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Biomimetic Asymmetric Reduction of Benzoxazinones and Quinoxalinones Using Ureas as Transfer Catalysts

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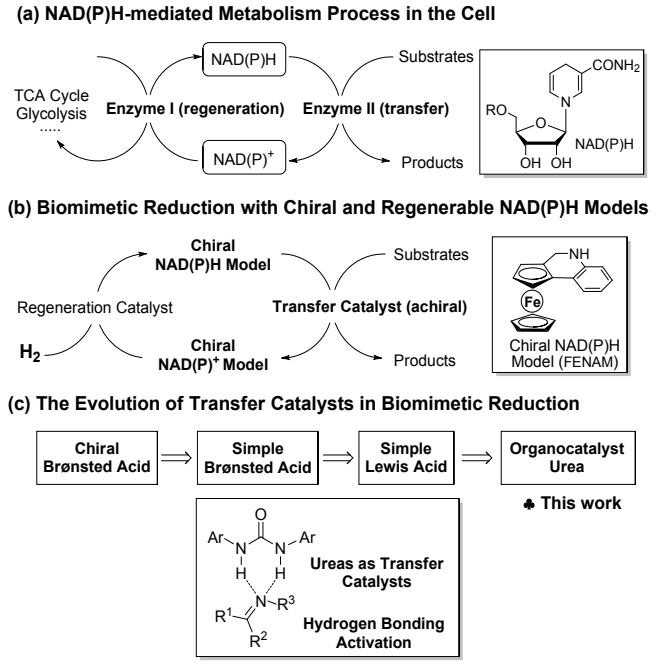
Using ureas as transfer catalysts through hydrogen bonding activation, biomimetic asymmetric reduction of benzoxazinones and quinoxalinones with chiral and regenerable NAD(P)H models was described, giving the chiral dihydrobenzoxazinones and dihydroquinoxalinones with high yields and excellent enantioselectivities. A key dihydroquinoxalinone intermediate of BRD4 inhibitor was synthesized using biomimetic asymmetric reduction.

The development of biomimetic science has brought great benefits to human life. The reduced nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) as crucial redox coenzymes play a vital role in the cells. The interconversion of the pyridine nucleotide coenzymes NAD(P)+ /NAD(P)H is widespread in over 400 enzymatic reactions (Scheme 1a).[1] Because these coenzymes are expensive and labile, synthetic NAD(P)H mimics have been continuously emerged over the past decades. Early works mainly focused on development of the stoichiometric NAD(P)H models such as dihydronicotinamide derivatives[2], Hantzsch esters (HEH)[3] and benzothiazolines[4] etc. The utilization of the stoichiometric models limits its further regeneration and leads to low atomic economy. Subsequently, regenerable NAD(P)H models were devised and the processes were realized by *in situ* regeneration mediated by homogeneous catalysts including rhodium[5], ruthenium[6], iron catalyst[7] and sodium dithionate[8], etc.[9] In terms of biomimetic asymmetric reduction, stereocontrol is mainly from chiral transfer catalysts.[6,7b] Nevertheless, chiral transfer catalyst screening is quite tedious in each biomimetic reduction. Very recently, a chiral and regenerable NAD(P)H model based on ferrocene-derived motif was designed and employed to biomimetic asymmetric reduction[10] (Scheme 1b). The readily available and bench-stable achiral Lewis acids[10] and Brønsted acids[11] could be used as transfer catalysts. These two types of transfer catalysts have different activation modes.[11] However, these catalysts have limited compatibility with acid-labile or polyfunctional substrates and tandem transformations.[12] Therefore, more mild and general transfer catalysts remain to be developed, especially those with potentially new activation modes, to further expand the generality of biomimetic asymmetric reduction.



Scheme 1. Biomimetic asymmetric reduction (BMAR) based on the coenzyme NAD(P)H and transfer catalysts.

Hydrogen-bonding interaction plays an important role in the molecular recognition and activation processes of various biologically important reactions. (Thio)urea based bifunctional catalysts capable of activating substrates through hydrogen-bonding activity have received much attention.[13] (Thio)urea

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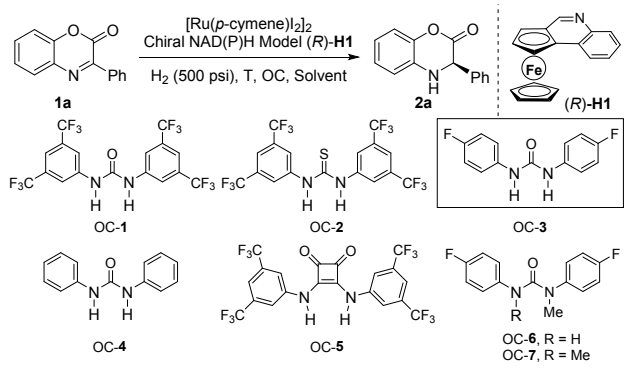
derivatives feature good functional group tolerance, cheap, moisture-insensitive, and readily accessible. Therefore, catalysis through hydrogen-bonding interaction has been introduced as a powerful methodology for asymmetric reaction.[13] However, no report on the application of this method to biomimetic reduction with chiral NAD(P)H models appeared. Hence, the development of a novel activation method in biomimetic reduction with chiral and regenerable NAD(P)H models is significant in organic chemistry. In this paper, we present the biomimetric asymmetric reduction through hydrogen-bonding activation strategy with urea derivatives (Scheme 1c).

Table 1. Optimization of reaction parameters[a]

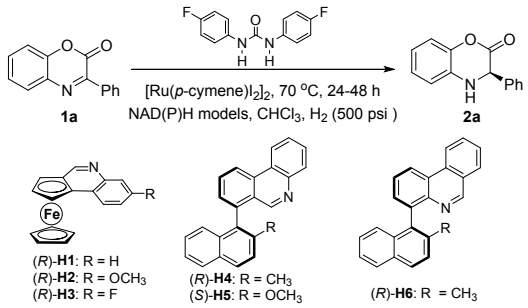


Entry	OC	Solvent	T (°C)	Convn (%)[b]	Ee (%)[c]
1	--	Toluene	50	<5	--
2	OC-**1**	Toluene	50	10	92
3	OC-**1**	Benzene	50	12	95
4	OC-**1**	DCM	50	28	93
5	OC-**1**	$CHCl_3$	50	24	96
6	OC-**1**	DCE	50	35	91
7	OC-**1**	THF	50	<5	--
8	OC-**1**	$CHCl_3$	60	30	96
9	OC-**1**	$CHCl_3$	70	82	96
10	OC-**1**	$CHCl_3$	80	60	92
11	OC-**2**	$CHCl_3$	70	<5	--
12	OC-**3**	$CHCl_3$	70	85	96
13	OC-**4**	$CHCl_3$	70	30	94
14	OC-**5**	$CHCl_3$	70	33	97
15	OC-**6**	$CHCl_3$	70	58	94
16	OC-**7**	$CHCl_3$	70	11	87

[a] Reaction conditions: **1a** (0.10 mmol), [Ru(*p*-cymene)I_2]$_2$ (0.5 mol%), (*R*)-**H1** (10 mol%), OC (20 mol%), Solvent (2 mL), H_2 (500 psi), 50 °C, 24 h. [b] Conversion was measured by analysis of ^{1}H NMR spectra. [c] Determined by HPLC.

To validate our proposed activation strategy, we chose benzoxazinone (**1a**) as the model substrate with chiral and regenerable NAD(P)H model (*R*)-**H1** and (thio)urea derivatives as transfer catalysts. The results of condition optimization were summarized in Table 1. The present study was initiated by direct biomimetic reduction in the absence of transfer catalyst, unfortunately, only <5% of the desired product was observed (Entry 1). To our delight, the reaction could be carried out smoothly using the urea derivatives. The desired product was obtained in 92% enantioselectivity albeit with low 10% yield (Entry 2). Next, a number of solvents were extensively examined. It was found that $CHCl_3$ was the best choice in terms of yields and enantioselectivities (Entries 2-7). Subsequently, considering the effect of temperature on the reaction, we tried to increase the temperature. When the reaction was carried out at 70 °C, the reaction gave the desired product with 82% yield and 96% ee value (Entry 9). However, when the reaction temperature is further increased, NAD(P)H model based on ferrocene-derived structure will be inactivated (Entry 10). Subsequently, we turned our attention to a series of organic hydrogen-bonding catalysts. While replacing urea with thiourea, the reaction didn't occur (Entry 11), which might ascribe to the strong poisonous effect of thiourea to ruthenium regeneration catalyst. We found that the urea and squaramide catalysts could make the reaction proceed smoothly and urea OC-**3** proved to be the best (Entries 9, 12-14). Besides, it was noted that the desirable hydrogenation product could be obtained albeit with low conversion using mono hydrogen bonding donor OC-**6** (58% conversion, 94% ee) and full *N*-methyl protected urea OC-**7** (11% conversion, 87% ee) as transfer catalyst (Entries 15-16).

Table 2. Optimization of chiral NAD(P)H models[a]



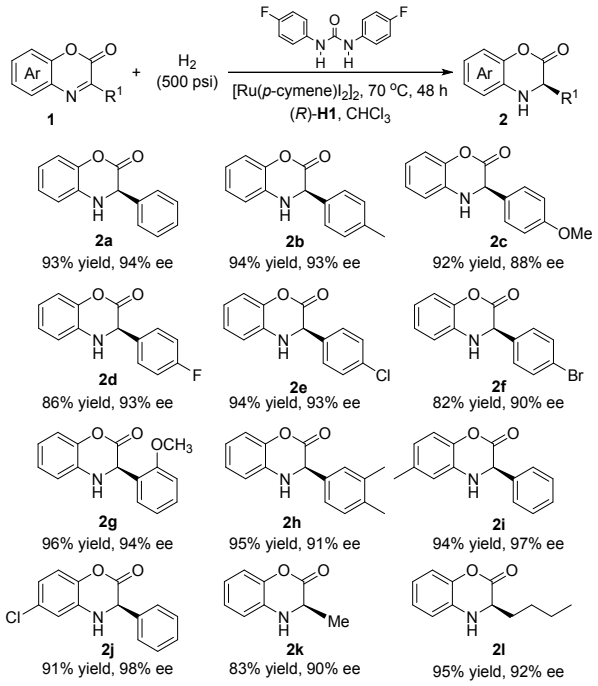
Entry	Chiral NAD(P)H model	Convn (%)[b]	Ee (%)[c]
1	(*R*)-**H1**	85	96
2	(*R*)-**H2**	45	94
3	(*R*)-**H3**	18	83
4	(*R*)-**H4**	9	14
5	(*S*)-**H5**	29	53
6	(*R*)-**H6**	<5	--
7[d]	(*R*)-**H1**	94	95

[a] Reaction conditions: **1a** (0.10 mmol), [Ru(*p*-cymene)I_2]$_2$ (0.5 mol%), Chiral NAD(P)H model (10 mol%), OC-**3** (20 mol%), $CHCl_3$ (2 mL), H_2 (500 psi), 70 °C, 24 h. [b] Conversion was measured by analysis of 1H NMR spectra. [c] Determined by HPLC. [d] 48 h.

Hereafter, further examinations focused on screening of chiral and regenerable NAD(P)H models (Tabel 2). NAD(P)H models with planar chirality were favourable and the best result was achieved with (*R*)-**H1**. It is worth noting that the electronic property of the substituents on the structure have obvious effect on the results (Entries 2-3). In addition, other

NAD(P)H models with axial chirality including the nitrogen atom close to the C2 axial stereocenter and the nitrogen atom far away from the C2 axial stereocenter have also been investigated. Unfortunately, these NAD(P)H models only deliver the trace amount of product (Entries 4-6). In order to enhance the conversion, the reaction time was increased to 48 h with improved activity and almost same ee. Therefore, the optimal conditions were established.

Scheme 2. The BMAR of benzoxazinones.[a]

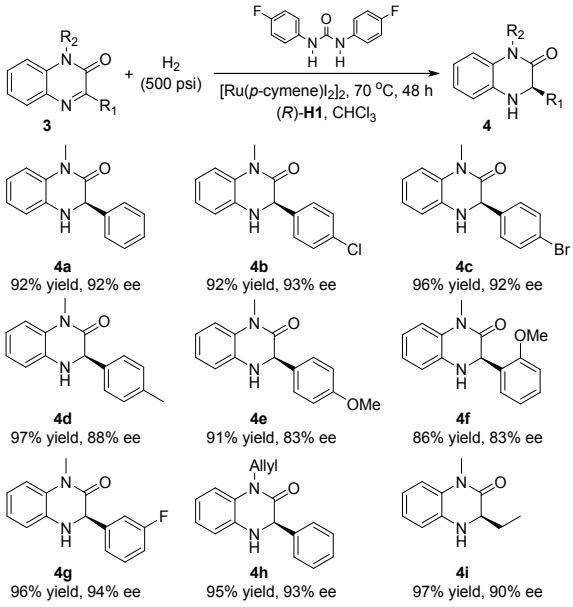


[a]Reaction conditions: **1** (0.20 mmol), [Ru(*p*-cymene)I_2]$_2$ (0.5 mol%), (*R*)-**H1** (10 mol%), OC-**3** (20 mol%), $CHCl_3$ (3 mL), H_2 (500 psi), 70 °C, 48 h.

With the optimized conditions in hand, the reaction scope of benzoxazinones was then evaluated, and the results are summarized in Scheme 2. These results revealed that this strategy was suitable for a series of benzoxazinones. The electronic and steric effect on the phenyl of the substrate slightly influenced the reactivities and enantioselectivities (**2a-2g**). For example, the ee value was decreased to 88% when the electron-donating group methoxy at the *para*-position of the aryl moiety (**2c**). Gratifyingly, the desirable product could be obtained with high reactivity and enantioselectivity when the methoxy group at the *ortho*-position of the aryl moiety (**2g**). Subsequently, we investigated disubstituents at the phenyl and different groups at the benzoxazinones skeleton (**2h-2j**). Moreover, the alkyl-substituted substrates were also amenable to the present reaction, delivering the products in high yields and excellent enantioselectivities (**2k-2l**).

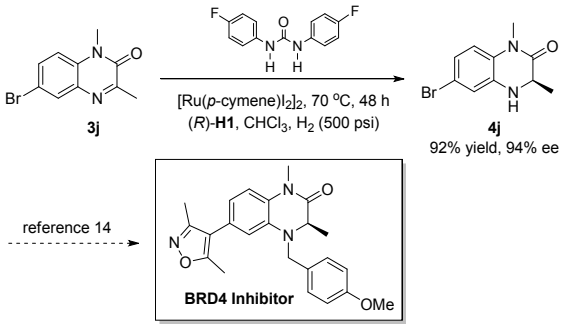
To expand the generality of this strategy, we next focused on biomimetic asymmetric reduction of quinoxalinones with the NAD(P)H model and urea catalyst. The results are depicted in Scheme 3. In the case of aromatic moiety, the reaction conditions tolerated both electron-donating and electron-withdrawing substituents (**4a-4g**). It was found that the enantioselectivity was slightly decreased when the methyl at the *para*-position (**4d**). Meanwhile, when the methoxy is at the *para*-position and *ortho*-position (**4e-4f**), the enantioselectivities were slightly lower than the methyl. Notably, when introducing fluorine group to *meta*-position of aryl structure, the reaction proceeded smoothly, giving the desired product with excellent enantioselectivity and yield (**4g**). Furthermore, allyl-substituted substrate was also well compatible to deliver the corresponding product with 95% yield and 93% enantioselectivity (**4h**). It is worth noting that the alkyl-substituted substrate was also investigated, 97% yield and 90% enantioselectivity could be obtained under the optimal condition (**4i**).

Scheme 3. The BMAR of quinoxalinones.[a]



[a] Reaction conditions: **3** (0.20 mmol), [Ru(*p*-cymene)I_2]$_2$ (0.5 mol%), (*R*)-**H1** (10 mol%), OC-**3** (20 mol%), $CHCl_3$ (3 mL), H_2 (500 psi), 70 °C, 48 h.

Scheme 4. The BMAR of bromine-substituted quinoxalinone and synthesis of key intermediate of BRD4 inhibitor.



As a member of the family of the bromodomain and extra-terminal domain (BET) proteins, bomodomain-containing protein 4 (BRD4) is a feasible drug target for cancer treatment on the basis of recent biological and pharmacological studies.[14] A series of novel dihydroquinoxalinone derivatives could be used as BRD4 inhibitors. Therefore, we performed a concise synthesis of the key intermediate of BRD4 inhibitor using the above methodology (Scheme 4). Under the standard condition,

bromine-substituted quinoxalinone **3j** afforded the desired product with 92% yield and 94% ee, which is a key intermediate for the synthesis of a BRD4 inhibitor.[14a]

Based on the experimental results, a plausible mechanism and transition state model are illustrated in Figure S1 (see Supporting Information). The urea catalysts promote the reduction through hydrogen-bonding activation. The chiral NAD(P)H model transfers the hydrogen atom from less steric face to the imine, leading to the (*R*)-products.

Conclusions

In summary, we have disclosed hydrogen-bonding activation strategy in the biomimetric asymmetric reduction with chiral and regenerable NAD(P)H models. This methodology could be extended to benzoxazinones and quinoxalinones substrates for furnishing chiral products with high yields and excellent enantioselectivities. A key dihydroquinoxalinone intermediate of BRD4 inhibitor was synthesized using the biomimetic asymmetric reduction methodology. This activation method will further broaden the generality of biomimetic asymmetric reduction. Further, other activation modes and substrates scope are under progress and the results will be presented in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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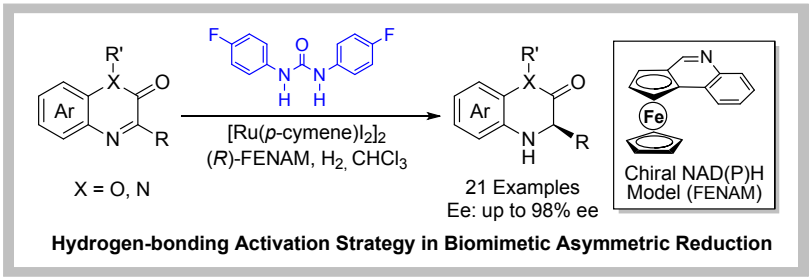

Hydrogen-bonding Activation Strategy in Biomimetic Asymmetric Reduction

Using ureas as transfer catalysts through hydrogen bonding activation, biomimetic asymmetric reduction of benzoxazinones and quinoxalinones has been developed, giving the chiral dihydrobenzoxazinones and dihydroquinoxalinones with high enantioselectivities. A key dihydroquinoxalinone intermediate of BRD4 inhibitor was synthesized using biomimetic asymmetric reduction.