NDIPhos as a platform for chiral supramolecular ligands in rhodium-catalyzed enantioselective hydrogenation†

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Chiral naphthalene diimide ligands (NDIPhos) were exploited in rhodium-catalyzed enantioselective hydrogenation. The key feature of these ligands is their ability to self-assemble via π–π interactions to mimic bidentate ligands, offering a complementary method to traditional supramolecular strategies. This concept was further substantiated by computations with the composite electronic-structure method rSCAN-3c.

Transition metal catalysis is instrumental to our daily life. It is indeed crucial to the production of high value-added molecules that are prevalent in our food, drugs, cosmetics, and agrochemicals. Two major breakthroughs in transition metal catalysis were related to the discovery of (1) bidentate ligands that form metal complexes of well-defined geometry through the chelation of the metal center for better control of the selectivity1 – currently the main players in catalysis – and (2) cationic organometallic complexes displaying weakly coordinating anions that readily ease the encounter with the substrates to accelerate transformations under milder reaction conditions.2 In search of new reactivity, synthetic chemists have designed hundreds of new bidentate ligands and thousands of new cationic complexes. However, these processes can become laborious as screening various catalysts can be hampered by limited access to libraries of structurally diverse ligands. This is particularly the case for bidentate ligands, whose preparation can be both time-consuming and expensive.

To overcome these drawbacks, the self-assembly of monodentate ligands via non-covalent interactions has emerged as a powerful strategy to mimic bidentate ligands around the metal center.3 This approach grants direct access to a large combinatorial library for catalysts through the straightforward preparation of monodentate ligands. Existing supramolecular approaches in transition metal asymmetric catalysis mostly rely on hydrogen bonding, coordination to a metal center, and electrostatic interactions to provide well-defined homo- and heterobidentate ligand-metal complexes as illustrated by the groups of Breit,4 Reek,5 Gennari,6 Nishibayashi,7 Takacs,8 van Leeuwen,9 Fan,10 and Vidal-Ferran (Fig. 1).11 However, in several cases, the incorporation of selective recognition units makes the synthesis of such assemblies more elaborate and costly than intended. Additionally, these non-covalent interactions can be disrupted by highly polar functional groups, which can drastically limit their efficiency and range of applications.

In this context, we wondered if we could develop a supramolecular approach that retains the benefits of self-assembled ligands but eliminates their negative aspects. Hence, our attention was drawn to π–π interactions that, if sufficiently strong, are less prone to be impacted by polar functionalities. To date, the use of π-stacking for the design of self-assembled ligands remains underexplored in transition metal catalysis unless it is combined with other non-covalent interactions.12

Fig. 1 Selected examples of supramolecular self-assembled ligands for transition metal catalysis.
Attempts have been made by the group of Gennari to use π–π interactions between perfluoro phenyls and electron-rich arenes, but without much success. The reason behind this result is likely the weakness of such interactions in solution. To overcome this issue, we assumed that naphthalene diimides (NDIs) that are well known for their ability to strongly self-assemble through π-stacking, could represent a viable solution to obtain stable formal bidentate ligands. While the use of NDIs has become increasingly popular in materials sciences, they have only been featured in a few applications in catalysis, mainly in π-anion catalysis by the group of Matull. Therefore, developing such an approach could expand the range of applications of NDIs in synthesis. Here we describe our efforts regarding the preparation of chiral self-assembled NDIPhos-based catalysts and their application to enantioselective hydrogenations as a proof of concept.

To validate our hypothesis regarding the capacity of NDI-derived ligands to undergo the anticipated self-assembly, we initially performed a computational analysis of the adduct formation of the model ligand L and Rh(COD)$_2$ by adapting a protocol from Grimme and co-workers for the study of non-covalent interactions (Fig. 2). This procedure relies on the composite electronic-structure method r$^2$SCAN-3c, which includes the D4-dispersion correction and a geometrical counterpoise correction. It was shown that this functional achieves comparable results to classical hybrid-DFT methods, but only with a fraction of the computational cost, making it particularly suitable for large systems like ours. After a conformational search at the GFN2-xTB(ALPB = CH$_2$Cl$_2$)-optimized level, additional numerical frequency calculations were performed using the r$^2$SCAN-3c(SMD = CH$_2$Cl$_2$) method. For further verification of the methods, control computations were performed at the (SMD = CH$_2$Cl$_2$)/M06-L/def2-TZVP level. As evidenced by an analysis of the non-covalent interactions (NCIs), the model ligand L already features intramolecular π-stacking interactions between the NDI moiety and the naphthyl group. Dimerization of L to (L)$_2$ was computed to be exergonic at the r$^2$SCAN-3c(SMD = CH$_2$Cl$_2$) level ($\Delta G = -10.0/ -15.6 \text{ kJ mol}^{-1}$) but slightly endergonic at the (SMD = CH$_2$Cl$_2$)/M06-L/def2-TZVP level ($\Delta G = -9.4 \text{ kJ mol}^{-1}$). The resulting structure features extensive π–π and CH–π interactions between the NDI and the naphthyl units. In (L)$_2$, both phosphorus atoms are oriented in a way that allows (L)$_2$ to act as a bidentate ligand to yield a cis-phosphite rhodium complex. The binding of Rh(COD)$^+$ at (L)$_2$ was computed to be highly favorable with all methods ($\Delta G = -81.8/ -90.6/-98.7 \text{ kJ mol}^{-1}$) and results in only insignificant structural changes of the (L)$_2$ fragment, thereby retaining the intramolecular interactions, notably the π-stacking. In contrast, the binding of Rh(cod)$^+$ is not surprising as only minor intramolecular interactions between the COD ligand and one of the aryl rings of L are retained in the Rh(COD)(L)$_2$ adduct. In parallel, we recorded the $^{31}$P NMR spectra of the mixture of [Rh(COD)$_2$]OTf and L1 (ratio 1:2 and ratio 1:1) in CD$_2$Cl$_2$. Here, the methyl group of L was replaced by an n-pentyl group to improve the solubility of the corresponding ligand. Both spectra display a doublet at 120.5 ppm with $J_{P,Rh} = 259.4 \text{ Hz}$, which is consistent with the two phosphites coordinating to the rhodium center in a cis-fashion (see ESI for details), while the formation of [Rh(COD)(L1)]OTf was not observed.

Encouraged by the computational analysis that indicates the defined binding of Rh$^+$ in the pre-associated (L)$_2$ system, we started to evaluate the potential of chiral ligand L1 in the Rh-catalyzed enantioselective hydrogenation of methyl (Z)-2-acetamido-3-phenylacrylate at room temperature under 20 atm of H$_2$ for 24 h (Table 1). Using [Rh(COD)(MeCN)$_2$]BF$_4$ as a...
In the case of a ligand prone to H-bonding coordination such as L3, which might be attributed to the fact that the π-stacking is not possible anymore. Other ligands were also tested but did not afford enantiomeric excesses superior to 90%.

Lastly, we explored the synthetic potential of L1 with various substrates (Fig. 4), using L2 and L3 as references. In the case of classic substrates such as methyl 2-acetamidoacrylate, dimethyl fumarate, N-(3,4-dihydronaphthalen-1-yl)acetamide, all the ligands provided fairly similar results for products 2–4. On the other hand, in the case of 2-acetamidoacrylic acid, we observed significant differences as L1 afforded 89% ee for 5, while L2 gave 5% ee, and L3 gave 37% ee. This clearly demonstrates that in the case of a ligand prone to H-bonding coordination such as

![Fig. 3 Comparison with other electron-deficient ligands.](image)

![Fig. 4 Scope for the rhodium-catalyzed enantioselective hydrogenation.](image)
In conclusion, we described a new class of self-assembled bidentate NDI-derived ligands featuring π–π interactions, which were successfully used in rhodium-catalyzed enantioselective hydrogenation of diverse substrates. The catalysts incorporating this NDIPhos ligand were generally highly selective, notably in the presence of polar functionalities such as carboxylic acids. Our current efforts are dedicated to the improvement of their design to expand their range of applications.

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Conflicts of interest

There are no conflicts to declare.

Notes and references


