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Enantioselective Synthesis of 2-Functionalized Tetrahydroquinolines through Biomimetic Reduction

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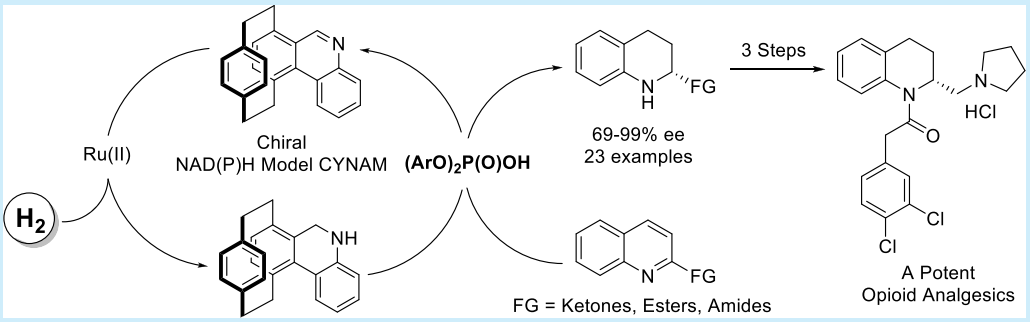

ABSTRACT: Biomimetic asymmetric reduction of 2-functionalized quinolines has been successfully developed with the chiral and regenerable NAD(P)H model CYNAM in the presence of transfer catalyst simple achiral phosphoric acids, providing the chiral 2-functionalized tetrahydroquinolines with up to 99% ee. Using this methodology as a key step, a chiral and potent opioid analgesic containing a 1,2,3,4-tetrahydroquinoline motif was synthesized with high overall yield.

A tetrahydroquinoline motif has been identified as a prevalent frame unit frequently found in bioactive natural products, agrochemicals, and pharmaceutical molecules. A wide range of tetrahydroquinoline derivatives have been used as antibiotics, antagonists, ligands, and antibacterial drugs (Figure 1).[1] Among them, it is worth noting that the chiral 2-functionalized tetrahydroquinolines are the privileged structural motifs in bioactive molecules.[2] For example, 1,2,3,4-tetrahydroquinoline-2-carboxylic acid has the basic skeleton of cyclic amino acids which provide plenty of opportunities for the further synthesis of other biological molecules.

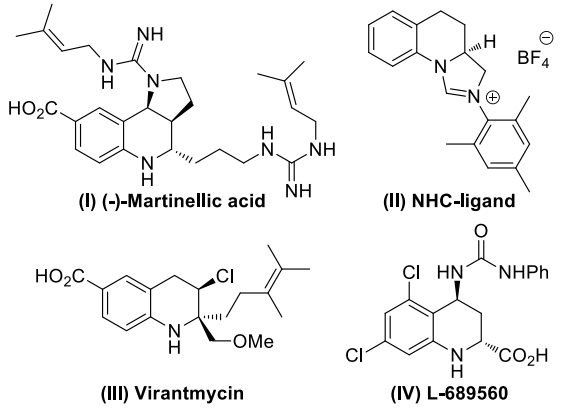

Figure 1. Selected bioactive molecules and ligands containing a core structure of chiral tetrahydroquinoline.

Owing to the remarkable importance of chiral tetrahydroquinolines, a series of powerful approaches have been developed.[3] The typical methods for building these core structures generally rely on transition-metal or organocatalyzed asymmetric hydrogenation of the corresponding quinolines.[4,5] In the above-mentioned methods, simple aryl and alkyl substituents of quinolines have been well studied. In contrast, other quinoline substrates with ketone, ester, and amide functionalities have been less investigated, especially for the substrates of quinoline-2-carboxylates, for which the reductive products are involved in nitrogen-containing heterocyclic α-amino acids.[6] In the field of 2-functionalized quinolines, some asymmetric catalytic systems have been conducted, such as transition-metal-catalyzed asymmetric hydrogenation using ruthenium[6a] or iridium[6b,c] and transfer hydrogenation employing Hantzsch esters and chiral Brønsted acids.[6e] Unfortunately, these catalytic systems only give a few examples of quinolines bearing ketone, ester, and amide functionalities. For example, the Agbossou–Niedercorn group

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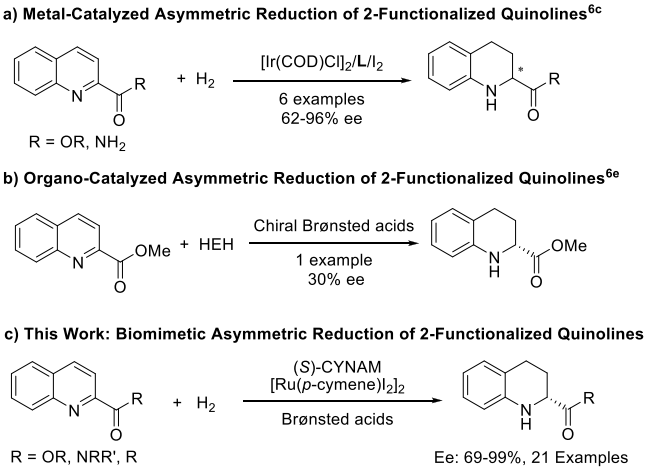
reported the iridium-catalyzed asymmetric hydrogenation of quinolines with ester and amide functionalities (Scheme 1a).[6b,c] In 2019, the Tsantrizos group reported the transfer hydrogenation using Hantzsch esters, and there was only one case of 2-functionalized tetrahydroquinolines with 30% ee (Scheme 1b).[6e] Hence, developing a facile catalytic system for the reduction of 2-functionalized quinolines with high enantioselectivities and broad substrate scopes is fairly necessary and urgent.

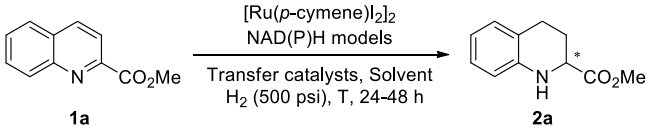
Scheme 1. Catalytic Asymmetric Reduction of 2-Functionalized Quinolines



It was worth noting that the substrates of quinolines with ketone functionalities have a selective reduction problem of ketone or quinoline. In order to solve this problem, biomimetic asymmetric reduction (BMAR) based on cofactor NAD(P)H models might be a good choice.[7] During the past few years, chiral and regenerable NAD(P)H models with planar-chiral structure have been designed, synthesized, and applied to the asymmetric reduction of the imines, quinolines, and other substrates.[8,9] Besides, BMAR also employs mild reaction conditions and has a good selectivity to the part of quinoline moieties. At the same time, considering hydrogen-bonding activation of 2-functionalized quinolines using a simple Brønsted acid, we envisaged that asymmetric reduction of 2-functionalized quinolines might be realized using the chiral and regenerable NAD(P)H models. Herein, we disclose the biomimetic asymmetric reduction of the 2-functionalized quinolines with excellent yield, enantioselectivity, and broad substrate scope, including esters, amides, and ketones (Scheme 1c).

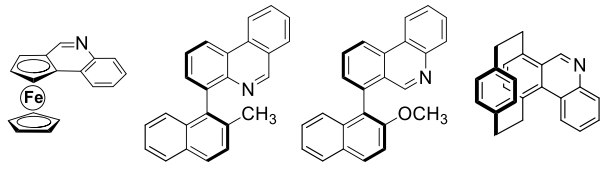
At the outset, methyl quinoline-2-carboxylate **1a** was selected as the model substrate. An initial background reaction was performed in the presence of a regeneration catalyst $[Ru(p\text{-cymene})I_2]_2$ and hydrogen gas without transfer catalysts and NAD(P)H models. The results indicated that only a trace amount of product was obtained (Table 1, entry 1). A similar result could be obtained when the NAD(P)H model (*R*)-**H1** was added to the reaction system (entry 2). Fortunately, the conversion could be increased to 35% in the presence of $TsOH{\cdot}H_2O$ (entry 3). Next, a series of Brønsted acid transfer catalysts were also investigated (entries 4 and 5). It was worth noting that the acid-containing nitro group could give the desirable product in 92% enantioselectivity and 44% conversion (entry 5). A subsequent screening of solvents

Table 1. Evaluation of Reaction Parameters[a]



Transfer Catalyst: Acid-**1**: PTSA; Acid -**2**: $(PhO)_2P(O)OH$
Acid-**3**: $(4\text{-}O_2NC_6H_4O)_2P(O)OH$

Chiral and Regenerable Models:



(*R*)-**H1** (*R*)-**H2** (*S*)-**H3** (*S*)-**H4**

entry	transfer catalysts	NAD(P)H models	solvent	conv. (%)[b]	ee (%)[c]
1	--	--	EtOAc	<5	--
2	--	(*R*)-**H1**	EtOAc	<5	--
3	acid **1**	(*R*)-**H1**	EtOAc	35	91
4	acid **2**	(*R*)-**H1**	EtOAc	23	91
5	acid **3**	(*R*)-**H1**	EtOAc	44	92
6	acid **3**	(*R*)-**H1**	$CHCl_3$	7	94
7	acid **3**	(*R*)-**H1**	toluene	10	86
8	acid **3**	(*R*)-**H1**	THF	28	88
9	acid **3**	(*R*)-**H1**	CH_3CN	<5	--
10[d]	acid **3**	(*R*)-**H1**	EtOAc	90	91
11[d]	acid **3**	(*R*)-**H2**	EtOAc	12	5
12[d]	acid **3**	(*S*)-**H3**	EtOAc	41	45
13[d]	acid **3**	(*S*)-**H4**	EtOAc	95	97
14[d,f]	acid **3**	(*S*)-**H4**	EtOAc	>95	97

[a]Conditions: **1a** (0.10 mmol), $[Ru(p\text{-cymene})I_2]_2$ (0.5 mol %), NAD(P)H models (10 mol %), transfer catalysts (5.0 mol %), solvent (2.0 mL), and H_2 (500 psi), at 50 °C for 24 h. [b]Measured by analysis of ^1H NMR. [c]Determined by chiral HPLC. [d]48 h. [f]60 °C.

(entries 5−9) has shown that ethyl acetate was the most effective. When the reaction time was prolonged to 48 h, the conversion increased to 90%.

Encouraged by the above results, we further examined different kinds of chiral and regenerable NAD(P)H models (entries 11−13). Two types of NAD(P)H models with the axial chirality proved to be ineffective (entries 11 and 12). Besides, a novel and more stable class of NAD(P)H models based on the skeleton of [2.2]paracyclophane was also investigated. The expected product could be obtained in 95% conversion and 97% ee (entry 13). To our delight, increasing the reaction temperature from 50 to 60 °C could result in full conversion and 97% ee (entry 14). On the basis of these results, the optimized reaction conditions were defined.

With the optimized reaction conditions in hand, we next investigated the substrate scopes (Scheme 2). At first, various kinds of carboxylate substrates are studied (**2a**−**2d**). These substrates performed well under the optimized conditions, giving the desired products with good yields and excellent enantioselectivities. In addition, different substituents such as electron-donating groups of methyl and methoxy on the benzoic ring were all compatible, delivering the corresponding products in high yields with moderate to excellent ee values (**2e**−**2g**). When substrates contain electron-withdrawing

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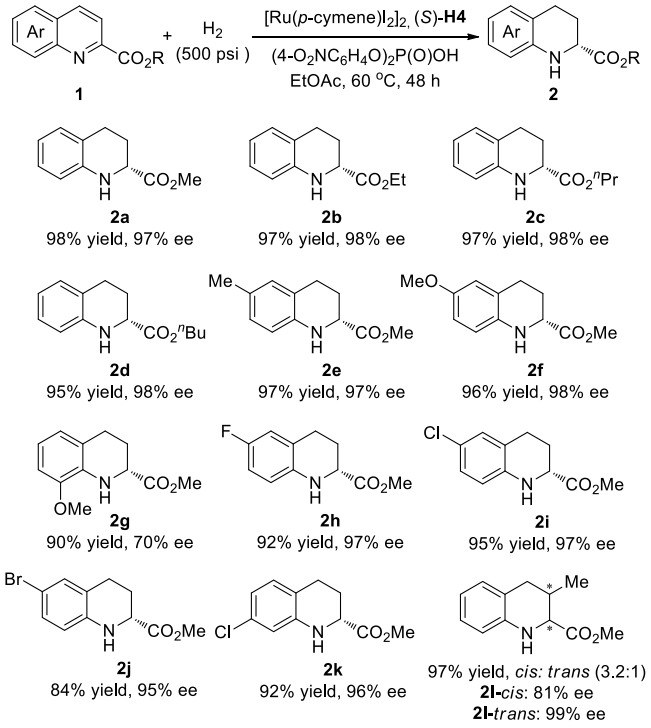
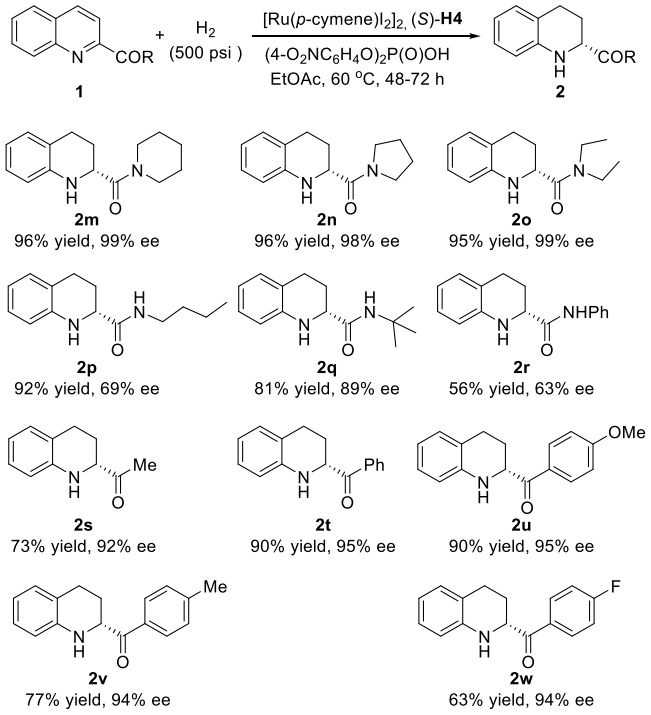
Scheme 2. Substrate Scope: 2-Ester Substituted[a]



[a]Conditions: **1** (0.15 mmol), [Ru(*p*-cymene)I_2]$_2$ (0.5 mol %), (*S*)-**H4** (10 mol %), (4-$O_2NC_6H_4O$)$_2$P(O)OH (5.0 mol %), EtOAc (2.0 mL), and H_2 (500 psi), at 60 °C for 48 h. [b]Isolated yields. [c]Determined by chiral HPLC.

Scheme 3. Substrate Scope: 2-Acyl and Amide Substituted[a]



[a]Conditions: **1** (0.15 mmol), [Ru(*p*-cymene)I_2]$_2$ (0.5 mol %), (*S*)-**H4** (10 mol %), (4-$O_2NC_6H_4O$)$_2$P(O)OH (5.0 mol %), EtOAc (2.0 mL), and H_2 (500 psi), at 60 °C for 48−72 h.

groups, the corresponding products (**2h**−**2j**) were obtained with 95−97% ee and 84−95% yields. When changing the position of the chloro substituent, the reaction could also give excellent yield and enantioselectivity (**2k**). It was found that disubstituted substrate could also be conducted successfully to furnish the desired products with 97% yield. In the reductive products, the ratio of *cis*/*trans* was as low as 3.2:1, and the enantioselectivity of the *trans* product was 99% but 81% ee for the *cis* product (**2l**).

To further demonstrate the versatility of our method, this biomimetic asymmetric reduction was also performed on a wide range of amide and ketone substrates (Scheme 3). It was worth noting that amide substrates containing five-membered or six-membered rings could deliver the products with high yields and excellent enantioselectivities (**2m**−**2n**). Acyclic structure substrates, especially dialkylated on the nitrogen atom of amide, performed very well in the optimized conditions (**2o**). A single alkylated substrate on the nitrogen atom of amide could lead to excellent yield, albeit with low 69% enantioselectivity (**2p**), which might be ascribed to intramolecular hydrogen bonding between NH and the N-atom of quinoline. However, 81% yield and 89% ee were obtained using the bulky *tert*-butyl-substituted amide substrate **1q**. When the phenyl-substituted amide substrate **1r** was employed, the desired product **2r** was generated in moderate yield and enantioselectivity (56% yield and 63% ee). Moreover, alkyl ketone substrate **1s** also worked well, giving the desired product **2s** in 73% yield and 92% enantioselectivity. Subsequently, the reaction was also found to be compatible with a series of aryl ketone substrates (**2t**−**2w**). The electronic effect of the substituents on the aromatic ring has an impact on the results. For example, the substrate-containing electron-donating group such as methoxy could give the corresponding product in 90% yield and 95% ee (**2u**). When the substituent was replaced with a methyl or fluorine group, moderate yields and high enantioselectivities were obtained (**2v**−**2w**).

On the basis of the above experimental results and putative mechanism on biomimetic reduction based on the NAD(P)H model, a plausible reaction mechanism was proposed in Figure 2. First, the NAD(P)H model (*S*)-**H4** was reduced *in situ* using a ruthenium complex and hydrogen gas. Then, in the presence of Brønsted acid and (*S*)-**H4**-**H**, the 2-functionalized tetrahydroquinolines were formed through 1,4-H addition, rapid enamine/imine isomerization, and 1,2-biomimetic asymmetric reduction. At the same time, the reductive NAD(P)H model of (*S*)-**H4**-**H** was converted into the (*S*)-**H4**. Subsequently, the NAD(P)H model could be regenerated with hydrogen to complete the catalytic cycle.

To demonstrate the synthetic utility of this method, the reaction on the gram scale was carried out at a 4.5 mmol scale (Scheme 4). To our delight, the desired chiral product **2n** was obtained without the loss of activity and enantioselectivity (94% yield, 98% ee). In addition, 80% yield of the NAD(P)H model (*S*)-**H4** could be recovered. Meanwhile, the methodology could be applied to the synthesis of bioactive molecules. Chiral compound **3** containing the 1,2,3,4-tetrahydroquinoline motif as a potent opioid analgesic,[2a] which could be synthesized in three steps from chiral biomimetic asymmetric reduction product (*R*)-**2n**, reduction with lithium aluminum hydride, acylation with 3,4-dichlorophenylacetyl chloride in the presence of potassium carbonate, and treatment with hydrochloric acid, gave the HCl salt **3** with overall 88% yield.

In conclusion, we have successfully developed biomimetic asymmetric reduction of 2-functionalized quinolines with the

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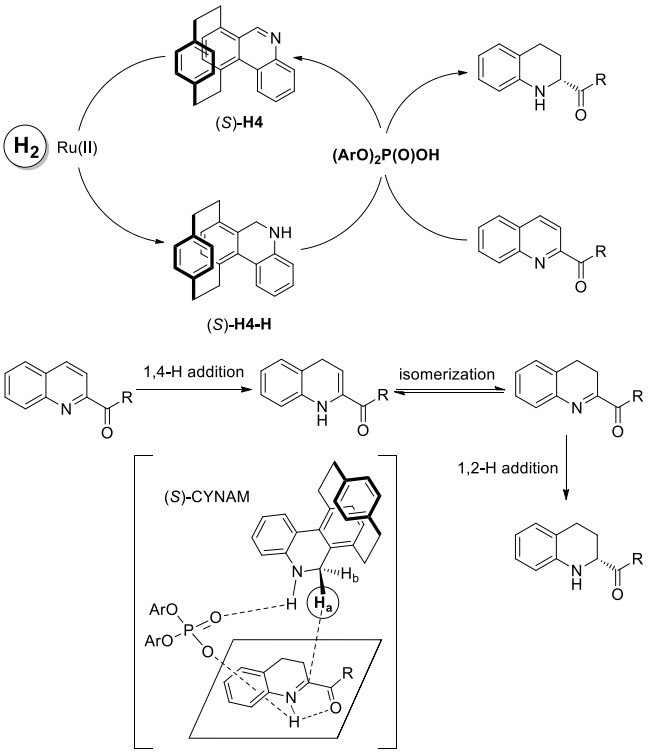
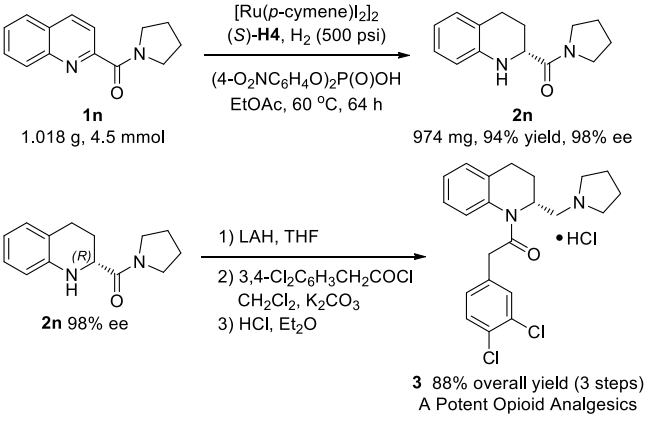


Figure 2. Proposed reaction mechanism.

Scheme 4. Scale-Up Experiment and Synthesis of the Bioactive Molecule



chiral and regenerable NAD(P)H model CYNAM in the presence of transfer catalyst simple phosphoric acid, providing the chiral 2-functionalized tetrahydroquinolines in high yields, excellent enantioselectivities, broad substrate scopes, and functional group tolerance. Further development of this chiral and regenerable NAD(P)H model in other biomimetic asymmetric reactions is currently ongoing in our group and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03430.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Author Contributions

§Z.Z. and J.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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