Efficient modular phosphorus-containing ligands for stereoselective catalysis

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Abstract: Over several years, our research team has contributed to ligand design for metal-catalyzed stereoselective transformations. This has been achieved with the synthesis and application to organic transformations of interest of an array of structurally diverse P-containing ligands. These range from highly modular enantiopure phosphine–phosphite ligands to supramolecularly regulated enantioselective phosphorus-based catalysts. Our research in supramolecular interactions has also led to the discovery of an unprecedented halogen-bonded rhodium-catalyst.

1. Introduction

Enantioselective catalysis with transition metals has become one of the most efficient tools for the synthesis of enantiopure (or highly enantioenriched) compounds. Ligand design to modify the intrinsic catalytic properties of the metal center involved in these transformations has been one of the principal research topics among synthetic chemists [1 - 4]. Phosphorus compounds (specially P(III)-derivatives) have offered unique opportunities to “tune” the steric and electronic features of the metal centers in homogeneous catalytic systems, leading to stable metal complexes that have been catalytically active in key transformations for academic and/or industrial synthetic chemists [5 - 8].

Since the first examples of the use of P-stereogenic monodentate phosphines reported by Horner [9] and Knowles [10], and the chelating C2-diphosphine DIOP by Kagan [11], a myriad of enantiopure phosphorus ligands have been developed and tested in numerous metal-catalyzed transformations. The carbon backbones of P-containing ligands are almost unlimited. Every conceivable type of molecular chirality has been incorporated into the ligands, and these have been functionalized with numerous binding groups for most metal centers [1 - 4].

Herein, we describe the efforts of our research team in the synthesis and application of phosphorus ligands in stereoselective catalysis, ranging from highly modular phosphine–phosphite (P–OP) ligands to the supramolecularly regulated P-containing catalysts.

2. Highly modular P–OP ligands

Metal complexes derived from hybrid bidentate P-containing ligands have been used widely in enantioselective catalysis [5 - 8]. Within this class of P-derivatives, P–OP ligands, which were first developed by the teams of Takaya [12] and Pringle [13], represent an important class of non-symmetric ligands. Their interesting stereoelectronic features have been exploited efficiently for homogeneous enantioselective catalytic transformations [14 - 16].

Efforts in our research team have been directed to the efficient syntheses of enantiopure P–OP ligands. First, we described the synthesis of a library of vicinal P–OP ligands **L1** (Fig. 1) by ring-opening of an enantiopure epoxide with

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a phosphorus nucleophilic reagent followed by *O*-phosphorylation of the resulting phosphino alcohol [17, 18]. Second, we sought to prepare geminal P–OP ligands (structures **L2** and **L3** in Fig. 1) by focusing on two strategies. On the one hand, **L2**-type ligands were prepared by an asymmetric carbonyl reduction of an acyl-phosphine followed by phosphorylation of the resulting geminal phosphino alcohol [19, 20]. On the other hand, **L3**-type ligands were obtained by *O*-phosphorylation of an enantiopure geminal phosphino alcohol containing a stereogenic phosphorus group, which is known in the literature [21, 22].

Fig. 1. General structures of the P–OP ligands developed by our research team.

The catalytic activity of the developed P–OP ligands is summarized in sections 2.1 to 2.3.

2.1 Application of P–OP ligands to the Rh-catalyzed asymmetric hydrogenation (AH) of functionalized alkenes

After structure optimization of the enantioselective catalyst by a ligand-tuning process [23], a first generation of efficient P–OP ligands for the Rh-catalyzed AH of functionalized alkenes (structures **L4** and **L5** in Fig. 2) were identified [17, 18, 24 - 28]. The optimal ligand structures combined an *anti*-phosphino alcohol moiety along with an enantiopure (*S_a*)-BINOL-derived phosphite fragment. Interestingly, the rhodium complexes derived from those P–OP ligands (**L4** and **L5**) were applied efficiently as catalysts for the AH of an array of structurally diverse functionalized olefins, including α -(acylamino) acrylates (32 examples), itaconic-acid derivatives (6 examples), α -aryl enamides (10 examples) and α -substituted enol esters (12 examples). Most of these substrates were hydrogenated with high catalytic activity (turnover frequency at 50% conversion (i.e., TOF_{1/2}) values up to >49000), low catalyst loadings (substrate to catalyst ratio up to 10000) and perfect enantioselectivities (up to 99% enantioselectivity (i.e., ee); see Fig. 2) [17, 18, 24 - 27]. Moreover, the practicality of these P–OP ligands was demonstrated by preparing direct precursors (or advanced intermediates) of active pharmaceutical ingredients by AH [29] employing the P–OP ligands developed by our research team [30].

Fig. 2. First generation of P–OP ligands for the AH of functionalized alkenes.

The most favored reaction manifold was identified by performing computational studies at the density functional theory (i.e., DFT) level on the reaction mechanism of the AH of methyl 2-acetamido acrylate **1** employing ligand **L4**

[18, 24]. A combination of steric and electronic effects left the lower-left quadrant as the lowest-energy direction of approach of the olefin to the rhodium center when employing **L4**. The final configuration of the hydrogenation products obtained with **L4** (or **L5**) could be predicted by placement of the double bond in the lower-left quadrant, coordination of the substrate to the Rh-center by the C=O and C=C bonds, and delivery of dihydrogen across the double bond from the side of the metal (Fig. 3). In agreement with this rule, experimental results demonstrated that the final configuration of the hydrogenation products derived from α -(acylamino)acrylates, itaconic-acid derivatives and their analogs, α -arylenamides and α -substituted enol ester could always be predicted to be (*R*)-, (*S*)-, (*R*)- and (*R*)- if ligands **L4** or **L5** are used.

Fig. 3. Rationalization of the stereochemical outcome of AH reactions employing **L4** and **L5**.

As a part of our ongoing efforts to develop higher-performing ligands, we designed a second generation of P–OP ligands by incorporating a more sterically hindered phosphite fragment [31]. Based on structural investigations of the rhodium pre-catalysts derived from **L6**, and supported by the computational studies previously discussed, we hypothesized that introduction of phenyl substituents at the 3- and 3'-positions of the [1,1'-biaryl]-2,2'-diol-derived phosphite group would translate into higher enantioselectivities than those obtained with 3- and 3'-unsubstituted ligands **L4** and **L5**. Remarkably, the rhodium complex derived from ligand **L6**, which incorporates the (*S_a*)-*o*-Ph-H8-BINOL moiety, provided perfect enantioselectivities (99% ee) for each model substrate representing the α -(acylamino)acrylate, itaconic-acid derivative, α -arylenamide or α -substituted enol ester classes of substrates [31]. Moreover, significant enhancements in the enantioselectivity were obtained for the challenging substrates **3–5** (up to 58% for product **5**, Fig. 4), for which many reported ligands fail to provide high enantioselectivities [32 - 34]. Overall, the optimal ligand **L6** provided very high enantioselectivities for a range of structurally diverse olefins.

Fig. 4. Rh-catalyzed AH of functionalized olefins with P–OP ligand **L6** and comparison of results with ligand **L4**.

2.2 Application of P–OP ligands beyond the Rh-catalyzed hydrogenation of typical substrates

Encouraged by our results on the use of P–OP ligands for AHs (section 2.1), we turned our attention to assess our rhodium-catalysts in understudied hydrogenative transformations, for which no satisfactory solutions in terms of efficiency, chemo- and/or stereoselectivity have been achieved [35]. Within this context, we initially aimed to resolve a

racemic mixture of vinyl sulfoxides by hydrogenation. Our interest in this transformation arose because this transformation had not been studied and from the interest in expanding the *repertoire* of synthetic methods for enantiopure (or highly enantioenriched) sulfoxides given their widespread applicability in chemistry [36 - 40].

After screening and optimization studies, we found that the rhodium complexes derived from the P-OP ligand **L6** performed efficiently as the optimal catalyst for the kinetic resolution (KR) of phenyl vinyl sulfoxide. With the lead catalyst in hand, KR studies were broadened to an array of structurally diverse vinyl sulfoxides (Fig. 5) [41]. Unreacted vinyl sulfoxides and hydrogenated products were isolated in high yields with high enantioselectivities regardless of the electronic and positional nature of the substituent at the aromatic ring (Fig. 5). This synthetic method represents an unprecedented approach for preparing optically active vinyl sulfoxides (compounds **6** and **8**) and their hydrogenated products (products **7** and **9**).

Fig. 5. Hydrogenative kinetic resolution of racemic vinyl sulfoxides with rhodium complexes derived from P-OP ligand **L6**.

Next, we shifted our attention to assessment of modular enantiopure P-OP ligands for the underexplored hydrogenative desymmetrization of achiral 1,4-dienes [35]. After screening and optimization studies, the P-OP ligand incorporating the (*S,S*)-TADDOL-derived phosphite unit **L7** was found to be the optimal ligand for this hydrogenative desymmetrization (Fig. 6) [42]. This result highlights the potential of a modular ligand design which, after structure optimization, allows the discovery of a high-performing catalyst for a given transformation. The substrate scope was expanded to a set of structurally diverse achiral 1,4-dienes providing access to enantioenriched secondary and tertiary alcohols with high chemo-, diastereo- and enantioselectivity (up to 92% ee, Fig. 6). In short, these results highlight the ability of the enantioselective catalyst incorporating ligand **L7** to selectively mediate the monohydrogenation of achiral 1,4-dienes and to distinguish between the two enantiotopic vinyl groups. With the aim of enabling access to these efficient hydrogenation catalysts by the “asymmetric catalytic community,” we recently published a practical, chromatography-free synthesis on the gram scale of the rhodium complexes derived from ligands **L4**, **L6** and **L7** [43].

Fig. 6. Hydrogenative desymmetrization of achiral 1,4-dienes with rhodium complexes derived from P-OP ligand **L7**.

2.3 Application of P–OP ligands to the Ir-catalyzed AH of C=N bonds in heterocyclic compounds

Heterocyclic compounds are omnipresent in biological systems and, therefore, are a pillar in life-science and biotechnological-science research [44 - 53]. Our research team reported the AH of an array of structurally diverse heterocyclic compounds catalyzed by Ir(I)-complexes derived from P–OP ligands. Quinolines **15** and **16** were selected as benchmark substrates to study AH reactions (Fig. 7). From a set of P–OP ligands with diverse electronic and steric features, Ir-complexes derived from ligand **L8** were selected as the optimal pre-catalyst [54]. The reaction was found to proceed with very high levels of conversion and enantioselectivities (up to 92% ee, rt, 80 bar H₂). The reaction with [Ir(Cl)(cod)(**L8**)] as a pre-catalyst was tolerant to substitution at the 2- and 6-positions of the quinoline scaffold, consistently giving high enantioselectivities. Several authors have reported that additives can improve catalytic activity [55, 56]. Remarkably, addition of 10 mol% of anhydrous HCl afforded higher conversions in the AH of quinoline derivatives without altering the enantioselectivity. Interestingly, a key building block (**16**) in the preparation of the antibacterial agent flumequine [57] was obtained in high yield and enantioselectivity (88% ee).

Fig. 7. AH of C=N containing heterocycles catalyzed by [Ir(Cl)(cod)(**L8**)].

[Ir(Cl)(cod)(**L8**)] pre-catalysts were applied satisfactorily to the AH of other six-membered C=N-containing heterocycles, such as benzoxazines (**17**), benzoxazinones (**18**), benzothiazinones (**19**) and quinoxalinones (**20** and **21**) (Fig. 7) [58]. After optimizing the reaction conditions, Ir-complexes derived from **L8** catalyzed the hydrogenation of benzoxazines **17** and benzoxazinones **18** with enantioselectivities ranging from 89% to 99% ee regardless of the positional and electronic nature of the substituents at the heterocyclic scaffold. AH of the thio- and aza-analogs of these derivatives was also studied. Interestingly, a sulfur group in compound **19** did not lead to a decrease in catalytic activity and a hydrogenated compound was obtained with excellent enantioselectivity (94% ee). Quinoxalinones **20** and **21** were also hydrogenated very efficiently using the [Ir(Cl)(cod)(**L8**)] complex because these compounds were hydrogenated at lower pressure and lower catalyst loading than their oxygen- and sulfur-analogs. Interestingly, the catalyst tolerated diverse substitution patterns at the nitrogen atom (i.e., no protecting group, Me-, MOM- or Bn- substituents) with excellent enantioselectivity (99% ee). In the best case, a substrate-to-catalyst ratio of up to 2000 was used, resulting in almost full conversion (96%) and perfect enantioselectivity (99%).

Compounds containing an indoline structural motif often have biological activity [59 - 61]. Although many rhodium, ruthenium and iridium complexes have been reported as catalysts for the AH of *N*-protected indoles to *N*-protected indolines, the direct hydrogenation of *N*-unprotected indoles has been explored less frequently. Zhou et al. [62] developed a strategy based on palladium catalysts and Brønsted acids as activators [56] for the AH of indoles. In this approach, the Brønsted acid breaks the aromaticity of the indole ring by in-situ generation of an iminium ion, which is hydrogenated further. Our research team expanded the strategy of Zhou et al. to iridium precursors and P–OP ligands (Fig. 8). The catalytic enantioselective synthesis of an array of diversely substituted indolines was reported using enantiomerically pure iridium complexes derived from P–OP ligand **L8** as pre-catalysts and stoichiometric amounts of camphorsulfonic acid (CSA) as the activator (Fig. 8) [63]. The best results were obtained using the environmentally benign solvent 2-methyl tetrahydrofuran to afford the corresponding indoline derivatives with high yield and enantioselectivities (up to 91% ee). The study also showed that a reusable heterogeneous Brønsted acid (i.e., DOWEX 50WX8 solid-supported sulfonic acid) could be used in this process with comparable results being observed to those with the homogeneous additive. Furthermore, the heterogeneous additive DOWEX 50WX8 was recycled and re-used up to two times with comparable catalytic activity throughout the cycles.

Fig. 8. AH of indoles catalyzed by $[\text{Ir}(\text{Cl})(\text{cod})(\text{L8})]$.

The applicability of $[\text{Ir}(\text{Cl})(\text{cod})(\text{P-OP})]$ pre-catalysts in the AH of C=N containing derivatives was expanded further to seven-membered heterocycles. Nitrogenated seven-membered heterocyclic motifs with stereogenic centers constitute an important pharmacophore [53], but examples of their direct preparation via AH are scarce [64 - 69]. Oxazepines (**24**), diazepines (**26**) and thiazepines (**27**) were hydrogenated in the presence of H_2 and $[\text{Ir}(\text{Cl})(\text{cod})(\text{P-OP})]$ pre-catalysts derived from ligands **L8** and **L9** (Fig. 9) [70]. Enantioselective catalysts derived from **L9** in combination with catalytic amounts of HCl exhibited excellent catalytic properties in the AH of alkyl substituted seven membered heterocycles (complete conversion and up to 91% ee). The AH of aryl-substituted seven membered derivatives required use of **L9** without an additive. The stereochemical outcome of the AHs has been rationalized using DFT calculations, which identified the position of the Cl ligand in the catalytically relevant iridium structures and several non-covalent interactions (i.e., $\text{N}-\text{H}\cdots\text{Cl}$, $\text{CH}\cdots\pi$, and $\text{CH}\cdots\text{H}-\text{Ir}$ interactions) as key features in determining the configuration of the hydrogenated products [70].

Fig. 9. Asymmetric hydrogenation of seven-membered heterocycles catalyzed by $[\text{Ir}(\text{Cl})(\text{cod})(\text{L9})]$.

3. Halogen bond-assembled metal catalysts

Phosphorus (III) ligands have had a central role in the design of new supramolecular systems due to their preeminence in homogeneous catalysis [71]. The “supramolecular synthetic toolbox” offers an efficient alternative to standard covalent chemistry when referring to the synthesis of catalyst’s backbones derived from bisphosphines [72 - 74]. One of the most visited strategies in supramolecular catalysis relies on the self-assembly of complementary ligands via non-covalent interactions [72 - 74]. Examples in the preparation of supramolecular bisphosphines employing hydrogen-bonding [75], metal-ligand [76] or ionic interactions [77] are well established. Our research team has recently reported the use of halogen bonding in functionalized monodentate phosphine ligands as a new approach to construct the ligand backbone in **L10-Rh** (**XBphos-Rh**, Fig. 10) [78]. **XBphos-Rh** adds to the few examples of bisphosphines reported in the literature showing a *trans*-coordination preference with rhodium. **XBphos-Rh** has been applied to the catalytic hydroboration of terminal alkynes (Fig. 10). This catalytic system has demonstrated efficiency and selectivity in the hydroborations of terminal alkynes by exhibiting a higher catalytic activity and enhanced ratios of the unconventional branched product **33** for all substrates and borylation agents studied, when compared with already reported mono- and bidentate phosphorus-rhodium catalysts (red figures in brackets in Fig. 10 indicate the ratio of yields for branched products employing **XBphos-Rh** and the analogous catalyst derived from triphenylphosphine).

Fig. 10. Hydroboration of terminal alkynes using **XBphos-Rh**.

4. Supramolecularly regulated catalysts

In the last decade, supramolecular interactions have been used increasingly in the design and preparation of efficient enantioselective catalytic systems [72 - 74]. Our research team has been working on a strategy for supramolecularly generating libraries of ligands that resemble a privileged structure in enantioselective catalysis. We have demonstrated that conformationally transformable ligands, which incorporate a polyether chain as the regulation site, behave as supramolecularly regulated ligands. The selectivity in the transformation of interest could be maximized by the choice of whether or not to use a regulation agent (RA) and, if so, which one (Fig. 11 shows a simplified image of the regulation strategy) [79]. The main advantage of this approach rests on the ability to modify the geometry of the catalytic site through supramolecular-reversible interactions.

Fig. 11. Supramolecular regulation strategy.

The sections below describe the efforts of our research team in the preparation of supramolecularly regulated metal-based catalysts for asymmetric hydroformylation, hydrogenation and allylic substitution reactions.

4.1 Supramolecularly regulated rhodium-catalysts for asymmetric hydroformylations (AHFs)

Hydroformylation reactions entail addition of a hydrogen and formyl groups to a C=C double bond [80 - 82]. The first example of supramolecularly regulated catalysts applied in AHFs developed by our research team combined the standard rhodium precursor in this chemistry (i.e., $[Rh(\kappa^2O,O'-acac)(CO)_2]$), the eight oxygen-containing polyethylenoxy spacer **L11** and the conformationally stable 3,3'-disubstituted [1,1'-biaryl]-2,2'-diol-derived phosphite group **A** (Fig. 12 shows the structure of these molecular fragments) [83]. Rhodium complexes of conformationally stable [1,1'-biaryl]-2,2'-diol-derived phosphite groups are known to enantioselectively catalyze AHFs [84], but the a priori suitability of polyethylenoxy spacers as regulation sites was demonstrated experimentally: ligand **L11A** forms very stable supramolecular complexes with alkali metal BARF salts [85] in 1:1 stoichiometries in organic solvents [86, 87]. Initial AHF studies using ligand **L11A** and a set of model alkenes demonstrated that use of the RA had a beneficial effect in the catalytic outcome of the AHF by increasing their conversions, regio- and enantio-selectivities. Among the RAs tested, CsBARF provided the highest regulation effects for almost all substrates [83].

Fig. 12. Supramolecularly regulated bisphosphites for rhodium-catalyzed asymmetric hydroformylations.

With the aim of developing higher performing supramolecularly regulated ligands than **L11A** for AHFs, the structural motifs for the regulation site were expanded (structures **L12**, (**R_a**)-**L13** and (**S_a**)-**L14** in Fig. 12) and conformationally stable phosphite group **C** (Fig. 12) was incorporated into our studies. The RA library was also broadened with new metal [87] and ammonium salts [88]. Correlating the selectivity in the AHF of the model substrates analyzed [87] to the RA was not trivial, but there was an observable trend linking the regioselectivity to the counter ion used: with ligand **L12A** and vinyl acetate as the substrate, BArF salts provided higher regioselectivities than did the BF₄ or ClO₄ analogs. Moreover, use of ammonium salts did not bring an advantage to the outcome of the AHFs. Thus, only alkali metal BArF salts were considered in subsequent optimization studies on AHFs.

The most representative catalytic results for AHFs of an array of substrates employing supramolecularly regulated bisphosphite ligands are shown in Fig. 13. With regard to the use of vinyl esters as substrates (hydroformylation products **34–36** in Fig. 13), the best catalytic results were obtained by combining bisphosphite ligand **L12A** and RbBArF as the RA [87]: perfect conversions and regio- and enantio-selectivities were obtained for the three substrates studied. Remarkable regulation effects were observed for all substrates (the enantioselectivity for the corresponding hydroformylation product **36** was 82% higher with RbBArF than without the RA, Fig. 13). Furthermore, the enantioselectivities achieved for **34** (99% ee) and **36** (96% ee) are the best values reported. Computational studies on the geometry of the catalyst resting states (i.e. [Rh(H)(CO)₂(**L12A**·RA)]) allowed to gain insight into the structural and geometric changes induced by the RA to the rhodium-based catalytic site. Based on the findings of this computational study, we postulated that the significant increase in enantiomeric excess provided by the RAs for hydroformylation products **34–36** might result from adaptation of the P–Rh–P bond angle of the catalyst from a non-ideal value to a value very close to that required for high enantioselectivity [87].

Our research team also studied the AHF of heterocyclic alkenes. The hydroformylation product **37** was obtained with excellent conversion and enantioselectivity (93% ee) by combining ligand **L13C** and KBArF as the RA (Fig. 13). This result is, to the best of the authors' knowledge, the highest reported enantioselectivity [89].

Fig. 13. Best catalytic results for AHF using supramolecularly regulated ligands with a RA (values in brackets denote the difference between the results with and without a RA).

These results demonstrate that appropriate combinations of ligands plus a RA can provide an adaptive catalytic system specific to the substrate geometry: enantioselectivity in these transformations can be maximized by the choice of

RA. These results also confirm the validity of our regulation design: easy generation of an efficient catalytic system by combining a ligand and a suitable RA.

4.2 Supramolecularly regulated rhodium-catalysts for AHs

Encouraged by the performance of supramolecularly regulated bisphosphite ligands in AHFs, research activities were shifted to developing supramolecularly regulated catalysts for AH reactions. A similar regulation strategy for rhodium-mediated hydrogenations had been reported by Fan et al. [90]. The rhodium complexes derived from ligands **L11B** and **L12B** were used throughout the entire study because they provided higher enantioselectivity than did their 3,3'-disubstituted analogs. These rhodium-complexes were evaluated in the AH of a set of structurally diverse functionalized alkenes. The most representative results for AH are summarized in Fig. 14, which shows the highest enantioselectivities and positive regulation effects. For the full set of results, the reader is referred to original manuscript [87]. In almost all reactions, conversion was complete and enantioselectivity was very high, with the values being equal to or only slightly lower than the best values reported for the highest performing ligands in AHs. In terms of regulation effects, modest but positive enhancements in enantioselectivities were observed with CsBArF and the (*R,R*)-bis(1-phenylethyl)ammonium BArF salt **42** for ligand **L11B** and **L12B**, respectively. These results confirm the validity of our regulation design: easy generation of an efficient catalytic system by combining a ligand and a suitable RA.

Fig. 14. Supramolecularly regulated asymmetric hydrogenation of alkenes (values in brackets denote the difference between the results with and without a RA).

4.3 Supramolecularly regulated palladium-catalysts for asymmetric allylic substitutions

Metal-catalyzed asymmetric allylic substitutions constitute a versatile tool for the formation of C–C and C–X bonds in a stereoselective manner. These reactions involve attack of a nucleophile to allyl-metal species. Palladium complexes derived from phosphorus ligands have been used typically as catalysts in this transformation [91 - 95]. Considering these precedents, our research team envisioned application of our regulation strategy to allylic substitutions [96].

Full conversions were obtained with the catalytic systems derived from bisphosphites **L12B** and the standard palladium precursors in this chemistry in combination with metal acetates or triflates as the RAs. In the case of the asymmetric allylic alkylations employing dimethyl malonate (DMM) as a reagent, the highest regulation effect was observed with RbOAc (enantioselectivity was 6% higher with RbOAc than without the RA, Fig. 15). When benzylamine was used as the nucleophile, the allylic substitution product was obtained with 46% ee employing La(OTf)₃ as the RA (16% enhancement in the ee, Fig. 15).

Fig. 15. Asymmetric allylic substitutions using supramolecularly regulated bisphosphite ligands (values in brackets denote the difference between the results with and without a RA).

5. Conclusions

Over the years, our research team has contributed to ligand design for metal-catalyzed transformations with the synthesis of an array of structurally diverse enantiopure phosphorus ligands. A vast library of highly modular P-OP ligands has been developed and applied to several key transformations for asymmetric synthetic organic chemistry (rhodium- and iridium-catalyzed asymmetric hydrogenations, rhodium-catalyzed hydrogenative kinetic resolutions and desymmetrizations, rhodium-catalyzed hydroformylations and palladium-catalyzed allylic substitutions). Our research team has also developed a library of supramolecularly regulated ligands that, while resembling a privileged structure in catalysis, include the possibility of regulating the catalytic site by offering a range of geometrically related catalytic centers. These supramolecularly regulated catalytic systems have been employed in asymmetric hydroformylations, asymmetric hydrogenations and asymmetric allylic substitutions. More recently, our interest in supramolecular interactions and their application in catalysis have led to the discovery of an unprecedented halogen bond-assembled rhodium-catalyst that has shown interesting catalytic features in the hydroboration of terminal alkynes (i.e. enhanced selectivity towards the branched products).

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