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Biomimetic Asymmetric Reduction Based on the Regenerable Coenzyme NAD(P)H Models

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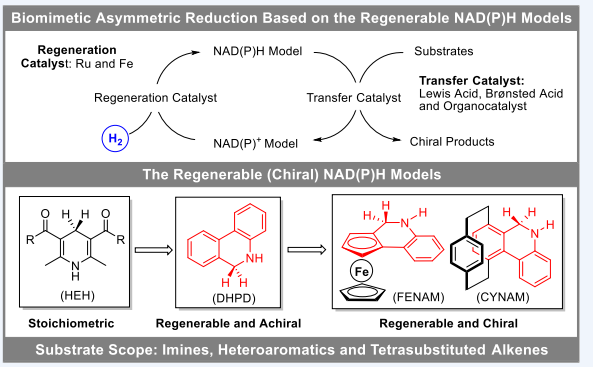
CONSPECTUS: In nature, the coenzyme NAD(P)H is utilized for the transfer of hydrogen and electrons in biocatalytic reduction, which involves the process of recycling, coenzyme usage, and reduction. Inspired by the biological system, a series of nonregenerable achiral and chiral NAD(P)H models were synthesized and employed. However, this approach faced intractable limitations, such as the need for an equivalent amount of mimics, accompanied by the production of byproducts, which resulted in poor atom economy and difficult separation of products. Therefore, the development of new and efficient methodologies for synthesis, regeneration, and application of the NAD(P)H models in organic synthesis is greatly desired.



To tackle these challenges, the regenerable achiral and chiral coenzyme NAD(P)H models were designed and synthesized based on the principles of biocatalytic reduction and applied them in biomimetic asymmetric reduction (BMAR) reactions. This Account summarizes our endeavors in rational design, synthesis, regeneration, and application of the NAD(P)H models. First, we will introduce the design and synthesis of regenerable and achiral coenzyme NAD(P)H models (dihydrophenanthridine and dihydropyrroloquinoxaline), which were successfully applied to BMAR of imines and heteroaromatics using homogeneous ruthenium complex as a regeneration catalyst, chiral phosphoric acid as a transfer catalyst, and hydrogen as the terminal reductant. Regenerable and achiral NAD(P)H models require the addition of chiral catalysts or chiral ligands for stereoselective control during the BMAR process. However, the screening of the chiral transfer catalysts is tedious. Narrow substrate scope further limited their application in organic synthesis. Therefore, we designed and synthesized regenerable and chiral NAD(P)H models (CYNAM and FENAM) with planar chirality, which were successfully applied in asymmetric reduction of imines and heteroaromatics using commercially available achiral Brønsted acids, Lewis acids, or organocatalysts as transfer catalysts and a homogeneous ruthenium complex as a regeneration catalyst. Notably, the original factor of enantioselective control is from the chiral NAD(P)H models. In addition, this strategy could also realize the asymmetric reduction of a myriad of electron-deficient tetrasubstituted alkenes, which are challenging substrates in transition metal catalyzed asymmetric hydrogenation. This methodology provides an efficient strategy for the synthesis of chiral building blocks and bioactive molecules. Finally, the detailed mechanism of BMAR, based on the regenerable NAD(P)H models, was elaborated through a combination of experiments and density functional theory calculations. In summary, we believe that the results presented in this Account hold significant implications beyond our work and have the potential for further applications in the field of biomimetic asymmetric catalysis and synthetic methodology.

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- Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. Dihydrophenanthridine: A New and Easily Regenerable NAD(P)H Model for Biomimetic Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2012**, *134*, 2442−2448.[2] This work demonstrates an easily

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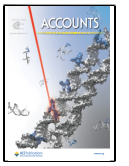

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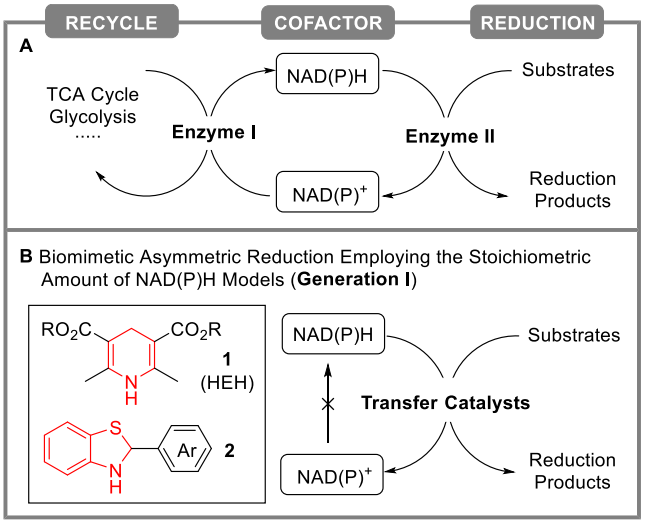
regenerable NAD(P)H model dihydrophenanthridine for biomimetic asymmetric hydrogenation of benzoxazinones, benzoxazines, quinoxalines and quinolines using chial Brønsted acids as transfer catalyst, giving a myriad of chiral heterocycles with excellent enantioselectivities under mild conditions.

- Wang, J.; Zhu, Z.-H.; Chen, M.-W.; Chen, Q.-A.; Zhou, Y.-G. Catalytic Biomimetic Asymmetric Reduction of Alkenes and Imines Enabled by Chiral and Regenerable NAD(P)H Models. *Angew. Chem., Int. Ed.* **2019**, *58*, 1813−1817.[3] A chiral and regenerable NAD(P)H model (FENAM) based on planar-chiral ferrocene was designed and synthesized. Biomimetic asymmetric reduction (BMAR) has been realized using bench-stable and achiral Lewis acids as transfer catalysts, which represents the first general BMAR process enabled by the chiral and regenerable NAD(P)H models.
- Zhu, Z.-H.; Ding, Y.-X.; Wu, B.; Zhou, Y.-G. Design and Synthesis of Chiral and Regenerable [2.2]-Paracyclophane-based NAD(P)H Models and Application in Biomimetic Reduction of Flavonoids. *Chem. Sci.* **2020**, *11*, 10220−10224.[4] This work demonstrates a stable chiral and regenerable [2.2]paracyclophane-based NAD(P)H model (CYNAM) and its application in BMAR of tetrasubstituted electron-deficient alkenes using simple achiral Lewis acids as transfer catalysts with excellent enantioselectivities.

1. INTRODUCTION

In cells, reduced nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NAD(P)H) are recognized as crucial enzyme cofactors, which serve as hydrogen transporters in more than 400 metabolic processes such as amino acid degradation, the citric acid cycle, and glycolysis (Scheme 1A).[5] These reactions are mainly dependent on the interconversion between the reduced NAD(P)H and the oxidized $NAD(P)^+$, the essence of which is the acceptance or donation of hydride ions by NAD(P)H/$NAD(P)^+$ at the C4 site of the pyridine ring.

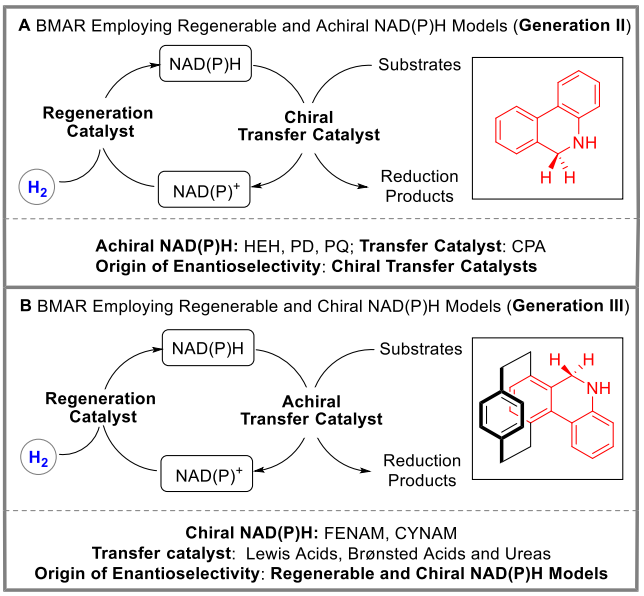
Scheme 1. (A) Biocatalytic Reduction with NAD(P)H in Cells and (B) BMAR Employing a Stoichiometric Amount of NAD(P)H Models (Generation I)



Therefore, the involvement of NAD(P)H in the process of cell metabolism has attracted extensive interest from scientists, leading to attempts to simulate this process. The key to simulating this process lies in the design, synthesis, and regeneration of NAD(P)H models. Over the past decades, a series of NAD(P)H models have been designed, synthesized, and applied in the field of biomimetic asymmetric reduction (BMAR) through the tireless efforts of chemists (Scheme 1B). These BMAR reactions involve a stoichiometric amount of achiral NAD(P)H model compounds such as Hantzsch ester **1** (HEH),[6] benzothiazoline **2**,[7] and some other chiral non-regenerable NAD(P)H models.[8] However, there are certain limitations to the involvement of these NAD(P)H models, for example, the need for a stoichiometric amount of the NAD(P)H models and the production of reductive byproducts such as Hantzsch pyridine, which result in low atom economy and difficult separation of products. Therefore, the effective and economic regeneration of cofactor NAD(P)H models and their efficient utilization are key issues.

Although the regeneration of the cofactor NAD(P)H and its applications in BMAR have been developed in the past few decades,[9−13] the rational design and synthesis of efficient regenerable NAD(P)H models for the transfer of hydrogen and electrons in BMAR still pose challenges. To address these challenges, two new generations of BMAR have been successfully explored based on the principle of biocatalytic reduction. In generation II of BMAR, regenerable and achiral NAD(P)H models were employed, with enantiocontrol originating from the chiral transfer catalysts (Scheme 2 A).

Scheme 2. (A) BMAR Employing the Regenerable and Achiral NAD(P)H Models (Generation II) and (B) BMAR Employing the Regenerable and Chiral NAD(P)H Models (Generation III)



In generation III of BMAR, regenerable and chiral NAD(P)H models were used, with enantiocontrol stemming from the chiral NAD(P)H models themselves (Scheme 2 B). These BMAR approaches have been successfully applied in the asymmetric reduction of imines, heteroaromatics, and tetrasubstituted electron-deficient alkenes, providing high yields and enantioselectivities.

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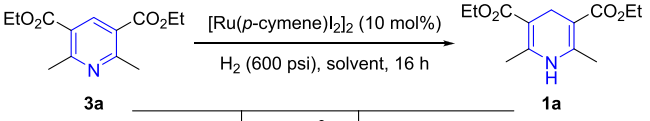
2. DESIGN, SYNTHESIS, AND APPLICATIONS OF REGENERABLE AND ACHIRAL NAD(P)H MODELS

2.1. Preliminary Attempt

Hantzsch esters (HEH) as efficient hydrogen donors have been widely used in the BMAR of imines, alkenes, ketones, and heteroaromatics.[6] However, these reductions suffered from the utilization of stoichiometric amounts of HEH. Inspired by the biological system, we aimed to reduce the hydrogen donor to a catalytic amount through metal-catalyzed regeneration of HEH using hydrogen gas as the terminal reductant. Considering that the dehydrogenation product of HEH is aromatic Hantzsch pyridine, it is envisaged that the regeneration of HEH **1** can be achieved by partial hydrogenation of Hantzsch pyridine **3**. Thus, we initially explored metal-catalyzed regeneration of the HEH **1a**, and found that a homogeneous ruthenium catalyst could effectively regenerate HEH **1a** from pyridine **3a** at 50−70 °C using hydrogen gas (Scheme 3).[1]

Scheme 3. Ruthenium-Catalyzed Regeneration of HEH



Solvent	Temp. (°C)	Conversion (%)
Toluene	50	10
THF	50	39
THF	70	64
THF [a]	70	69

[a] Hantzsch ester **1a** was used instead of **3a**

After successfully realizing the *in situ* regeneration of Hantzsch esters, we applied this strategy to BMAR. Notably, the key to this biomimetic asymmetric reduction is that there should be no background reaction. The regeneration catalyst should not directly reduce the substrate; otherwise, racemic product would form. To our delight, when the cyclic imine benzoxazinone **4a** was used, no background reaction occurred with hydrogen gas in the presence of the regeneration catalyst $[Ru(p\text{-cymene})I_2]_2$. Encouraged by this result, the BMAR of **4a** was investigated using a catalytic amount of HEH in the presence of homogeneous $[Ru(p\text{-cymene})I_2]_2$ and chiral phosphoric acid **CPA-1** (Figure 1), utilizing hydrogen gas as the terminal reductant (Scheme 4).[1] As a result, the corresponding chiral amine **5a** was obtained with 98% ee and 93% yield. The electronic properties and position of substituents on the aromatic ring of **4** had only a marginal effect on reactivities and enantioselectivities.

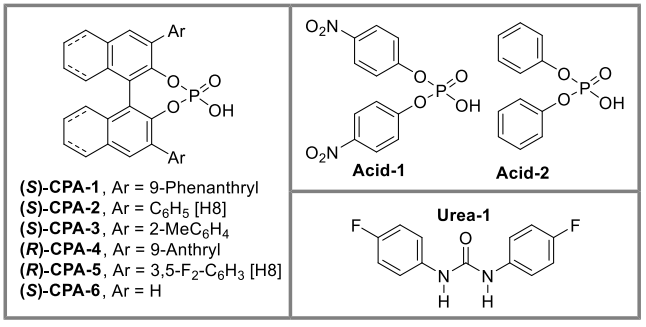
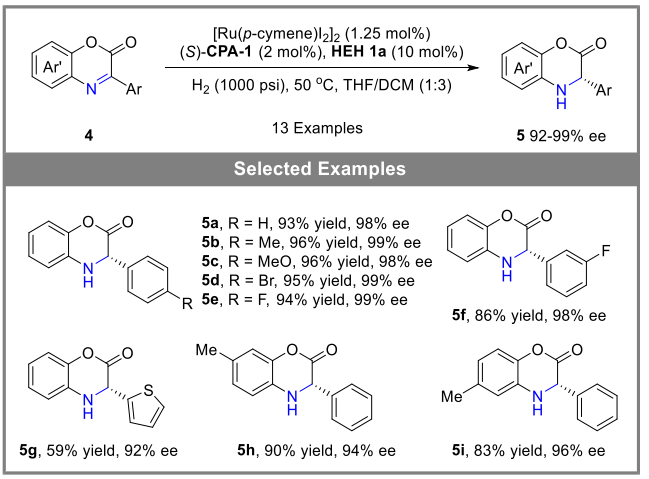


Figure 1. Representative transfer catalysts in BMAR.

Scheme 4. BMAR of Benzoxazinones Using a Catalytic Amount of HEH



Notably, the substrate scope of this BMAR was expanded to imines and quinolines. Although the desired reductive products could be obtained with excellent yields, the optical purity was low (only 77% ee of 2-phenyltetrahydroquinoline was obtained). This can be attributed to the strong background reaction of these substrates under the harsh regeneration conditions (1000 psi H_2, 50 °C) of HEH. Nevertheless, the above work demonstrated that the BMAR is feasible by employing catalytic amounts of NAD(P)H models. Therefore, the development of new and easily regenerable NAD(P)H models is necessary.

2.2. Design and Synthesis of Regenerable and Achiral NAD(P)H Models

In our previous preliminary attempt, the regeneration of Hantzsch ester was realized and applied to the BMAR of benzoxazinones. However, the substrate scope was limited due to the harsh regeneration conditions. Hence, we aimed to design and synthesize new, efficient coenzyme NAD(P)H models that meet the following criteria: (a) convenient synthesis from simple starting materials, (b) easy regeneration under mild conditions, (c) high hydride transfer ability, and (d) easy control of enantioselectivity and wide substrate generality.

Following these guidelines, a series of regenerable and achiral phenanthridines **6** (abbreviated as PD) and pyrrolo-[1,2-*a*]quinoxalines **7** (abbreviated as PQ) were synthesized through 1−3 steps including coupling, formylation, and cyclization using 2-iodoanilines (Scheme 5 A).[2,14,15] Then, the regeneration of these NAD(P)H models was tested (Scheme 5 B). Pleasingly, these NAD(P)H models could be regenerated with hydrogen in the presence of a ruthenium complex.

2.3. BMAR with Regenerable and Achiral NAD(P)H Models

With a series of regenerable and achiral NAD(P)H models in hand, their application in BMAR was explored. Asymmetric hydrogenation of readily available imines is a straightforward and effective method for the rapid synthesis of chiral amines. We selected imine benzoxazinones **4** as substrates to investigate the possibility of BMAR in the presence of a catalytic amount of regenerable and achiral NAD(P)H model phenanthridine.

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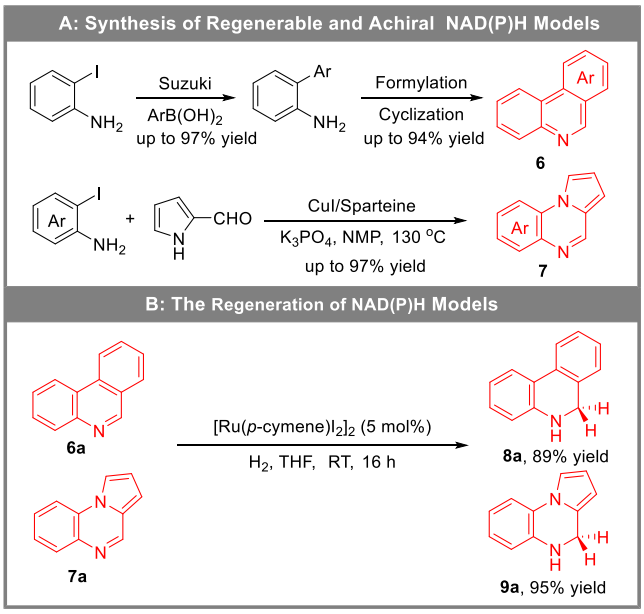
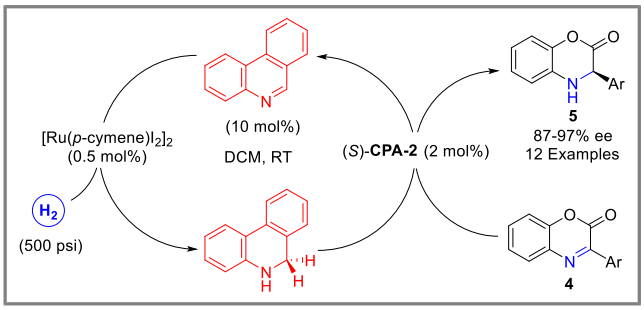
Scheme 5. Synthesis and Regeneration of NAD(P)H Models: Phenanthridines and Pyrrolo[1,2-*a*]quinoxalines



To our delight, the reductive products **5** could be obtained with excellent ee values (87−97%) using the chiral (*S*)-**CPA-2** as the transfer catalyst (Scheme 6).[2] So, the new generation of BMAR was successfully realized using the regenerable and achiral NAD(P)H models under mild conditions.

Scheme 6. BMAR of Benzoxazinones Using Regenerable and Achiral NAD(P)H Models



In sharp contrast, when Hantzsch ester **1** was used instead of dihydrophenanthridine (DHPD) **8a** under identical conditions, an obvious reversal of enantioselectivity was observed with the same chiral transfer catalyst (*S*)-**CPA-2**.[2] The combination of experimental studies and DFT calculations revealed that this phenomenon is primarily caused by the different hydrogen transfer modes. In the transition state, the imine, NAD(P)H model, and chiral phosphoric acid build up a "three-point contact model" through the hydrogen bonding interactions. The effect of steric hindrance is beneficial in controlling the enantioselectivity. DHPD **8a** undergoes a 1,2-hydrogen transfer process, while the HEH performed a 1,4-hydrogen transfer process, resulting in hydrogen transfer from different faces of the substrates (Figure 2).

Subsequently, BMAR of cyclic imine benzoxazines **10** was further examined using PD or PQ as the regenerable NAD(P)H model, affording the reductive products **11** with excellent yields and enantioselectivities (Scheme 7).[2,14]

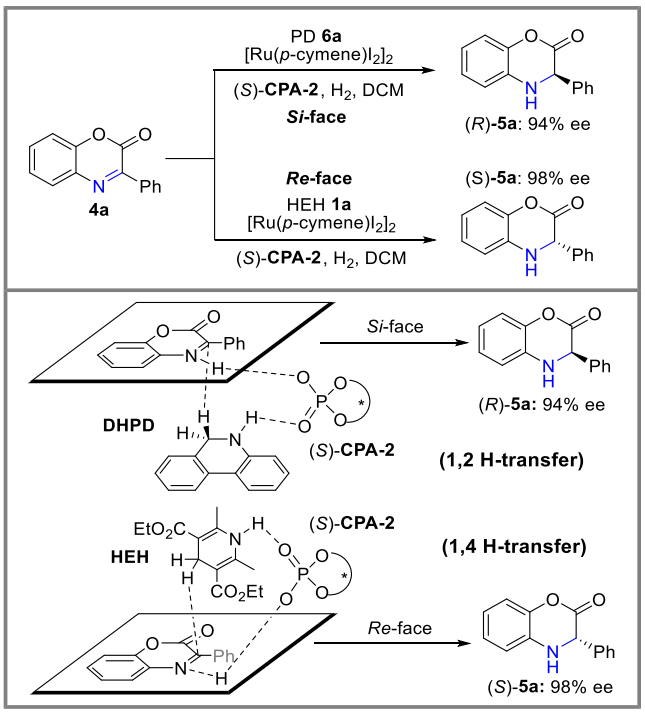
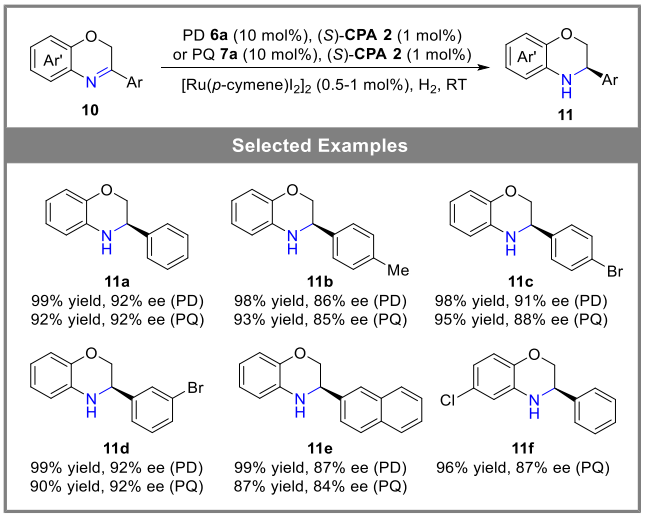


Figure 2. Reversal of Enantioselectivity and the Hydride Transfer Pathways of DHPD **8a** and HEH **1a**.

Scheme 7. BMAR of Benzoxazines Using PD 6 or PQ 7



The organic hydride donors release hydride in a thermodynamically driven dehydroaromatization process. To explore the hydride transfer ability of different types of NAD(P)H models (HEH, DHPD, and DHPQ), three parallel competing reactions were tested for the reduction of **10a** with **CPA-6** in D-chloroform (Scheme 8).[14] These results indicated that the hydride transfer ability sequence was HEH **1b** > DHPD **8a** > DHPQ **9a**, providing valuable guidance for the design and synthesis of new and efficient NAD(P)H models.

Subsequently, an efficient method for the synthesis of chiral fluorinated propargylamines **13** was developed through the chemoselective BMAR of the C═N bond of fluorinated propargylketimines **12** using the above strategy employing the PD **6b** as NAD(P)H model (Scheme 9).[15] The C≡C triple bond remained inert under the standard conditions. Notably,

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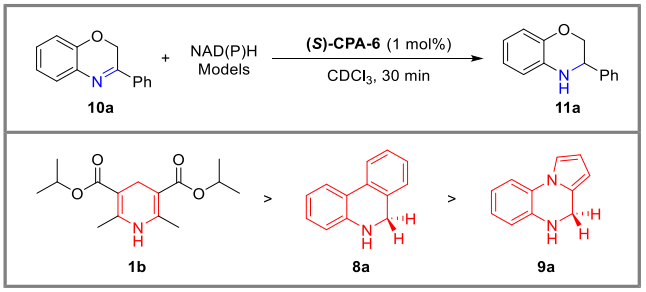
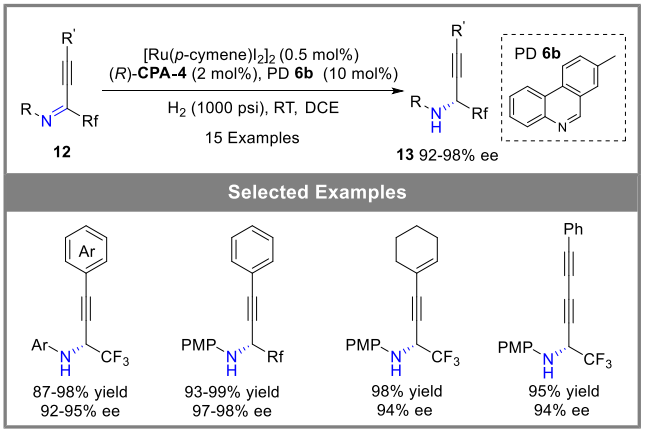
Scheme 8. Hydride Transfer Ability Sequence



no desired reductive product was observed using the CPA/HEH system.

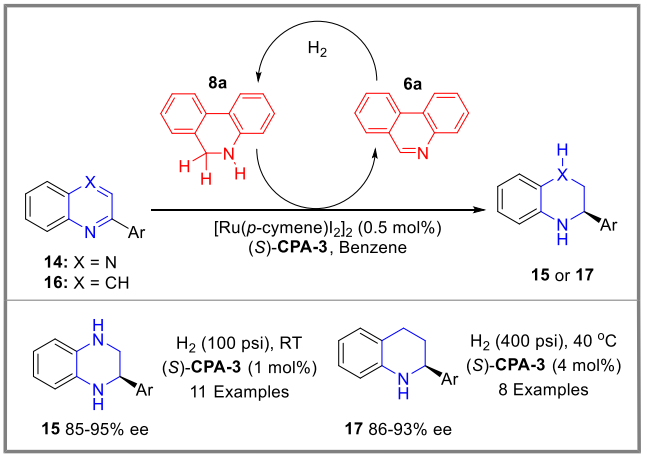
Scheme 9. BMAR of Fluorinated Ketimines 12 Using PD



After the successful BMAR of the imine substrates, this strategy was also extended to the reduction of aromatic quinoxalines **14** and quinolines **16**, resulting the formation of chiral products **15** and **17** with excellent yields and enantioselectivities (Scheme 10),[2] which are important building blocks for the synthesis of chiral agrochemicals and pharmaceuticals.

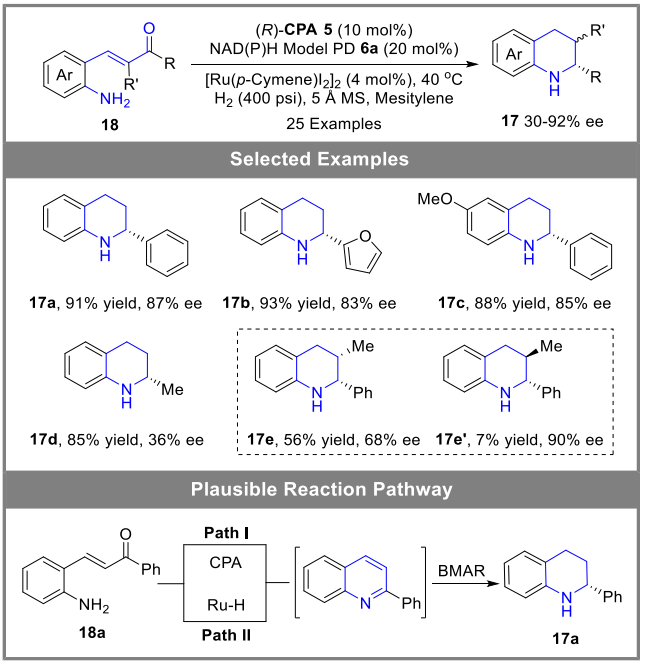
Furthermore, a multistep one-pot method for the synthesis of chiral tetrahydroquinolines was developed from the 2-aminochalcones **18** using the CPA-**5** as the transfer catalyst

Scheme 10. BMAR of Quinoxalines and Quinolines Using PD



and phenanthridine as the regenerable NAD(P)H model, with up to 92% ee and 96% yield (Scheme 11).[16]

Scheme 11. Synthesis of Chiral Tetrahydroquinolines by One-Pot Cascade BMAR Using PD



After our realization of the generation II BMAR based on coenzyme NAD(P)H models by employing the homogeneous ruthenium complex as a regeneration catalyst, a homogeneous earth-abundant iron complex as phenanthridine regeneration catalyst was reported by Beller's group for BMAR of α-keto esters and benzoxazinones.[17,18] Very recently, Du and co-workers reported BMAR of benzoxazinones using Lewis acid borane as the phenanthridine regeneration catalyst with hydrogen gas as the terminal reductant.[19]

3. DESIGN, SYNTHESIS, AND APPLICATIONS OF REGENERABLE AND CHIRAL NAD(P)H MODELS

Over the course of several decades of development, the regeneration of the coenzyme NAD(P)H models has been successfully achieved through the simulation of the coenzyme cycle process in vivo, and finally simulation of the three biomimetic parts of the cycle, coenzyme, and reduction in the biocatalytic process. With tireless efforts, a series of regenerable and achiral NAD(P)H models have been successfully synthesized and applied to BMAR in conjunction with chiral transfer catalysts. However, the synthesis and selection of chiral transfer catalysts are difficult, and the reaction requires tedious screening for different types of substrates, which further limited its application in the field of BMAR. To solve the problems of cumbersome screening of chiral transfer catalysts and the limitation of the diversity of chiral transfer catalysts as well as the regeneration of NAD(P)H models, we envisioned that regenerable and chiral NAD(P)H models could be synthesized to transfer the control of enantioselectivity from the transfer catalyst to the NAD(P)H models. In this way, the use of chiral transfer catalyst could be avoided, and BMAR could be directly achieved using readily available simple Brønsted acids, Lewis acids, or organocatalysts as transfer catalysts. This advance-

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ment would provide greater opportunities for the development of new biomimetic asymmetric reactions.

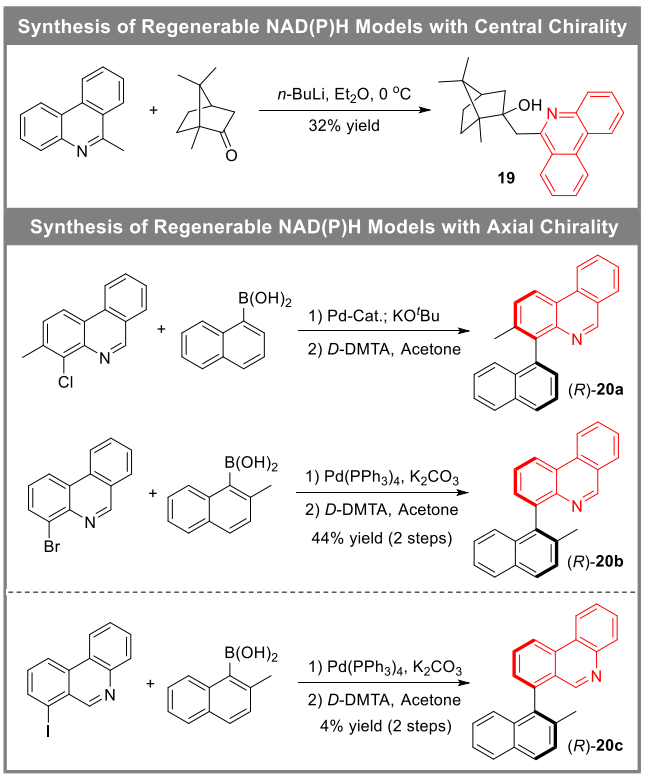
3.1. Design and Synthesis of Regenerable and Chiral NAD(P)H Models

In previous work, dihydrophenanthridine is the key structural moiety for the regeneration of NAD(P)H models. It not only facilitates the hydrogen transfer process but also enables *in situ* regeneration with hydrogen gas under mild conditions. Therefore, regenerable and chiral NAD(P)H models containing the dihydrophenanthridine moiety should be rationally designed. These regenerable chiral NAD(P)H models should have the following distinct features: (1) high hydrogen transfer ability, (2) facile regeneration with hydrogen gas under mild conditions, (3) excellent control of enantioselectivity, and (4) simple synthesis with finely tuned chiral environment. Guided by these principles, a series of regenerable and chiral NAD(P)H models containing the dihydrophenanthridine moiety, exhibiting central, axial, or planar chirality, were synthesized.

3.1.1. The Synthesis of Chiral NAD(P)H Models with Central Chirality. Considering that the NAD(P)H models with central chirality are relatively easy to synthesize, a chiral fragment derived from the chiral natural product camphor was introduced through lithiation of 6-methylphenanthridine and subsequent nucleophilic addition to camphor. This process yielded the NAD(P)H model with central chirality, **19**, in moderate 32% yield (Scheme 12).[20]

3.1.2. The Synthesis of the Chiral NAD(P)H Models with Axial Chirality. Recently, axially chiral compounds have been widely used in asymmetric catalysis as the core skeleton of chiral ligands and organocatalysts. Hence, we turned our attention to the design and synthesis of a series of axially chiral NAD(P)H models with the dihydrophenanthridine moiety.

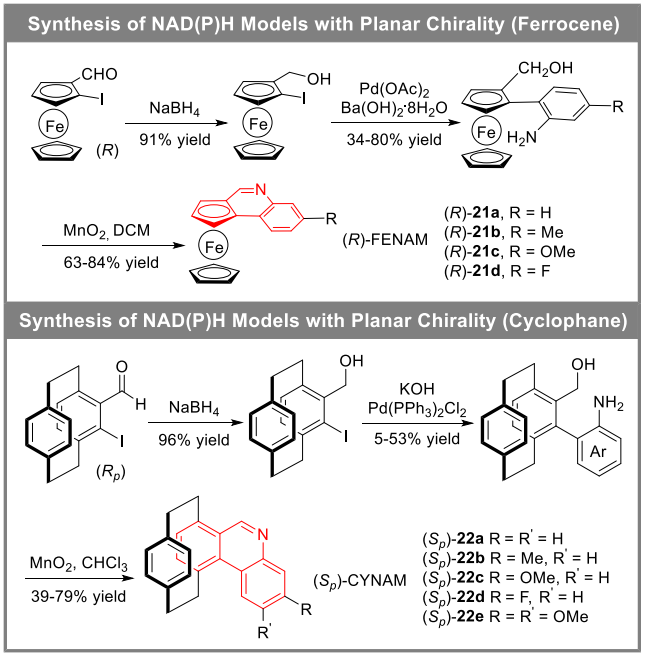
Scheme 12. Synthesis of Regenerable and Chiral NAD(P)H Models with Central and Axial Chirality



The axially chiral NAD(P)H models **20** were synthesized through the chemical resolution of the corresponding racemates with tartaric acid derivatives (Scheme 12).[20] For NAD(P)H models **20a** and **20b**, the nitrogen atom at the active C═N site is in close proximity to axial chirality. For the NAD(P)H models **20c**, the carbon atom of the active C═N site is far away from axial chirality.

3.1.3. The Synthesis of Chiral NAD(P)H Models with Planar Chirality. In addition to centrally and axially chiral frameworks, planar-chiral frameworks are also widely used as privileged frameworks in chiral ligands and organocatalysts. Inspired by the broad application of planar chirality in asymmetric catalysis, a series of planar-chiral NAD(P)H models based on the ferrocene or paracyclophane framework were designed and synthesized. Starting from commercially available chiral (*S*)-iodoferrocene-carboxaldehyde, a series of ferrocene-based regenerable and chiral NAD(P)H models (abbreviated as FENAM) **21** with different steric and electronic effects were prepared by reduction, palladium-catalyzed coupling, and oxidative cyclization.[3] Furthermore, a series of [2,2]paracyclophane-based regenerable and chiral NAD(P)H models (abbreviated as CYNAM) **22** were synthesized using sodium borohydride reduction, Suzuki coupling, and oxidative cyclization from the known chiral 5-formyl-4-iodo[2.2]paracyclophane (Scheme 13).[4]

Scheme 13. Synthesis of Regenerable and Chiral NAD(P)H Models with Planar Chirality



With a series of chiral and regenerable NAD(P)H models with different chirality (central, axial, and planar chirality) in hand, their regeneration with hydrogen gas was investigated using a ruthenium complex as a catalyst. To our delight, these chiral NAD(P)H models could be regenerated with hydrogen gas under mild conditions.

3.2. Applications of Regenerable and Chiral NAD(P)H Models

After completing the design, synthesis, and regeneration of chiral NAD(P)H models, their application in BMAR was

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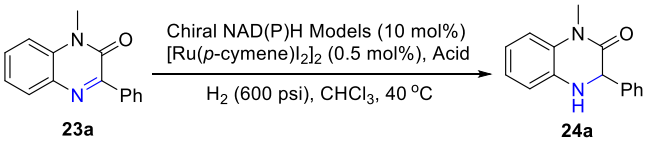
explored. Considering that there is a chiral environment in the framework of the chiral NAD(P)H model itself, the commercially available achiral Brønsted acids, Lewis acids, or organocatalysts could be used as hydrogen transfer catalysts, which can avoid the problem of synthesis and screening of the chiral transfer catalysts. Furthermore, the following challenges might arise: (a) the occurrence of background reactions that could lead to decreased enantioselectivity, (b) controlling the enantioselectivity during the hydrogen transfer process with chiral NAD(P)H models, and (c) ensuring compatibility between the regeneration catalysts, transfer catalysts, chiral NAD(P)H models, and substrates.

In a previous study, it was found that benzoxazinones and quinoxalinones did not undergo background reactions under ruthenium and hydrogen gas conditions. Therefore, these substrates were selected to explore the application of regenerable and chiral NAD(P)H models in BMAR with the ruthenium complex as a regeneration catalyst, a simple achiral phosphoric acid as a transfer catalyst, and hydrogen gas as a terminal reductant (Scheme 14). Unfortunately, no desired

Scheme 14. BMAR of Quinoxalinones 23a with Regenerable and Chiral NAD(P)H Models



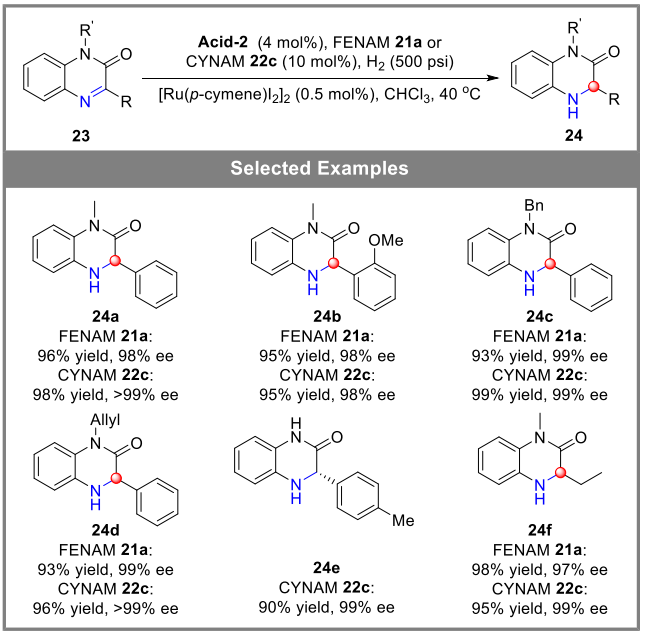
Chiral NAD(P)H Models	Acids	Conversion (%)	Ee (%)
19	**Acid-1**	<5	-
20a	**Acid-2**	<5	-
20b	**Acid-2**	<5	-
20c	**Acid-2**	12	16
21a	**Acid-2**	78	97
22a	**Acid-2**	94	98

product was obtained using the chiral NAD(P)H model **19** with central chirality. Detailed mechanism studies indicated that while model **19** could be reduced with hydrogen gas, the hydride could not be transferred owing to hindered steric interactions and intramolecular hydrogen bonding. Subsequently, the axial-chiral NAD(P)H models **20a** and **20b** were investigated under the same standard conditions, but no desired product was observed. The nitrogen atom of the active C═N site in the NAD(P)H model was too close to the bulky *ortho*-substituent, hindering the formation of hydrogen bonding between the hydroxyl and nitrogen atom, thereby impeding the hydride transfer process. Gratifyingly, 12% conversion and 16% ee of the desired product was obtained using **20c** as regenerable NAD(P)H model, just by moving the nitrogen atom further from the axial stereogenic center, reducing steric hindrance.[20]

To our delight, excellent conversion and enantioselectivity could be obtained using the NAD(P)H models **21a** and **22a** with planar chirality under the standard conditions.[20,21] These results demonstrated the feasibility of generation III of BMAR using regenerable and chiral NAD(P)H models. Subsequently, the regenerable and chiral NAD(P)H models were further explored in BMAR of imines, heteroaromatics, and tetrasubstituted electron-deficient alkenes using simple achiral Brønsted acids, Lewis acids, and organocatalysts as the transfer catalysts and the homogeneous ruthenium complex as the regeneration catalyst, respectively.

3.2.1. Achiral Brønsted Acids as Transfer Catalysts. In the previous explorations, good to excellent yields and excellent enantioselectivities were obtained in BMAR of quinoxalinones **23** using regenerable and planar chiral NAD(P)H models. Subsequently, the substrate scope of the reaction was tested and a series of 3,4-dihydroquinoxalin-2(1*H*)-ones **24** were obtained with excellent yields and ee values (Scheme 15).[20,21] Similar results were obtained when

Scheme 15. BMAR of Quinoxalinones 23 with FENAM and CYNAM



the substituents on the nitrogen were changed. Even quinoxalinone **23e** with free *N*-H could work well.[21] To our delight, up to 95% yield and 99% ee could be obtained for the alkyl substituted quinoxalinones **23f**, which resulted in poor ee in Lewis base-catalyzed hydrosilylation.[22a]

Further extension in the BMAR of benzoxazinones **4** using FENAM or CYNAM as regenerable and chiral NAD(P)H models was tested. Satisfactory outcomes with 92−99% ee were achieved regardless of aryl, heteroaryl, and alkyl substituents (Scheme 16).[20,21] Notably, for alkyl-substituted benzoxazinones such as 3-ethyl-2*H*-benzoxazin-2-one, only moderate ee was obtained using the previous HEH/**CPA-1** system.[22b]

Chiral dihydroquinazolones are identified as important and common structural motifs in bioactive and pharmaceutical molecules. Owing to the importance of optically active dihydroquinazolones, the BMAR of quinazolinones **25** was explored with regenerable and chiral NAD(P)H model FENAM in the presence of achiral Brønsted acids.[23] The reaction demonstrated a wide range of substrate scope, giving the reductive products **26** with up to 98% ee (Scheme 17).

To further showcase synthetic utility of this approach, the chiral bromodomain protein divalent inhibitor was prepared from the chiral **26h** through methylation, palladium-catalyzed Suzuki coupling, and dialkylation, resulting in a good overall yield without any loss of optical purity (Scheme 18).[24]

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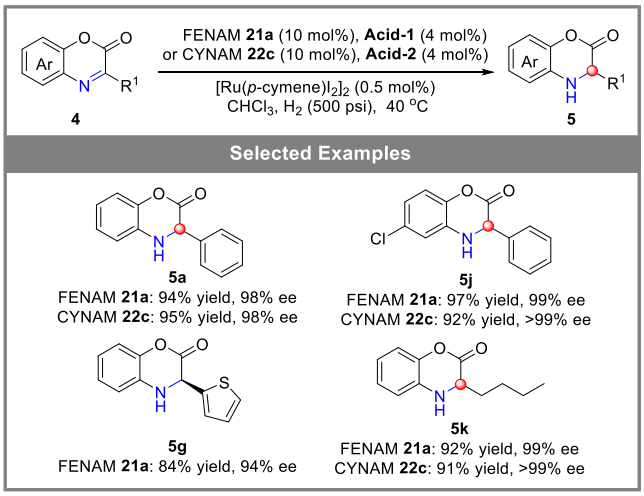
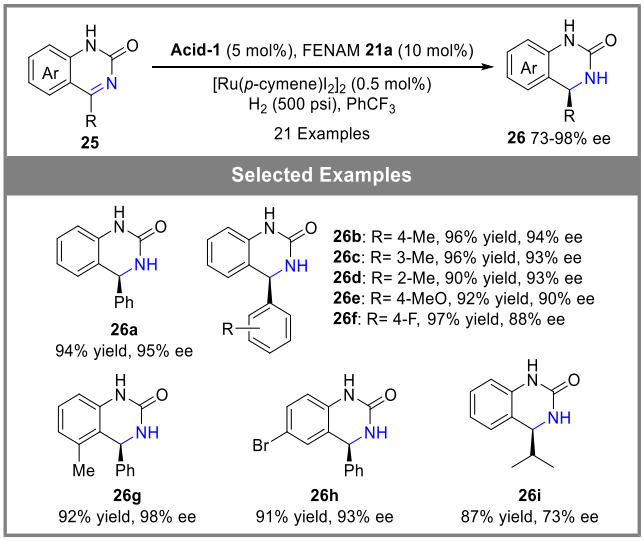
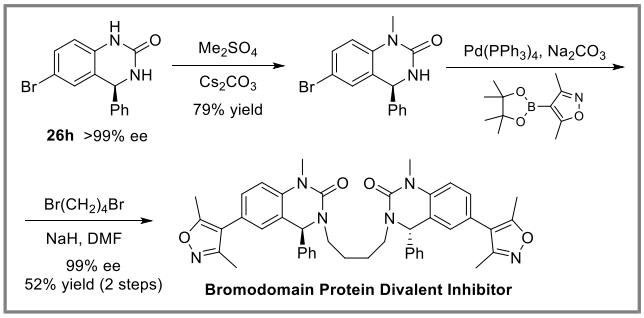
Scheme 16. BMAR of Benzoxazinones 4 with FENAM and CYNAM



Scheme 17. BMAR of Quinazolones 25 with FENAM

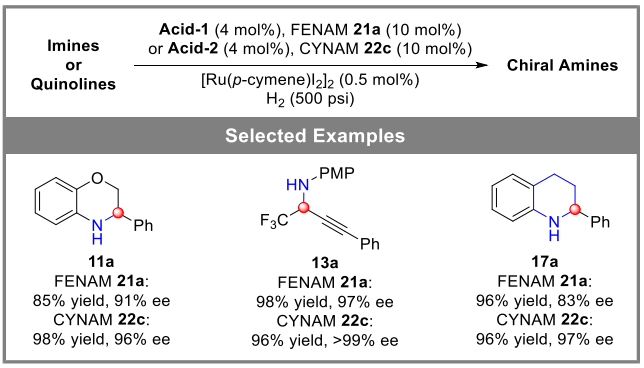


Scheme 18. Synthesis of Bioactive Molecules



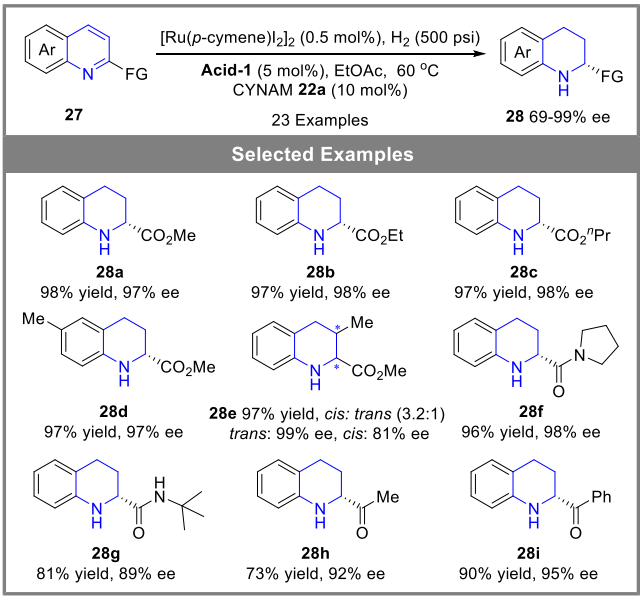
Further extending the utility of this strategy, the BMAR of some other imines such as benzoxazines **10**, fluorinated ketimines **12**, and heteroaromatic quinolines **16** was explored. Pleasingly, the corresponding chiral amines such as dihydrobenzoxazines **11**, fluorinated amines **13**, and tetrahydroquinolines **17** could be obtained with excellent enantioselectivities and yields (Scheme 19).[20,21]

Scheme 19. BMAR of Imines and Quinolines Using FENAM and CYNAM



Compared with the asymmetric reduction of simple quinolines, the asymmetric reduction of functionalized quinolines is a challenge, especially for the quinolines bearing ketone, ester, and amide functional groups. The main problem lies in achieving chemoselectivity between the ketone and quinoline hydrogenation. To our delight, the BMAR of 2-functionalized quinolines **27** with regenerable and chiral NAD(P)H model CYNAM **22a** in the presence of simple achiral Brønsted acid-1,[25] affording the corresponding chiral 2-functionalized tetrahydroquinolines **28** with up to 98% yield and 99% ee (Scheme 20). This reaction had a broad substrate scope and functional group tolerance, including ester, amide, and ketone groups.

Scheme 20. BMAR of 2-Functionalized Quinolines 27



To further verify the practicability of this methodology, the reaction was carried out at the gram scale, affording the desired chiral product with 94% yield without any loss of ee value, and the chiral NAD(P)H model CYNAM **22a** could be recovered with 80% yield. In addition, a chiral potent opioid analgesic **29** could be conveniently synthesized from chiral product **28f** (Scheme 21).[26]

Due to the difficulty of controlling the two continuous chiral centers in the process of hydrogenation and the large resistance

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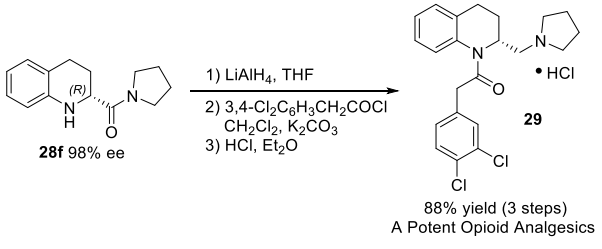
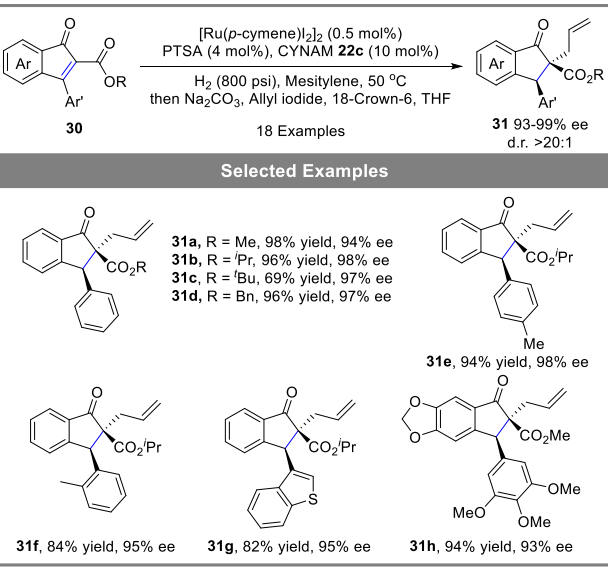
Scheme 21. Synthesis of Potent Opioid Analgesic 29



of the chelated group in the substrate, as well as the excessive force generated by the catalyst and the chelating group, the direct asymmetric hydrogenation of functionalized tetrasubstituted alkenes is still a challenge. In 2021, the BMAR of tetrasubstituted alkene 2,3-substituted 1*H*-inden-1-ones **30** was realized using the regenerable and chiral NAD(P)H model CYNAM as the reducing agent, the ruthenium complex as the regeneration catalyst, and *p*-toluenesulfonic acid (PTSA) as the transfer catalyst. (Scheme 22).[27] The corresponding chiral

Scheme 22. BMAR of Tetrasubstituted Electron-Deficient Alkenes 30 with CYNAM

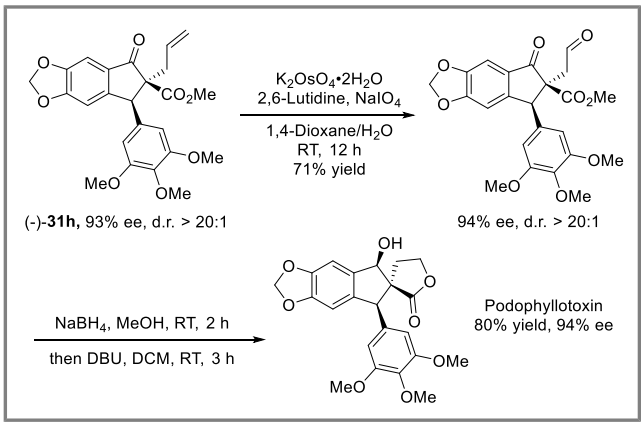


compounds bearing a quaternary stereocenter were obtained with excellent yields and enantioselectivities by *in situ* alkylation in order to avoid the keto−enol tautomerism of products.

Furthermore, a podophyllotoxin derivative,[28] a potent compound with antitumor activity, could be synthesized via osmium-catalyzed oxidation of the olefin, reduction, and lactonization starting from the chiral BMAR product **31h** (Scheme 23).

3.2.2. Achiral Lewis Acids as Transfer Catalysts. Lewis acids could efficiently promote various types of reactions through coordination and chelation with the functional groups in the substrates.[29] If they are combined with chiral ligands, the chiral Lewis acid catalysts could realize a series of asymmetric reactions. However, their further application is limited due to the feedback of electrons to the ligand upon coordination with the Lewis acid, which reduces the acidity of the Lewis acid and affects the activity of the Lewis acid to activate the substrate.

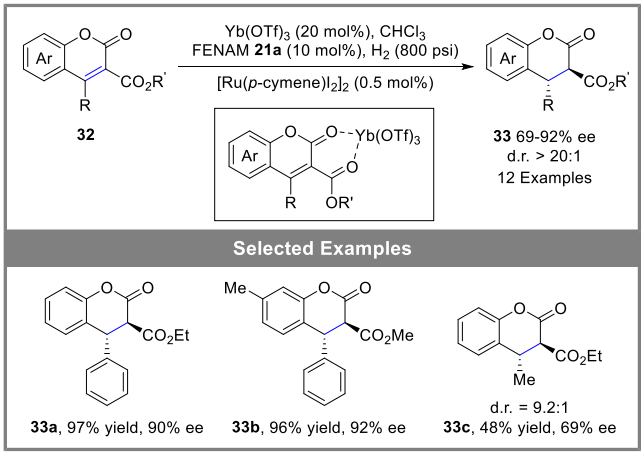
Scheme 23. Synthesis of Chiral Bioactive Molecule with BMAR as Key Step



Encouraged by our results of BMAR of unsaturated compounds using achiral Brønsted acids as the transfer catalyst in the presence of regenerable and chiral NAD(P)H models, we envisioned whether it could be possible to use commercially available Lewis acids as transfer catalysts in the BMAR via coordination activation without binding to chiral ligands.

Based on this hypothesis, the functionalized tetrasubstituted electron-deficient alkenes **32** were selected to test the feasibility of BMAR of C=C through Lewis acid coordination of the carbonyl group. To our delight, excellent yields, diastereoselectivities, and enantioselectivities could be obtained using readily available rare earth Lewis acid $Yb(OTf)_3$ as a transfer catalyst (Scheme 24).[3] The alkyl-substituted

Scheme 24. BMAR of Tetrasubstituted Electron-Deficient Alkenes 32 with Achiral Lewis Acid as Transfer Catalyst



substrate **32c** offered moderate diastereoselectivity and enantioselectivity. Notably, the side product of decarboxylation could be suppressed by optimizing with different kinds of Lewis acids. In addition, this methodology provided an effective route for the synthesis of 3,4-*trans*-disubstituted dihydrocoumarins **33**, which are widely present in natural products and biological molecules.

In 2020, we further extended the use of Lewis acid as the transfer catalyst for the BMAR of flavonoids **34** in the presence of regenerable and chiral NAD(P)H models (Scheme 25),[4] providing a broad range of chiral flavanones **35** with excellent

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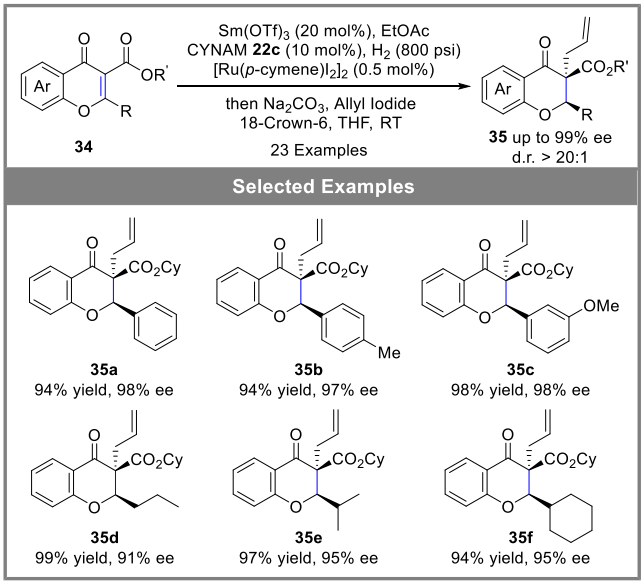
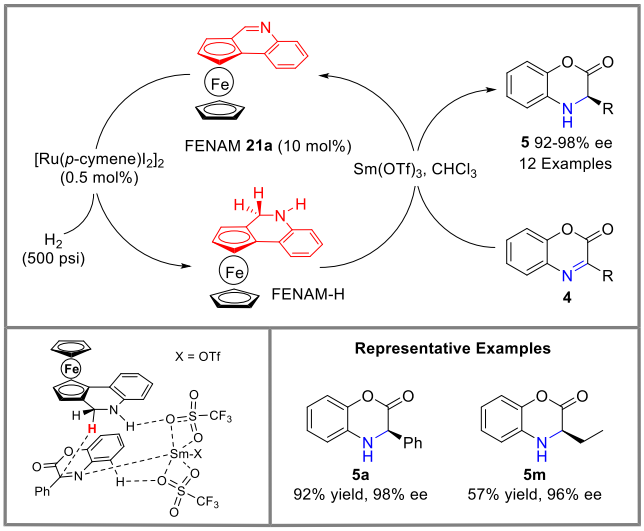
yields, diastereoselectivities, and enantioselectivities by *in situ* alkylation.

Scheme 25. BMAR of Tetrasubstituted Alkene Flavonoids Using CYNAM



Encouraged by the successful BMAR of tetrasubstituted alkenes using Lewis acid as the transfer catalyst, this strategy was also exploited for the BMAR of imines, as the Lewis acid also could activate imines by coordination with the C═N moiety. Through optimization of the conditions, the desired reductive product dihydrobenzoxazinones **5** could be obtained with up to 98% yield and 98% ee (Scheme 26).[3]

Scheme 26. BMAR of Benzoxazinones with Lewis Acid

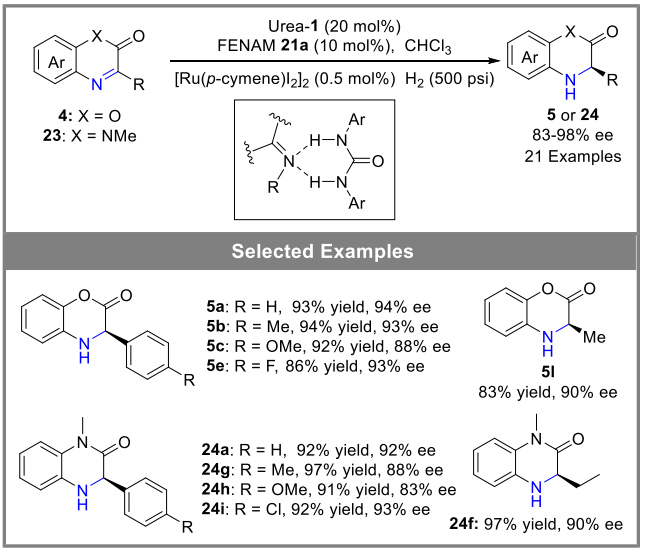


After our paper was published, a new type of manganese-based catalyst was developed for the regeneration of the chiral NAD(P)H models and employed in the BMAR of benzoxazinones and benzoxazines by Hu's group, giving the products with good to excellent enantioselectivities.[30]

3.2.3. Achiral Urea as Transfer Catalyst. In recent decades, (thio)urea-based bifunctional organocatalysts have been successfully applied to various asymmetric catalytic reactions through the activation of hydrogen-bonding interactions.[31] Compared with metal catalysts, the (thio)urea organocatalysts offer advantages such as strong functional group tolerance, affordability, good reproducibility, and ease of preparation and modification.

Inspired by the successful application of simple achiral Brønsted acids and Lewis acids as transfer catalysts in BMAR and considering that (thio)ureas are a class of efficient hydrogen bond activators, we considered whether they can effectively activate imines and carbonyl compounds. Therefore, we attempted to use the urea-based organocatalyst urea-1 as a transfer catalyst to activate substrates in the BMAR with the regenerable and chiral NAD(P)H models as the hydrogen source. Gratifyingly, a series of dihydrobenzoxazinones **5** and dihydroquinoxalinones **24** were obtained with excellent yields and ee values using urea as a transfer catalyst (Scheme 27). The electronic and steric effects of aryl as well as alkyl of substrates had a marginal effect on reactivities and ee values.[32]

Scheme 27. BMAR with Urea as Transfer Catalyst



3.2.4. Transfer Catalyst Free BMAR. For the BMAR, the transfer catalyst is typically required to facilitate the hydrogen transfer from NAD(P)H models to the substrates. Recently, we discovered that the BMAR of the tetrasubstituted alkene 3-sulfonyl coumarins **36** performed smoothly with the regenerable and chiral NAD(P)H model CYNAM **22e** in the absence of the transfer catalyst, just by adjusting the reaction temperature to 90 °C (Scheme 28).[33] The high temperature could accelerate the hydrogen transfer and not affect the enantioselectivity. This methodology provided an effective strategy for the synthesis of chiral 3,4-dihydrocoumarins **37**, which are widely found in natural products and bioactive molecules.

3.3. The Mechanism of BMAR with Regenerable and Chiral NAD(P)H Models

To gain insight into the BMAR process using regenerable and chiral NAD(P)H models, a detailed mechanistic study including the nonlinear effect, isotope-labeling experiments, and density functional theory calculation was carried out.

3.3.1. Nonlinear Effect. In order to understand the detailed mechanism of the BMAR process, the relationship

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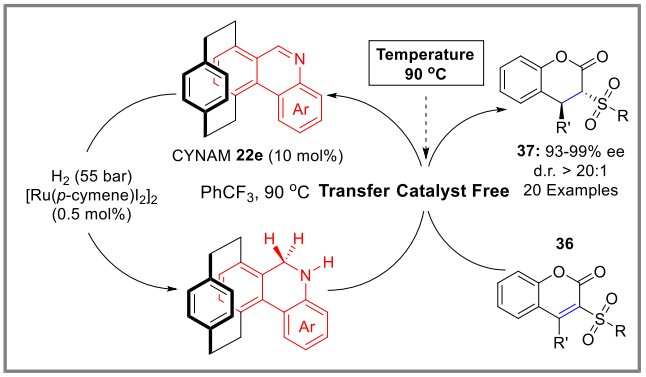
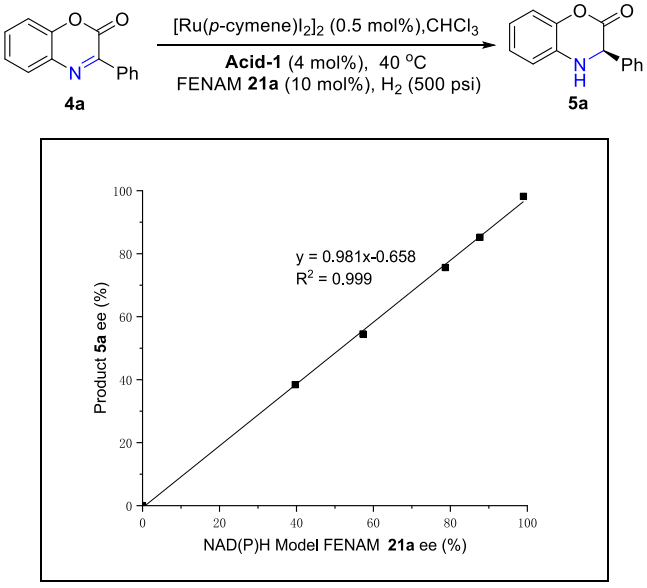
Scheme 28. Transfer Catalyst Free BMAR with CYNAM



between the ee value of the chiral NAD(P)H model FENAM **21a** and the chiral reductive product **5a** was investigated, and the results are presented in Scheme 29.[3,20] It is found that the

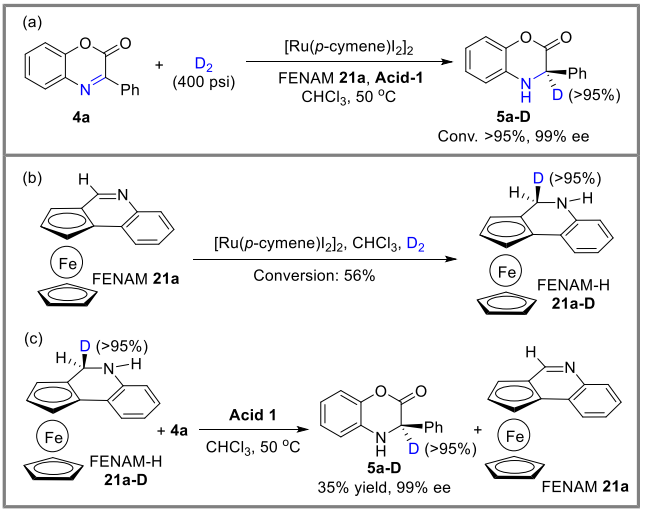
Scheme 29. Relationship between the Optical Purity of the Reductive Product 5a and FENAM 21a



optical purity of the chiral reductive product **5a** was completely proportional to the chiral NAD(P)H model FENAM **21a** and there was an obvious linear effect in the presence of achiral Brønsted acid or Lewis acid as a transfer catalyst.

3.3.2. Isotope-Labeling Experiments. To further explore the BMAR process, several isotope experiments were carried out. The model substrate **4a** could be reduced under D_2 to afford the deuterated reductive product **5a-D**, and the deuterium incorporation is 95% (Scheme 30a). The result showed that D_2 was the terminal reducing agent in the biomimetic reduction reaction. Meanwhile, the regenerable and chiral NAD(P)H models FENAM **21a** could be regenerated in the presence of D_2 with 56% yield, and the deuterium atom was added to the less sterically hindered face with the deuterium incorporation as high as >95% (Scheme 30b). In addition, no deuterium incorporation was observed in the recovered FENAM **21a**. Finally, one equivalent of deuterated NAD(P)H model was subjected to the reaction, giving the deuterated reduced product (99% ee) with >95% deuterium incorporation (Scheme 30c).[20] These results

Scheme 30. Isotope-Labeling Experiments



indicate that the deuterium atom in the NAD(P)H model **21a-D** selectively transferred to the substrate with less steric hindrance under the activation of Brønsted acid. Similar results were observed in the BMAR of tetrasubstituted electron-deficient alkene in the presence of CYNAM **22a** with achiral Lewis acid as a transfer catalyst.[4]

3.3.3. The Density Functional Theory Calculations. In addition, theoretical investigations were conducted to gain an in-depth understanding of the reaction pathway. The energy profiles for the BMAR of C═N and C═C were computed using achiral Brønsted acid or Lewis acid as the transfer catalyst and the regenerable and chiral NAD(P)H models.[20] When Brønsted acid activated the C═N bond of **4a**, O···H and N···H dual hydrogen-bond interactions formed through the Brønsted acidic site (proton) and the Brønsted basic site (phosphoryl oxygen) to accelerate hydride transfer. This process overcame an energy barrier of 15.9 kcal/mol (C−BA−C═N) to give P-1−C═N with a relative energy of −2.5 kcal/mol. During the BMAR of C═N using Lewis acid $Yb(OTf)_3$ as the transfer catalyst, the coordination of **4a** via N atom to the Yb center of $Yb(OTf)_3$ formed the complex C−LA−C═N with relative energy of −7.3 kcal/mol to give the C−LA−C═N with a relative energy of −11.4 kcal/mol, which overcomes an energy barrier of 10.6 kcal/mol. Compared with Brønsted acid or Lewis acid-assisted C═N reduction, $Yb(OTf)_3$-assisted C═N reduction exhibited the lowest energy barrier among the considered pathways (8.9 kcal/mol and 15.9 or 10.6 kcal/mol).

Based on the experimental and DFT results, a plausible mechanism for BMAR reaction activated by achiral Brønsted acid or Lewis acid as a transfer catalyst with regenerable and chiral NAD(P)H model was illustrated (Scheme 31). The proposed reaction mechanism involves several steps: first, the chiral NAD(P)H model FENAM-H is hydrogenated from the FENAM under Ru/hydrogen gas condition; subsequently, the asymmetric transfer hydrogenation of C═N is carried out with FENAM-H using Brønsted acid or Lewis acid as transfer catalyst, affording chiral products and FENAM; finally, FENAM undergoes hydrogenation once again to regenerate FENAM-H for the next cycle. The stereochemistry of this reaction can be explained by the stable transition state, which is generated from the hydrogen-bonding interactions through the transfer catalyst, C═N bond, and chiral NAD(P)H model.

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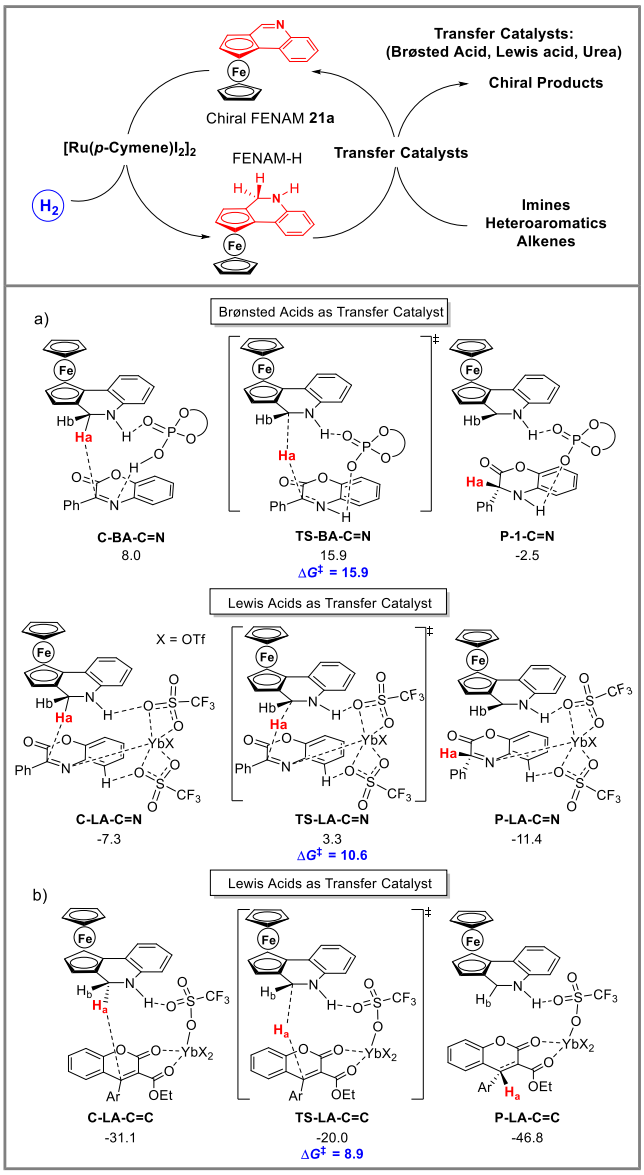
Scheme 31. Proposed BMAR Reaction Pathway and the Transition State Mode



4. SUMMARY AND OUTLOOK

This Account outlined our recent progress in the design and synthesis of two types of regenerable NAD(P)H models based on the principles of biomimetic reduction, as well as their applications in BMAR reactions. One is regenerable and achiral NAD(P)H models (dihydrophenanthridine, and dihydropyrroloquinoxaline) based on the phenanthridine framework, which were designed, synthesized, and applied in BMAR of imines and heteroaromatics. These systems employed a ruthenium complex as the regeneration catalyst, a BINOL-derived chiral phosphoric acid as the transfer catalyst, and hydrogen gas as the terminal reducing agent. The other is regenerable and chiral NAD(P)H models with central, axial, and planar chiralities; among them, the regenerable and chiral NAD(P)H models based on the planar-chiral ferrocene and paracyclophane are the most efficient and have been successfully applied in BMAR of imines, heteroaromatics, and tetrasubstituted electron-deficient alkenes using readily available achiral Brønsted acids, rare earth Lewis acids, or organocatalyst ureas as transfer catalysts, even without transfer catalysts only by adjusting the reaction temperature. Furthermore, mechanistic studies, including nonlinear effect analysis, isotope-labeling experiments, and density functional theory calculations for BMAR were carried out to help understand the asymmetric reduction process and the function of the regenerable coenzyme NAD(P)H models. More importantly, this biomimetic methodology provides an efficient strategy for the facile synthesis of chiral drugs and natural products.

Although progress has been made in regenerable NAD(P)H models for BMAR, there are still several challenges that continue to arouse more interest in the field, mainly including (1) the development of some simple and efficient methods for synthesis of regenerable and chiral NAD(P)H models, (2) the development of new, easily tunable, and more stable chiral regenerable NAD(P)H models, such as those with spiro chiral skeletons, (3) the development of some earth-abundant and readily available regeneration catalysts, such as those based on Fe, Ni, and Mn catalysts, and (4) the expansion of the application of regenerable and chiral NAD(P)H models in field of asymmetric catalysis. The NAD(P)H is also involved in the oxidation process in cells. Although the regenerable and chiral NAD(P)H models have been successfully applied in BMAR, their application in the biomimetic asymmetric oxidation reaction such as asymmetric dehydrogenation is a worthwhile research direction. We hope that our efforts summarized in this Account will provide valuable insights for readers in the rational design and synthesis of novel and efficient regenerable NAD(P)H models, as well as the further expansion of their applications in biomimetic asymmetric reactions.

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Author Contributions

CRediT: **Mu-Wang Chen** methodology (equal), writing-original draft (equal); **Bo Wu** methodology (equal), writing-review & editing (equal); **Zheng Liu** methodology (equal), writing-review & editing (equal); **Yong-Gui Zhou** conceptualization (equal), writing-original draft (equal).

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Notes

The authors declare no competing financial interest.

Biographies

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