Engineered Non-Covalent π Interactions as Key Elements for Chiral Recognition

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Abstract

Molecular recognition and self-assembly are often mediated by intermolecular forces involving aromatic π -systems. Despite the ubiquity of such interactions in biological systems and in the design of functional materials, the elusive nature of aromatic π interaction results in that they have been seldom used as a design element for promoting challenging chemical reactions. Described here is a well-engineered catalytic system into which non-covalent π interactions are directly incorporated. Enabled by a lone pair- π interaction and a π - π stacking interaction operating collectively, efficient chiral recognition is successfully achieved in the long-pursued dihydroxylation-based kinetic resolution. Density functional theory calculations shed light on the crucial role played by the lone pair- π interaction between the carbonyl oxygen of the cinchona alkaloid ligand and the electron-deficient phthalazine π moiety of the substrate in the stereoselectivity-determining transition states. This discovery serves as a proof-of-principle example showing how the weak and unpredictable non-covalent π interactions, if ingeniously designed, could be a powerful guide in attaining highly enantioselective catalysis.

Introduction

Attractive non-covalent interactions (NCIs), such as hydrogen bond, ion pair, and van der Waals forces, have been integral to biocatalysis, and their application to chemical catalysis has been accelerated over the past two decades¹⁻⁵. Prominent examples of the latter include thiourea-catalyzed asymmetric Strecker reaction⁶, chiral ion pair-catalyzed fluorination reaction⁷, and chiral phosphoric acid-catalyzed Ugi reaction⁸. Particularly, NCIs involving p systems have drawn increasing attention as they underpin many important structural phenomena in molecular biology and materials science⁹⁻¹¹. These include p-p¹²⁻¹⁴, XH-p¹⁵⁻¹⁶, cation-p¹⁷⁻²⁰, anion-p²¹⁻²² and lone pair-p interactions²³⁻²⁵ (Fig.1a). Recent advances in theoretical and computational chemistry have now reached the stage at which non-covalent p interactions can be modeled accurately, thus often attributed to when rationalizing the observed reactivity and selectivity in a variety of chemical transformations^{3,26-28} (Fig.1b). However, the direct incorporation of specific p interactions into the design of catalysts as a key stereocontrol element remains a long-standing challenge²⁹⁻³⁰. This is ascribed to the potential competition and synergetic cooperation between the relatively weak and unpredictable p interactions and other types of intermolecular forces operating simultaneously, which makes the precise control of such interactions hardly possible and highly context-dependent. Moreover, the detailed understanding of the reactivity- and selectivity-determining transition states at the molecular level for individual catalytic process is still lacking. These obstacles, even though having been overcome gradually through the synergistic efforts from experimental, theoretical, and computational chemists, still hamper the exquisite design of catalytic systems with precise control of reactivity and selectivity.

We envisioned if the weak, yet important non-covalent interactions were purposely utilized in the design of catalysts, it might open up a new avenue in enabling challenging chemical transformations that were previously considered difficult or even hardly possible to occur. We initiated our studies aimed at

identifying appropriate catalytic systems in which non-covalent p interactions are presumably essential for stereocontrol. The cinchona alkaloid and its derivatives, as privileged catalysts and ligands used in asymmetric catalysis³¹⁻³², contain versatile p-character groups with varying steric and electronic properties. In cinchona alkaloid-catalyzed asymmetric reactions, the corresponding stereochemical outcomes are mainly governed by the absolute configuration of C9³³⁻³⁴. An effective *bi*-functional catalysis mode may operate through the interaction between the cinchona alkaloid and a combination of electrophiles and nucleophiles connected by its quinuclidine *N*-C9-p scaffold (Fig.1c). Taking the enantioselective functionalizations of alkenes as an example, the quinuclidine nitrogen coordinates to the electrophile which subsequently reacts with the double bond of the substrate. An efficient asymmetric induction requires a p acceptor component (in blue) at C9 stereocenter in the cinchona alkaloid¹³. This would engage in an effectively operating p-p interaction between the p acceptor and alkene's double bond that was a prototype of electron-rich p systems (in red). Such a "sandwich-like" mode would significantly facilitate enantio-face control of the alkene double bond (Fig.1c, left). In comparison, to achieve efficient chiral recognition of an alkene substrate bearing an existing stereocenter at the allylic position, a p donor moiety (in red) at C9 in the cinchona alkaloid and a p acceptor moiety (in blue) adjacent to the stereocenter in the alkene substrate are needed¹³. This would enable a desirable non-covalent p interaction that incorporates the substrate's stereocenter into the corresponding catalyst-substrate interaction framework, thus rendering a kinetic resolution process with potentially superior stereoselectivity (Fig.1c, right).

We chose the Sharpless asymmetric dihydroxylation (SAD)-based kinetic resolution as a platform to investigate our proposed *bi*-functional catalysis strategy that utilizes non-covalent p interactions as key stereocontrol elements. The classic SAD reaction is widely applied to convert prochiral alkene substrates into chiral vicinal diols with excellent stereoselectivities. In stark contrast, the application of the powerful SAD reaction for the kinetic resolution of racemic olefin substrates such as allylic alcohol and its derivatives has been considered as an unsolved problem³³. Despite of some sporadically reported cases³⁵⁻⁴¹, SAD-based kinetic resolution has been proven to be generally ineffective. The reasons for such orthogonal stereochemical scenarios had not yet been well understood³³. Thus, further investigation into such a catalytic system would not only help shed light on the intricate origin of enantioselectivity in this important catalytic reaction, but also stimulate understanding on the underlying principles of p interactions as well as developing catalysts with assembling properties based on these non-covalent forces. We reported herein an unprecedented discovery that uses well-orchestrated non-covalent p interactions as crucial design elements in asymmetric catalysis. Relying on the favorable interaction between the lone pair electrons on the C9 carbonyl of the cinchona alkaloid and the electron-deficient phthalazine p-system in the substrate, a highly efficient SAD-based kinetic resolution of racemic allylic substrates is realized (Fig.1d). Density functional theory calculations indicate that the favored transition state is stabilized by this lone pair-p interaction, which is absent in the disfavored transition state. To the best of our knowledge, very few examples exist that uses such weak yet essential non-covalent p interactions as the control elements in an asymmetric catalytic reaction⁴²⁻⁴³.

Results And Discussion

Experimental studies on the development of effective non-covalent p interactions. Guided by the above analysis, our investigations started to focus on cinchona alkaloid ligands with a large, delocalized p-system, such as piperonylate in ligand **A**, to test the validity of our hypothesis (Fig.2a). Because the aromatic ring in piperonylate is flanked with both electron-donating and withdrawing substituents, its p-electron distributions are considerably polarizable thus conducive for potential p-p interactions^{12-13,44-45}. Considering the potential undesired p-p interaction between the piperonylate moiety and the alkene's double bond that would preclude the stereocenter outside of the catalyst-substrate interaction (Fig.2b, left), an appropriate electron-poor p-character group that could compete in the p-p interaction with the piperonylate should be introduced in the racemic substrate (Fig.2b, right). Thus under the catalysis of $K_2OsO_2(OH)_4$ and cinchona alkaloid **A**, AD-based kinetic resolutions of racemic alkene substrates with a variety of electron-poor p systems were conducted (Fig.2c). Racemic **1** bearing electron-deficient pyridine as the p acceptor was recovered in 33% ee at 56% conversion, and the corresponding selective factor was only obtained as 2. Then substrates including more electron-deficient aryl rings, such as pyrimidine and pyridazine, were explored. However, racemic **2** and **3** were only kinetically resolved with selective factors of 2 and 3, respectively. Subsequently, racemic **4** with larger aromatic p-system (i.e., 4-chorophthalazine) was examined, and its selectivity factor was slightly improved. Replacing the chloride with a methoxy group in the substrate **5** resulted in a less effective kinetic resolution. Considering that the extended arenes could probably engage in better p-p interactions^{1,46}, we attached the phthalazine ring with a phenyl group. To our delight, the selectivity factor was increased to 5, presenting a promising prospect for further optimization. *Para*-substituted fluoride and methoxy group in the phenyl ring enable slightly more efficient kinetic resolution of racemic **7** and **8**, respectively. Gratifyingly, increasing the number of the methoxy groups in the phenyl ring led to a dramatic increase in the efficiencies for the kinetic resolution. With 3,4,5-tri-methoxyl-substitution in the extended phenyl ring, racemic **10** underwent catalytic kinetic resolution with a selectivity factor of 32, yielding the recovered (*R*)-**10** in 92% ee at 53% conversion. Finally, retaining the 3,4,5-tri-methoxyl substituted phenyl ring in the conjugated p-system while changing the phthalazine to a pyridazine ring in racemic **11** resulted a drastically decreased selectivity factor of 2, indicating the importance of the phthalazine in the non-covalent p interaction with the piperonylate of the catalyst.

We further investigated the nature of the non-covalent p interaction through varying the p-components at C9 of the cinchona alkaloids (Table 1). In addition to ligand **A**, it was found that benzoate moieties at C9 of **B**, **C**, and **D** (Table 1a) all lead to successful kinetic resolutions ($s > 10$). However, the benzoate moiety with extended conjugation in **E** fails to lead to an efficient kinetic resolution (Table 1a). Unexpectedly, replacing the benzoate moiety with sole aryl rings, such as phenyl, naphthyl, benzyl or electron-deficient phthalazine groups, all leads to dramatic decreases in selectivity factors (ligands **F**, **G**, **H**, **I** and **(DHQ)₂PHAL**, Table 1b), hinting on the critical role played by the carbonyl group in stereocontrol. Then we used aliphatic esters in the absence of aromatic rings, and high selectivity factors were surprisingly obtained (Table 1c). For instances, with simple ester groups, such as acetate in **J** and

cyclopropanecarboxylate in **K** (*R*)-**10** was kinetically resolved in 86% and 94% ee's at around 50% conversions, respectively. These unexpected results imply that a lone pair-p interaction between the carbonyl oxygen of the ligand and the p-auxiliary of the substrate⁴⁷⁻⁴⁸ might be involved in the stereoselectivity-determining transition state, which has not yet been reported as a controlling factor in asymmetric catalysis. Then increasing the steric hindrance of the ester group, for instances, using the adamantyl substituent in **L**, still results in a successful kinetic resolution. In contrast, when the trifluoroacetate **M** was examined, the corresponding selectivity factor drastically decreased to 2. This remarkable electronic effect supports the lone pair-p interaction as a key element in the AD-based kinetic resolution, since the electron-deficient trifluoromethyl group might withdraw the lone pair electrons of the carbonyl thus disrupt its interaction with p system in the ligand. A further evidence of the central role played by the lone pair-p interaction was appreciable from the result obtained with ligand **N**, where the more electron-rich Weinreb amide moiety allows racemic **10** to be resolved with the selectivity factor of 34.

Investigation on the origins of stereoselectivity. To understand the origins of chiral recognition for this kinetic resolution, we chose to use both the structurally simplest substrate (racemic **12**) and ligand (**J**) to perform the AD-based kinetic resolution (Fig. 3a). At 59% conversion, the recovered **12** was obtained in 90% ee with a selectivity factor of 13. The diol product **13** was obtained with a diastereomeric ratio of 7:1 and the enantio-purity of the major diastereomer was found to be only modest (67% ee), as expected based on the proposed *bi*-functional catalysis modes in Fig. 1c. The absolute stereochemistry of the major enantiomer of the recovered **12** was confirmed to have (*R*)-configuration at its allylic carbon (for details, please see the Supporting Information), indicating that the more reactive enantiomer of **12** has the (*S*)-configuration. The corresponding stereoselectivity-determining transition states (TSs) for this reaction were explored using density functional theory (DFT) calculations. Due to the flexibility of the substrate and the ligand, thorough conformational searches for the TSs were performed (for details, please see Supporting Information). The corresponding lowest energy TSs for the (*S*)- and (*R*)-substrates are shown in Fig. 3b. TS-(*S*) is lower in energy than TS-(*R*) ($\Delta\Delta G = -1.6$ kcal/mol, $\Delta\Delta E = -3.1$ kcal/mol), which supports the experimental result that (*R*)-**12** was kinetically resolved with good selectivity. In the [3+2] cycloaddition TSs, two C-O bonds are being formed in a concerted fashion⁴⁹. There are no obvious steric clashes in the TSs. Distal to the forming bonds, two important sets of non-covalent interactions were identified. In both TSs, parallel displaced p-p interactions between the quinoline moiety of the ligand and the tri-methoxyphenyl group of the substrate are present (3.4 Å and 3.3 Å, respectively). In the favored transition state **TS-(*S*)**, a lone-pair p interaction between the carbonyl group of the ligand and the phthalazine moiety of the substrate is evidenced clearly by the short distances of the carbonyl oxygen to the centroid of and to the plane of the diazine ring (2.94 Å and 2.87 Å, respectively)^{24,50}. However, this type of interaction is absent in the disfavored transition state **TS-(*R*)**, which may contribute to the difference in energy of these two TSs. Further calculations using truncated model show that the lone-pair p interaction is -3.1 kcal/mol, which is the main contributor to the stereoselectivity (Fig. 3c). The p-p interaction is relatively strong in its magnitude (-8.1 kcal/mol), which may contribute to the binding of substrate with the catalyst but plays a much smaller role in controlling

the stereoselectivity, as both TSs have such an interaction in a similar magnitude. To unravel the nature of the lone pair-p interactions, we performed energy decomposition analysis (EDA) (Fig. 3c, center box) to separate ΔE_{int} (−3.1 kcal/mol) into chemically meaningful energy terms, including Pauli repulsions ($\Delta E_{\text{pauli}} = 3.6$ kcal/mol), electrostatic interactions ($\Delta E_{\text{eletat}} = -2.8$ kcal/mol), orbital interactions ($\Delta E_{\text{orb}} = -1.4$ kcal/mol) and London dispersion forces ($\Delta E_{\text{disp}} = -2.5$ kcal/mol)⁵¹. These results indicate that electrostatic interactions and London dispersion forces are the two largest components, contributing 42% and 37% to the total stabilizing interactions, respectively.

Reaction scope. Having identified the crucial role of the lone pair-p interaction between the cinchona alkaloid ligand and the alkene substrate in stereocontrol, we finally demonstrated the generality of the reaction scope (Table 2). A number of alkene substitution patterns in the racemic allylic ethers were found to be well accommodated, including 1-substituted, 1,1-disubstituted and (*E*)-1,2-disubstituted alkenes. For mono-substituted alkenes, R¹ group varying among methyl, ethyl, *n*-propyl, decyl, benzyl, 3-pentyl, cyclobutyl, cyclopentyl and cyclohexyl substituents were all compatible with this strategy. The resolved chiral allylic ethers were obtained with 84% to 97% ee's at practical conversions (Table 2a). We are pleased to find that the p moiety in (*R*)-**16** can be easily removed to reveal its alcohol version without loss of the stereochemical fidelity. It is worth mentioning that these simple allylic ethers or their corresponding alcohols have been hardly accessed with high ee's either by direct asymmetric reduction of prochiral ketones or by asymmetric 1,2 addition to aldehydes. Racemic allylic ethers bearing 1,1-disubstituted alkenes (Table 2b) and (*E*)-1,2-disubstituted alkenes (Table 2c) were also successfully resolved under identical conditions. Unsuccessful substrates include (*Z*)-disubstituted alkenes and trisubstituted alkenes (Table 2d). Allylic ether **28** gave no conversion even with increased reaction time or catalyst loading, as *cis*-double bonds are challenging substrates in OsO₄-catalyzed dihydroxylations⁵². *Tri*-substituted alkene **29** provided practical conversion but with low ee.

Conclusions

In conclusion, we have developed a highly efficient catalytic system based on modified cinchona alkaloids. A *bi*-functional catalysis strategy was proposed and subsequently tested in the Sharpless asymmetric dihydroxylation-based kinetic resolution of racemic olefins. Rationally designed and well-engineered non-covalent p interactions are incorporated as key elements for stereocontrol to tackle this persistent challenge in asymmetric catalysis. A relatively weak lone pair-p interaction between the ligand and the substrate was discovered to play a crucial role in differentiating the enantiomeric substrates during chiral recognition. Fully integrated experimental and computational studies provide strong support of such non-covalent p interactions in the stereodetermining transition states. Further investigations and applications exploiting the lone pair-p interaction that was originally discovered in biological systems are expected to reveal whether nature also utilizes this type of non-covalent force in the biosynthesis of natural products and guide the development of new chiral catalysts in the laboratory. We anticipate that this discovery will stimulate wider utilization and manipulation of non-covalent p interactions at the outset of rational catalyst design to solve other challenging problems in asymmetric catalysis.

Declarations

Data availability

The data that support the findings of this study are available within the paper and its supplementary information files. Raw data are available from the corresponding author on reasonable request. Materials and methods, experimental procedures, characterization data, ^1H , ^{13}C , NMR spectra and mass spectrometry data are available in the Supplementary Materials.

Supplementary Information is available in the online version of the paper.

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Author Contributions

M. Y. J., Q. Z. and G. T. developed and conducted the reactions. D. X. and P. Y. conducted the computational studies. X. X., P. Y. and C. X. designed and directed the investigation and prepared the manuscript. All correspondence should be sent to C.X. (xuc@sustech.edu.cn) and P.Y. (yupy@sustech.edu.cn).

Competing interests The authors declare no competing interests.

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Tables

Tables 1-2 are in the supplementary files section.

Figures

Figure 1

Orchestrated non-covalent π interactions as a crucial design element in asymmetric catalysis. a, Non-covalent interactions involving π systems. b, Representative examples using non-covalent π interactions to rationalize the observed enantioselectivities. TS, Transition State. c, Designing cinchona alkaloids-based, new *bi*-functional catalysis modes using non-covalent π interactions for both asymmetric induction (left) and chiral recognition (right). E: electrophiles. d, Lone pair- π interaction as a key stereocontrol element in asymmetric dihydroxylation-based kinetic resolution.

Figure 2

Development of effective non-covalent π interactions between the catalyst and the alkene substrate for AD-based kinetic resolution. a, Using cinchona alkaloid ligand **A** with the piperonylate moiety as a large, delocalized π system in AD-based kinetic resolution. b, Proposed possible π - π interactions in the racemic alkene substrates/Ligand **A**-OsO₄ complexes. c, Screening an appropriate π moiety in the alkene substrate that could establish desired π - π interactions with the piperonylate moiety in ligand **A**. General condition: K₂OsO₂(OH)₄ (0.4 equiv), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3.0 equiv), ligand **A** (1.0 mol%) and alkene (0.1 mmol) in 1.0 mL ^tBuOH-H₂O (v/v = 1:1), 0 °C. $s = \ln[(1-c)(1-ee)]/\ln[(1-c)(1+ee)]$. Conversion (conv or c) was determined by ¹H NMR analysis of the crude mixture.

Figure 3

Combined experimental and computational investigation on the origins of stereoselectivity for the AD-based kinetic resolution using a model system. a, Experimentally observed stereoselectivities for both recovered (*R*)-12 and the diol product 13 from the AD-based kinetic resolution. b, Representative DFT-computed transition state structures TS-(*S*) and TS-(*R*) for this reaction. c, Energy decomposition analysis for truncated structures of TS-(*S*) and TS-(*R*). Relative energies are given in kcal/mol.

Supplementary Files

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