), H_2 (1 bar with subst. **1**, 5 bar with subst. **15**), r.t., 16 h. [b] Yields and *ee*s determined by GC equipped with a chiral column.[8]

With both substrates, phosphinamines behaved poorly, giving low conversions and *ee*s (Table 5, entries 2-3 and 7-8). Remarkably, the heterocombinations **L25**/**L30** and **L25**/**L33** showed opposite stereochemical preference than the corresponding homocombinations (Table 5, entry 4 vs. 1 and 2; entry 10 vs. 6 and 8), consistent with the heterocomplex being the main catalyst in the reaction environment. Unfortunately, both activity and enantioselectivity of these heterocomplexes were lower than those of phosphite homocomplexes. Ligands **L25**, **L30** and **L33** were tested also in Pd-catalyzed asymmetric allylic substitution, giving again a peculiar stereochemical outcome but no improvement in terms of enantioselectivity.[8]
Although the catalytic results were somehow disappointing, to the best of our knowledge this was the first report in which the importance of using electronically matching ligands to maximize the heterocomplex formation is clearly discussed. In other contributions, this effect is given limited[28] or no emphasis,[29] whereas the selective heterocomplex formation is mostly attributed to supramolecular interactions.

3. Supramolecular ligands

In the last 10-15 years, the interest for the development of new supramolecular ligands – i.e. ligands possessing, besides the donor atom(s) required for metal coordination, a functional group capable of non-covalent interactions – has grown significantly.[30] Such non-covalent interactions can occur between ligands, leading to formation of the so-called 'supramolecular bidentate ligands' (Scheme 5 A and B), or between ligand(s) and substrate (Scheme 5 C), giving rise to a substrate orientation effect similar to the one exerted by metalloenzymes. In particular, the formation of *complementary* interactions between ligands can allow the selective or exclusive formation of heteroleptic complexes from ligand mixtures (Scheme 5 A), thus overcoming an intrinsic limitation of the mixed ligand approach (see Paragraph 2.3). For this reason, since 2002-2003 several groups started developing chiral monodentate ligands capable of different kinds of non-covalent interactions.



Scheme 5. Non-covalent interactions for the formation of heterocomplexes (A), for the formation of heterocomplexes (B), and for substrate coordination (C).

In this context, after exploring the strategies described in Paragraph 2 (i.e., variation of the ligand ratio and use of electronically matching ligands) to maximize the formation of monodentate ligand heterocomplexes, we also pursued the supramolecular approach.
Our first attempt in this sense was the development of BINOL-phosphites bearing either an electron-rich (methoxyarene) or an electron-poor (perfluoroarene) substituent,[9] with the aim to achieve preferential formation of the Rh-heterocomplexes by means of π-π interactions.[31] Unfortunately, although in some cases the ligand heterocombinations gave better *ee*s (up to 99% *ee*) than the corresponding homocombinations in olefin hydrogenation, no selective formation of Rh-heterocomplexes could be detected by ^{31}P NMR. Thus, π-π interactions turned out to be too weak (in solution) to drive the equilibrium towards the heterocomplexes.

3.1. Acid-base interactions

In 2008, we set to investigate an alternative approach to the selective formation of heterocomplexes relying on ionic interactions. Indeed, we reasoned that the electrostatic interaction between ligands bearing opposite charge could shift the equilibrium towards the heterocomplexes, as it had just been preliminarily shown (although with no catalytic applications) by van Leeuwen and co-workers.[32] Our strategy consisted in

combining ligands bearing an acidic and a basic group, respectively, which would react forming the desired ion pair. To this end, a small library of BINOL-phosphites bearing a carboxylic acid and a tertiary amino group, respectively, was synthesized (selected examples are shown in Figure 7).[10]

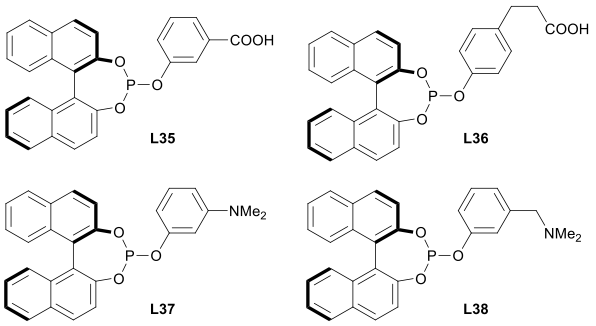
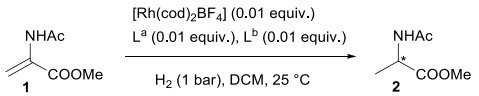


Figure 7. Selected examples from our library of acidic (**L35**-**36**) and basic BINOL-phosphites (**L37**-**L38**).[10]

Acidic and basic phosphites were combined in the presence of $[Rh(acac)(C_2H_4)_2]$ and the formation of Rh-complexes was monitored by ^{31}P NMR, while the formation of the amine-carboxylic acid salt was verified by IR. Unfortunately, only moderate selectivity for the heterocomplexes was observed (up to 70:30 heterocomplex/homocomplexes). Homo- and heterocombinations of acidic and basic ligands were tested in the hydrogenation of methyl 2-acetamidoacrylate **1**, and in some cases enhanced *ee*s were obtained with the heterocombinations (Table 6).

Table 6. Selected results in Rh-catalyzed hydrogenation of methyl 2-acetamidoacrylate (**1**) using acidic and basic BINOL phosphites **L35**-**38**.[a]



Entry	L^a	L^b	Yield (%)[b]	*ee* (%),[b] abs. config.
1	**L35**	**L35**	100	80, *S*
2	**L36**	**L36**	100	80, *S*
3	**L37**	**L37**	100	84, *S*
4	**L38**	**L38**	30	86, *S*
5	**L35**	**L38**	100	90, *S*
6	**L36**	**L38**	100	88, *S*

[a] Reaction conditions: ligands (0.0077 mmol L^a and 0.0077 mmol L^b), $[Rh(cod)_2BF_4]$ (0.007 mmol), **1** (0.7 mmol), DCM (1 mL), H_2 (1 bar), r.t., 24 h. [b] Yields and *ee*s determined by GC equipped with a chiral column.[10]

Although low selectivity in the heterocomplex formation was achieved, to the best of our knowledge this is the first use of ligand-ligand ion-pairing interactions for a catalytically relevant complex.[33]

3.2. Hydrogen bonding interactions

After the seminal contribution by Breit and Seiche in 2003,[34o] hydrogen bonding has rapidly become the most studied and exploited non-covalent interaction for achieving the formation of 'supramolecular bidentate ligands' from both ligand homocombinations[34] and heterocombinations.[29b-c, 35] This success is due to the easy synthesis and stability of several functional groups capable of hydrogen bonding and to the fact that hydrogen bonds can form dynamically and reversibly in the environment where catalysis is to take place, without need to preliminarily prepare the ligand-ligand assembly. As shown in Scheme 5 A, only when the ligand-ligand interaction is *complementary*, it is possible to selectively form the heterocomplexes from binary ligand mixtures.[30g,35] However, also the ligand-ligand assemblies formed from *non-complementary* interactions (Scheme 5 B) can warrant enhanced catalytic performances – compared to simple monodentate ligands – because their complexes are rigid and conformationally restricted as those of bidentate ligands.[30g,34]
In 2010 we reported a new family of BINOL-phosphites, named PhthalaPhos, bearing a bis-phthalamide residue able to act both as a donor and as an acceptor of hydrogen bond in non-complementary interactions.[12] Owing to the modular structure (see Figure 8) and easy preparation of these ligands (4 steps from phthalic anhydride), we could synthesize a small library of 19 representatives, differing from each other in: i) the 3,3'-substitution of the BINOL moiety; ii) the ancillary amide residue (i.e., the one not bearing the phosphite); iii) the linker between the two units.

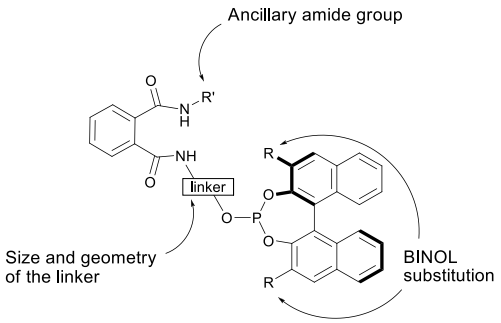


Figure 8. General structure of the PhthalaPhos ligands with possible sites of diversity.

The library was screened in the Rh-catalyzed hydrogenation of several pro-chiral substrates including dehydroamino esters, *N*-acyl enamides and α,β-unsaturated esters. Consistent with the expected role of the phthalamide residue, both size/geometry of the linker connecting the phosphite group to it, and the ancillary amide group strongly influenced yield and enantioselectivity (highly diverse results were obtained throughout the library).[12] The best results are shown in Table 7: benchmark substrates **1**, **3** and **15** could be hydrogenated with nearly full enantioselectivity. Remarkably, outstanding *ee* values (96% and 99%, respectively) were obtained also with the challenging substrates **17** and **18**, precursors of industrially relevant chiral building blocks. The *ee* obtained with **18** was the highest ever reported for this substrate at that time. Notably, almost in all cases the simple monophosphites **L49** and **L50**, devoid of the phthalamide moiety, gave lower *ee* and/or yield compared to the best PhthalaPhos ligand.
NMR, IR and computational experiments (DFT) carried out on a representative ligand (**L42**, Table 7) and on its Rh-complex $[Rh(cod)(\mathbf{L42})_2BF_4]$ allowed to confirm that, in this pre-catalytic

complex, two hydrogen bonds are present between the coordinated ligands' phthalamide groups (Figure 9).[12b]

Table 7. Selected results from the screening of the PhthalaPhos and BenzaPhos library in the Rh-catalyzed asymmetric hydrogenation of olefins.[a]

Substrate	NHAc COOMe **1**	NHAc Ph COOMe **3**	NHAc Ph **15**	NHAc **17**	NHAc COOMe Ph **18**
P_{H2}	1 bar	1 bar	5 bar	20 bar	50 bar
Best PhthalaPhos ligand	**L39**	**L40**	**L41**	**L42**	**L43**
ee, abs. conf.[b]	> 99%, *R*	99%, *R*	99%, *R*	96%, *R*	99%, *R*
Best BenzaPhos ligand	**L44**	**L45**	**L46**	**L47**	**L48**
ee, abs. conf.[b]	99%, *R*	> 99%, *R*	> 99%, *R*	> 99%, *R*	> 99%, *R*
Reference ligand	**L49**	**L49**	**L49**	**L49**	**L49**
ee, abs. conf.[b]	84%, *R*	70%, *R*	90%, *R*	53%,[c] *R*	32%,[c] *R*
Reference ligand	**L50**	**L50**	**L50**	**L50**	**L50**
ee, abs. conf.[b]	90%, *R*	83%, *R*	94%, *R*	96%,[d] *R*	90%,[c] *R*

[a] Reaction conditions: substrate/ligand/$[Rh(cod)_2BF_4]$ = 100:2.2:1, solvent = DCM, c_0 (substrate) = 0.024 M, T = 25 °C, 24 h. [b] Yields and *ee*s determined by GC equipped with a chiral column.[12,13] Yield = 100% in all cases, unless otherwise stated. [c] Yield < 50%. [d] Slower kinetics compared to **L42**.

Thus, in the pre-catalytic complex the two coordinated molecules of **L42** behave as a 'supramolecular bidentate ligand'.

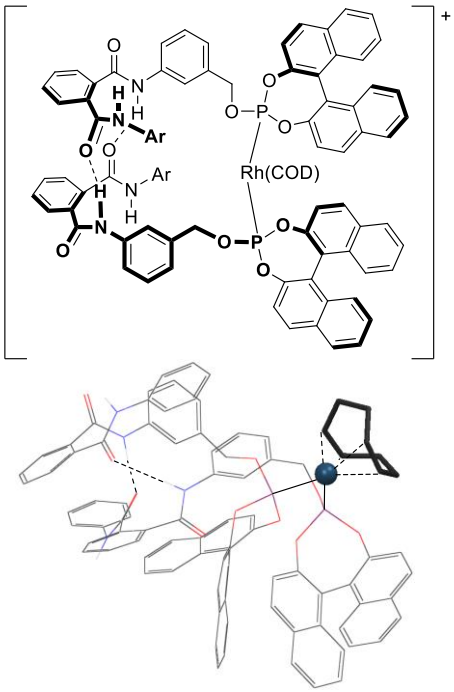


Figure 9. DFT-calculated structure of the pre-catalytic complex $[Rh(\mathbf{L42})_2(cod)BF_4]$ (wires and tubes: grey = C, red = O, blue = N, magenta = P; CPK spheres: blue = Rh).

However, the results of several control experiments carried out using modified versions of ligand **L42** and of the hydrogenation substrates demonstrate that, in the hydrogenation catalytic cycle, the role played by the phthalamide group is different,[12a] and probably consists in a substrate orientation effect.[36] We built the computational model of a conceivable intermediate of the catalytic cycle (Figure 10 A, substrate: **17**, ligand: **L42**) where a hydrogen bond between an amide oxygen of **L42** and the substrate's NH is present.

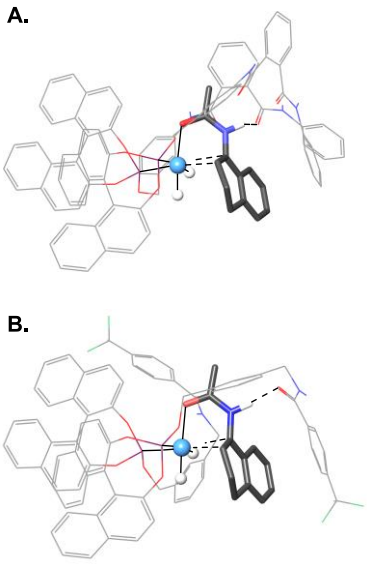


Figure 10. DFT-optimized structures of dihydride intermediates of the Rh-catalyzed hydrogenation of **17** in the presence of ligand **L42** (A) and **L47** (B), respectively [wires (P-ligands) and tubes (substrate **17**): grey = C, light grey = amide H atoms, black = heteroatoms (N, O, P); CPK spheres: black = Rh, grey = H. All H atoms bound to carbon are omitted].

As the outstanding performances of the PhthalaPhos ligands seemed to be due to their ability to form a single hydrogen bond with the reaction substrate, we reasoned that their structure could be further simplified by replacing the phthalamide residue with a simple benzamide. In this way, we created a new library

of ligands (Figure 11), called BenzaPhos, which could be prepared in only two steps from commercially available compounds.[13]

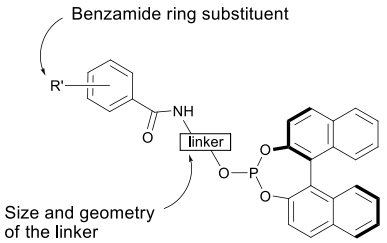


Figure 11. General structure of the BenzaPhos ligands with possible sites of diversity.

Owing to the modular structure and trivial synthesis of these ligands, the following approach was adopted for ligand synthesis, screening and optimization in Rh-catalyzed hydrogenation: firstly, a 13-member library of ligands bearing an unsubstituted benzamide group and differing in the linker was prepared and screened with several pro-chiral olefin substrates. Once some hits were identified, structural modifications were introduced in the benzamide group of the best three ligands, and a small second-generation library was created, which gave improved results with some substrates.[13] The BenzaPhos ligands showed a scope similar to PhthalaPhos and also in this case, for each substrate, yields and *ee* values widely ranged from ligand to ligand. The best ligands (shown in Table 7) gave outstanding results (99% or > 99% *ee*) with substrates **1**, **3**, **15** and **18**, and the *ee* obtained with substrate **17** (> 99%) was the best ever reported.

Control experiments (with modified versions of ligand **L47** and of substrate **17**) analogous to those carried out with the PhthalaPhos ligands suggest that, in the catalytic cycle, the role of the bezamide group consists in coordinating the substrate. A computational model of a catalytic cycle intermediate was built (Figure 10 B), where a hydrogen bond between the ligand and the substrate's NH is present.

Recently, we have started testing the PhthalaPhos ligands in other transition metal-catalyzed reactions, obtaining some interesting results in Pd-catalyzed asymmetric allylic alkylation (AAA) reactions.[37] We investigated the synthesis of two types of chiral alkaloid scaffolds – 1-vinyltetrahydroisoquinoline[14b] and 4-vinyltetrahydrocarbazole[14a] – by cyclization of suitable allylic carbonates.

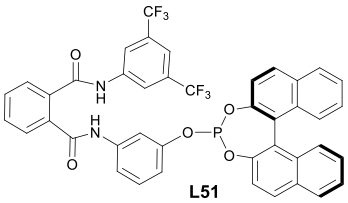
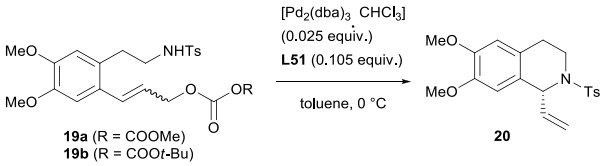


Figure 12. Phosphite **L51**, best ligands in the synthesis of 1-vinyltetrahydroisoquinoline (**20**) and 4-vinyltetrahydrocarbazole (**22**) by Pd-catalyzed intramolecular AAA.

For both these reactions, phosphite **L51** (Figure 12) turned out to be the best ligand, and thus was used for reaction optimization. For the synthesis of 1-vinyltetrahydroisoquinoline **20**,[14b] optimization of the reaction parameters led to identify toluene as the best solvent and 0 °C as the temperature ensuring the best compromise between catalytic activity and enantioselectivity.

Table 8. Synthesis of 1-vinyltetrahydroisoquinoline **20** by Pd-catalyzed of allylic carbonates under optimized conditions.[a]



19a (R = COOMe)
19b (R = COO*t*-Bu)

20

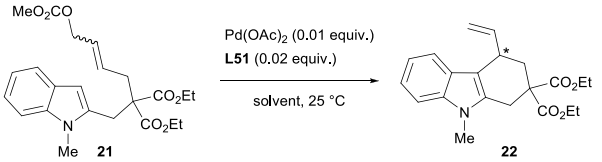
Entry	Substrate	*t* (h)	Conv. (%)[b]	*ee* (%),[c] abs. config.
1	(*E*)-**19a**	16	100	73, *R*
2	(*Z*)-**19a**	104	100	62, *R*
3	(*E*)-**19b**	44	100	83, *R*

[a] Reaction conditions: substrate/**L51**/$[Pd_2(dba)_3 \cdot CHCl_3]$ = 100:10.5:2.5, solvent = toluene, c_0 (substrate) = 13.9 mM, T = 0 °C. [b] Conversions determined by ^{1}H NMR analysis of the crude reaction mixture. [c] *ee*s determined by GC equipped with a chiral column.[14b]

Under these conditions, it was found that the same enantiomer of product **20** (*R*) is obtained preferentially, irrespective of the double bond configuration of substrate **19a** (Table 8, entries 1 and 2). However, the cyclization of (*Z*)-**19a** was slower and gave slightly lower *ee* than that of (*E*)-**19a**. Moreover, increasing the size of the leaving group led to a notable increase of the enantioselectivity (Table 8, entry 3). Also the nature of the nucleophile strongly affected the reaction outcome: when the Ts group was replaced with $COCF_3$, the reaction became sluggish (104 h at r.t. required for full conversion) and poorly enantioselective (9% *ee*).[14b]

Contrary to the previous reaction, in the synthesis of 4-vinyltetrahydrocarbazole **22** the best results were obtained in different solvents when (*E*)- and (*Z*) -**21** were used as substrate (Table 9), and no benefit was obtained from using a bulkier leaving group nor from running the reaction at low temperature.[14a] Moreover, full conversions could be obtained with a 1 mol% catalyst loading.

Table 9. Synthesis of 4-vinyltetrahydrocarbazole **22** by Pd-catalyzed of allylic carbonates under optimized conditions.[a]



21 **22**

Entry	Substrate	Solvent	Conv. (%)[b]	*ee* (%),[c] abs. config.
1	(*E*)-**21**	toluene	100	70, *S*
2	(*Z*)-**21**	DCM	100	75, *R*

[a] Reaction conditions: substrate/**L51**/$[Pd(OAc)_2]$ = 100:2.1:1, c_0 (substrate) = 15 mM, T = 25 °C. [b] Conversions determined by ^{1}H NMR analysis of the crude reaction mixture. [c] *ee*s determined by GC equipped with a chiral column.[14a]

Moreover, compared to the 1-vinyltetrahydroisoquinoline synthesis, a different stereochemical outcome was observed (Table 9):[14a] under the optimized conditions (1 mol% catalyst, r.t.), substrate (*E*)-**21** formed preferentially product (*S*)-**22** (70% *ee*), while (*Z*)-**21** led to (*R*)-**22** with 75% *ee*. This kind of stereodivergent behavior is precedented in the literature,[38] and should be a consequence of the slow equilibration (compared to the cyclization step) of the diastereomeric π-allyl-Pd complexes generated by oxidative addition of the catalyst to either the (*E*)- or the (*Z*)-allylic carbonates **21**.[39]

4. Summary and outlook

The revival of chiral monodentate ligands that took place in the 1999-2003 period opened up new perspectives for the search of new enantioselective transition metal catalysts. This shift of paradigm put in question the generally accepted idea that only chiral bidentate ligands can secure high enantioselectivity, and set the scene for the ligand mixture approach (2003-2004), which has been increasingly exploited in the next years, until present.[17a,40] In their turn, the intrinsic limitations of using ligand mixtures (i.e., mainly, co-formation of homocomplexes and heterocomplex) aroused a renewed interest in supramolecular ligands. However, it was soon understood that the supramolecular approach has a potential going beyond the mere selective formation of heteroleptic complexes, and covering also substrate activation by means of ligand-substrate interactions. Our contributions in this area in the 2005-2015 period, summarized in this Personal Account, reflect these developments quite well: we started from ligand mixtures to approach supramolecular catalysis (initially as a means to achieve selective heterocomplex formation and then as a substrate activation strategy). Doing so, we introduced some original aspects, such as: i) using chiral *tropos* ligand mixtures; ii) varying the L^a/L^b ratio and combining electronically matching ligands to maximize the heterocomplex formation; iii) investigating the use of ligand-ligand interactions to achieve selective heterocomplex formation; iv) developing highly efficient supramolecular ligands which are also structurally simple and synthetically accessible.

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Keywords: noncovalent interactions • asymmetric catalysis • P ligands • ligand mixtures • atropoisomerism

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