Concise Report

Biomimetic synthesis, Chirality, Reduction, Tetrahydroquinoline, One-pot

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Enantioselective Synthesis of Tetrahydroquinolines *via* One-Pot Cascade Biomimetic Reduction†

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Summary of main observation and conclusion A novel and efficient protocol for the synthesis of chiral tetrahydroquinoline derivatives with excellent enantioselectivities and high yields has been developed through one-pot cascade biomimetic reduction. The detailed reaction pathway includes the acid-catalyzed and ruthenium-catalyzed formation of aromatic quinoline intermediates and biomimetic asymmetric reduction.

Background and Originality Content

Tetrahydroquinolines are identified as significant and prevalent structural motifs in bioactive natural products and pharmaceutical molecules.[1] Many molecules exhibit diverse biological activities such as antihypertensive, antidiabetic, antibacterial and antimalarial activity.[1,2] For example, it also could be used as androgen receptor agonist and progesterone receptor antagonist.[2] All these molecules have a core skeleton of tetrahydroquinoline (Figure 1). In addition, tetrahydroquinolines could also be served as one class of valuable synthetic intermediates for organic synthesis and industrial applications.[1]

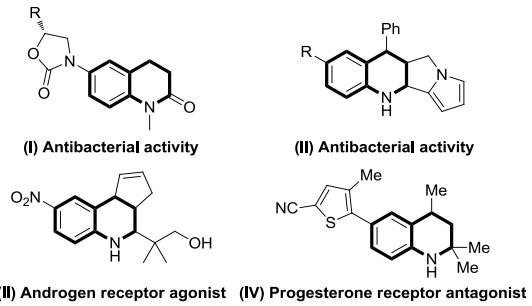


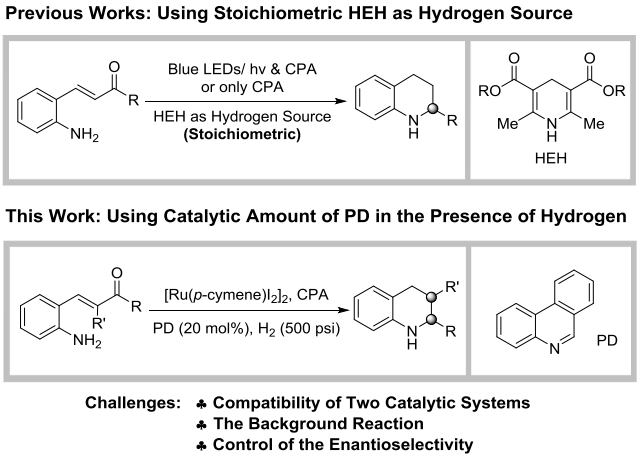
Figure 1 Bioactive molecules containing the tetrahydroquinoline motif.

Owing to the remarkable significance, a variety of powerful and efficient approaches have been developed for synthesis of chiral tetrahydroquinolines.[3] Among the various methods, enantioselective hydrogenation of aromatic quinolines was considered as the most straightforward access to produce the chiral compounds. A series of catalytic hydrogenation systems have been established in terms of this field.[4,5] Despite the success of the hydrogenation reaction, aromatic compounds such as quinolines need to be synthesized in advance.

The combination of two different catalytic processes in one-pot reaction, which the intermediates separation was not required, could significantly increase the synthetic efficiency.[6] In the field of tetrahydroquinolines synthesis, many methods such as catalytic cascade reactions from easily available starting materials have also been successfully developed.[7] According to retrosynthetic analysis, 2-aminochalcones also might be a good choice as the substrate for consecutive one-pot catalytic reaction.[8] Using this strategy, in 2013, Rueping's group reported the reaction for synthesis of chiral tetrahydroquinolines *via* consecutive photocyclization/asymmetric transfer hydrogenation.[9] Soon after, Yang and coworkers developed a similar approach through visible-light-induced cyclization/chiral phosphoric acid-catalyzed transfer hydrogenation.[10] In 2018, Cheon's group also reported the two step one-pot consecutive process including cyclization/ asymmetric reduction using chiral phosphoric acid as the sole catalyst (Scheme 1).[11] However, these reactions all required the stoichiometric amount of NAD(P)H model Hantzsch esters (HEH) as hydrogen source in the reduction and suffered from restriction on the HEH regeneration, leading to low atomic economy and difficulty in product isolation. Therefore, it is necessary to develop a novel and efficient method using the catalytic amount of NAD(P)H model in the presence of hydrogen gas. Furthermore, the one-pot multi-step reaction for synthesis of chiral tetrahydroquinolines employing the regenerable hydrogen sources has not been reported up to date.

Recently, biomimetic asymmetric hydrogenation of imines and heteroaromatics with catalytic amount of NAD(P)H models such

Scheme 1 Catalytic enantioselective synthesis of tetrahydroquinolines



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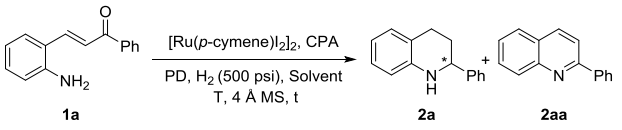
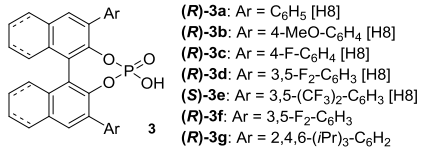
as phenanthridine (PD) has been successfully reported.[12,13] Hence, we envisaged chiral tetrahydroquinolines could be obtained by one-pot cascade reaction from readily available 2-aminochalcones using the PD instead of HEH in the catalytic amount (Scheme 1). It was noted that there might be many challenges in this reaction. Firstly, the major challenge was compatibility between two catalytic systems for regeneration and transfer hydrogenation. Secondly, how to control the enantioselectivity and the background reaction also should be solved.

Results and Discussion

At the outset, we chose easily available 2-aminochalcone (**1a**) as model substrate for this one-pot reaction. The results of condition optimization were summarized in Table 1. This reaction was initially studied by employing different chiral phosphoric acids in the toluene (Table 1, entries 1—7). It was found that the substrate **1a** could be completely converted into quinoline and tetrahydroquinoline. Among these tested chiral phosphoric acids, phosphoric acid (***R***)-**3d** proved best, 73% yield and 84% ee were observed (entry 4). Next, we turned our attention to the solvent effect. Pleasingly, this reaction proceeded smoothly in the different aromatic solvents, the substrate could be completely consumed (entries 4, 8, and 9). Considering the enantioselectivity, mesitylene was the best choice. A series of other solvents such as DCM, EtOAc and THF were proved to be ineffective, and lower enantioselectivities were obtained (entries 10—12). Subsequently, considering the fact that different molecular sieves might have an effect on the yield and enantioselectivity, the other molecular sieves were evaluated. The desired product was observed in 65% yield and 88% ee value by utilizing 5 Å molecular sieves (entry 13). When the one-pot reaction was performed in the presence of 5 Å molecular sieves, the metal catalyst loading was also tested. Fortunately, the increase of metal catalyst loading could significantly improve the yield. This reaction provided the best result with 91% yield and 87% ee value at 4.0 mol% metal catalyst (entry 14). To our delight, prolonging time of the reaction could get excellent yield and slightly higher 88% ee value (entry 15). Furthermore, when the temperature was lowered to 30 °C, the ee value of **2a** could be further improved to 90% with slightly low 86% yield (entry 16). Therefore, considering the enantioselectivity and yield, the optimal reaction temperature was 40 °C.

Table 1 Optimization of reaction parameters[a]





(***R***)-**3a**: Ar = C_6H_5 [H8]
(***R***)-**3b**: Ar = 4-MeO-C_6H_4 [H8]
(***R***)-**3c**: Ar = 4-F-C_6H_4 [H8]
(***R***)-**3d**: Ar = 3,5-F_2-C_6H_3 [H8]
(***S***)-**3e**: Ar = 3,5-$(CF_3)_2$-C_6H_3 [H8]
(***R***)-**3f**: Ar = 3,5-F_2-C_6H_3
(***R***)-**3g**: Ar = 2,4,6-(*i*Pr)$_3$-C_6H_2

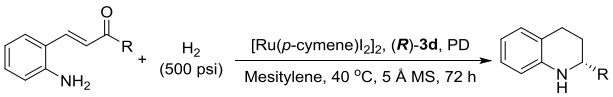
entry	CPA	solvent	conv.[b]/%	ee **2a**[c]/%	yield **2a**[d]/%
1	(***R***)-**3a**	Toluene	>95	74	49
2	(***R***)-**3b**	Toluene	>95	74	40
3	(***R***)-**3c**	Toluene	>95	82	63
4	(***R***)-**3d**	Toluene	>95	84	73
5	(***S***)-**3e**	Toluene	>95	48	43
6	(***R***)-**3f**	Toluene	>95	70	31
7	(***R***)-**3g**	Toluene	>95	62	66
8	(***R***)-**3d**	*p*-Xylene	>95	85	60
9	(***R***)-**3d**	Mesitylene	>95	86	57
10	(***R***)-**3d**	DCM	73	73	52
11	(***R***)-**3d**	EtOAc	84	76	80
12	(***R***)-**3d**	THF	46	57	39
13[e]	(***R***)-**3d**	Mesitylene	>95	88	65
14[f]	(***R***)-**3d**	Mesitylene	>95	87	91
15[g]	(***R***)-**3d**	Mesitylene	>95	88	93
16[h]	(***R***)-**3d**	Mesitylene	>95	90	86

[a] Reaction conditions: **1a** (0.10 mmol), [Ru(*p*-cymene)I_2]$_2$ (0.5 mol%), PD (20 mol%), solvent (2.0 mL), H_2 (500 psi), CPA (10 mol%), 4 Å MS (30 mg), 40 °C, 42 h. [b] Measured by analysis of ^{1}H NMR. [c] Determined by chiral HPLC. [d] Measured by analysis of ^{1}H NMR. [e] 5 Å MS (30 mg). [f] 5 Å MS (30 mg), [Ru(*p*-cymene)I_2]$_2$ (4.0 mol%). [g] 5 Å MS (30 mg), [Ru(*p*-cymene)I_2]$_2$ (4.0 mol%), 72 h. [h] 5 Å MS (30 mg), [Ru(*p*-cymene)I_2]$_2$ (4.0 mol%), 30 °C, 72 h.

With the optimized conditions in hand, a variety of substrates were investigated (Table 2). When introducing the methyl group to the *para*-position of the phenyl ring, the reaction gave the desired product in good yield and high enantioselectivity (**2b**). The enantioselectivities slightly decreased when the methyl group was at the *ortho*-position or *meta*-position (**2c**—**2d**). Different groups at the *para*-position all could furnish products in good yields and moderate enantioselectivities (**2e**—**2f**). When the substrates with more electron-donating groups such as methoxyl participate in this reaction, satisfied result with high yields and up to 90% ee value could be obtained (**2g**—**2h**). Disubstituted substrates could also proceed smoothly under the optimal conditions (**2i**—**2j**). A range of halogen substituted substrates were also well-tolerated to produce the corresponding chiral products, respectively, in moderate yields and excellent enantioselectivities (**2k**—**2m**). Notably, naphthyl substituted substrate proceeded smoothly to afford the desired products in 96% yield and 90% ee value (**2o**). In addition, the substrates bearing furanyl and alkyl groups were well compatible in this system, and the desired products were obtained in good yields (**2p**—**2q**).

Next, we explored the substrate scope of different substituents on the benzo ring (Scheme 2). Various substrates, such as methoxyl group and halogen group, all performed very well under the optimized conditions, the products were obtained in good yields and enantioselectivities (**2r**—**2u**). In addition, the positions

Table 2 Substrate scope[a]

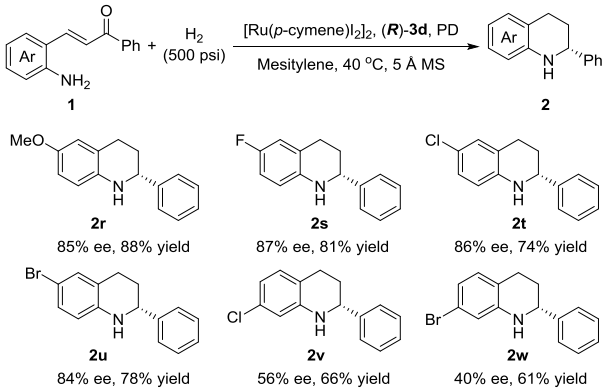


entry	R	ee[b]/%	yield[c]/%
1	Ph	87	91 (**2a**)
2	4-MeC_6H_4	91	94 (**2b**)
3	3-MeC_6H_4	87	96 (**2c**)
4	2-MeC_6H_4	78	92 (**2d**)
5	4-CyC_6H_4	86	89 (**2e**)
6	4-*t*-BuC_6H_4	80	96 (**2f**)
7	4-MeOC_6H_4	90	92 (**2g**)
8	3-MeOC_6H_4	85	92 (**2h**)
9	3,4-$Me_2C_6H_3$	87	95 (**2i**)
10	3,5-$(MeO)_2C_6H_3$	84	82 (**2j**)
11	4-FC_6H_4	89	86 (**2k**)
12	4-ClC_6H_4	92	86 (**2l**)
13	4-BrC_6H_4	91	83 (**2m**)
14	3-ClC_6H_4	86	88 (**2n**)
15	2-Naphthyl	90	96 (**2o**)
16	2-Furanyl	83	93 (**2p**)
17	Methyl	36	85 (**2q**)

[a] Conditions: **1** (0.20 mmol), [Ru(*p*-cymene)I_2]$_2$ (4.0 mol%), PD (20 mol%), mesitylene (3.0 mL), H_2 (500 psi), (***R***)-**3d** (10 mol%), 5 Å MS (30 mg), 40 °C, 72 h. [b] Determined by chiral HPLC. [c] Isolated yields.

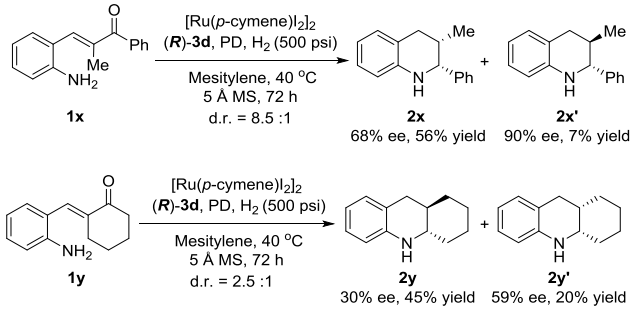
of the substituent show obvious influence on the yields and enantioselectivities (**2v**—**2w**). For example, when the chloro group was at the 7-position, the ee value obviously decreased to the 56%, compared with the result of the chloro group at the 6-position (86% ee). To further demonstrate the versatility of our method, 2,3-disubstituted tetrahydroquinolines were also obtained under the standard reaction conditions (Scheme 3).

Scheme 2 Substrate scope[a]



[a] Conditions: **1** (0.20 mmol), $[Ru(p\text{-cymene})I_2]_2$ (4.0 mol%), PD (20 mol%), mesitylene (3.0 mL), H_2 (500 psi), (***R***)-**3d** (10 mol%), 5 Å MS (30 mg), 40 °C, 72—96 h.

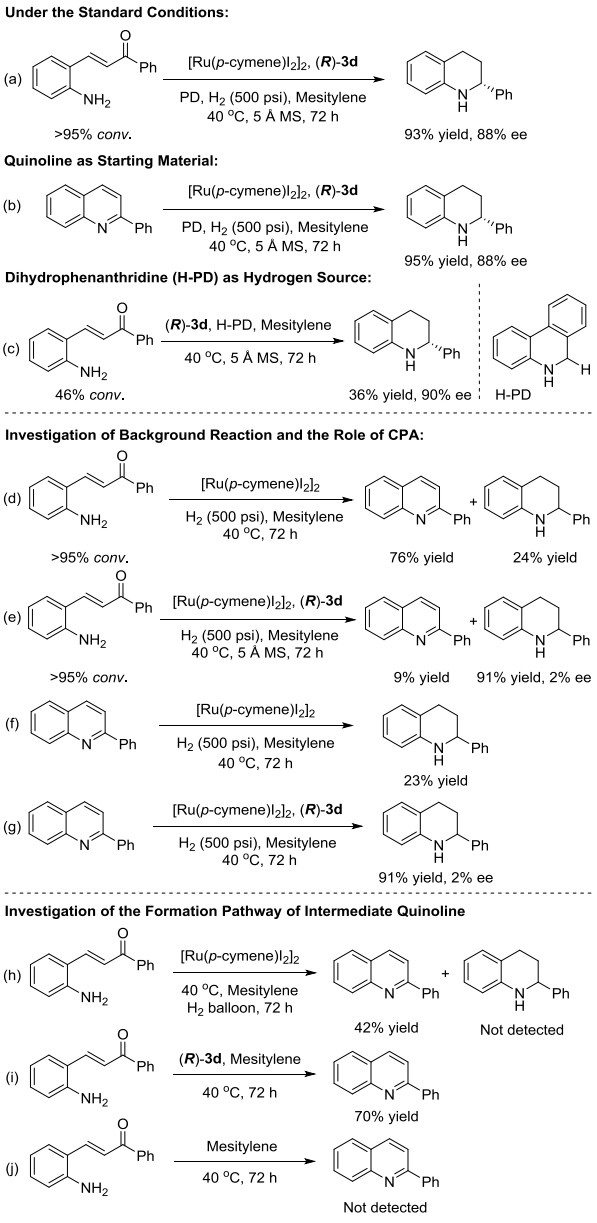
Scheme 3 Enantioselective synthesis of 2,3-disubstituted tetrahydroquinolines[a]



[a] Conditions: **1** (0.20 mmol), $[Ru(p\text{-cymene})I_2]_2$ (4.0 mol%), PD (20 mol%), mesitylene (3.0 mL), H_2 (500 psi), (***R***)-**3d** (10 mol%), 5 Å MS (30 mg), 40 °C, 72 h.

To clarify the detailed reaction mechanism, several control experiments were carried out, as shown in Scheme 4. First, 2-aminochalcone was conducted under the standard conditions, affording chiral product in 93% yield and 88% ee (Scheme 4a). When 2-aminochalcone is replaced with quinoline, this reaction could give the similar yield and enantioselectivity (Scheme 4b). The comparison of result reflects that quinoline was the reaction intermediate. In addition, quinoline could be isolated, which further confirms this conclusion. When 2-aminochalcone was served as substrate and dihydrophenanthridine (H-PD) was used as hydrogen source, the reaction furnished the target product in 36% yield and 90% ee (Scheme 4c). Compared with previous 88% ee value, this result reveals that this system might have background reaction. Subsequently, the background reaction was investigated. These results demonstrate that there is obvious background reaction in this system. When chiral phosphoric acid was added to the reaction, it was noted that the background reaction was more serious, delivering tetrahydroquinoline in 91% yield (Schemes 4d—4g). In addition, quinoline could be hydrogenated using ruthenium and hydrogen gas (Schemes 4f and 4g). Using 2-aminochalcone as substrate and hydrogen balloon instead of high

Scheme 4 The control experiments



pressure, only quinoline product was obtained (Scheme 4h). It should be concluded that the carbon-carbon double bond could be hydrogenated from analysis of the two reactions (Schemes 4d and 4h). Besides, chiral phosphoric acid also promotes the formation of quinoline (Scheme 4i). In the sole solvent of mesitylene, the product quinoline cannot be generated (Scheme 4j).

According to above experimental results and previous related studies, a plausible reaction mechanism is proposed (Figure 2). First, 2-aminochalcone exists in the stable (*E*)-configuration under the normal conditions, then the amino group cannot approach the carbonyl group for the next condensation reaction. There are two paths to form quinoline intermediate. On the one hand, chiral phosphoric acids could promote conversion of the stable but unreactive (*E*)-configuration into the unstable but reactive (*Z*)-configuration. The detailed process includes: protonation of the carbonyl group, and then the formation of iminium ion with electron transfer. Next, the carbon-carbon bond could rotate quickly.[14] Subsequently, isomerization, dehydration and cyclization proceed smoothly, providing the aromatic quinolines. On the other hand, the carbon-carbon double bond could be hydrogenated using

ruthenium and hydrogen gas. Hence, the carbon-carbon bond could rotate quickly. The amino group could approach the carbonyl group for the next dehydration and dehydrogenation. Besides, PD could be reduced *in situ* by ruthenium complex and hydrogen gas. The reduced PD could accomplish biomimetic asymmetric reduction of quinoline intermediates in the presence of chiral phosphoric acids. Meanwhile, the PD was regenerated with ruthenium metal and hydrogen gas for the next catalytic cycle.

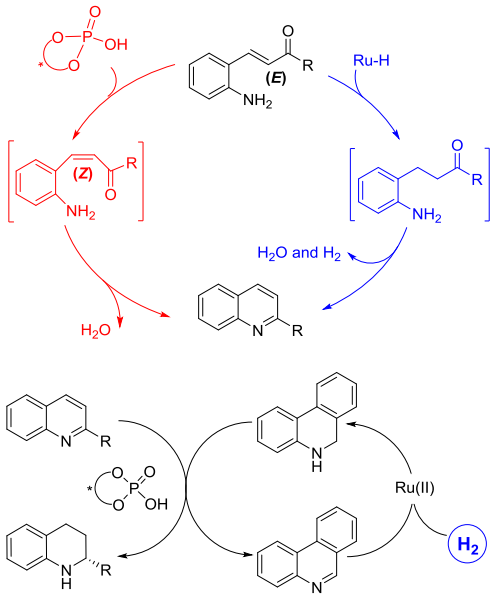


Figure 2 Plausible reaction mechanism.

Conclusions

In summary, we have developed a facile synthesis of chiral tetrahydroquinolines with high yields and enantioselectivities *via* one-pot cascade biomimetic reduction. This efficient method employs easily available starting materials 2-aminochalcones served as substrates and catalytic amount of phenanthridine as regenerable NAD(P)H model. Furthermore, the reaction process and mechanism are clearly explained. The mechanistic studies suggest two separate pathways for formation of intermediate quinoline from the stable (*E*)-configuration of 2-aminochalcone. Further researches of other one-pot biomimetic reactions are under investigation by our group, and will be reported in due course.

Experimental

General procedure for synthesis of tetrahydroquinolines: A mixture of $[Ru(p\text{-cymene})I_2]_2$ (7.8 mg, 0.008 mmol, 4.0 mol%), chiral phosphoric acid (***R***)-**3d** (11.6 mg, 0.02 mmol, 10 mol%), phenanthridine (7.2 mg, 0.04 mmol, 20 mol %), 5 Å molecular sieves (30 mg) and substrates **1** (0.20 mmol) in mesitylene (3.0 mL) was stirred at room temperature for 5 min in glove box, and then the reaction mixture was transferred to an autoclave. The hydrogenation was performed at 40 °C (oil bath temperature) under hydrogen gas (500 psi) for 72—96 h. After careful release of the hydrogen gas, the autoclave was opened and the reaction mixture was directly purified by column chromatography on silica gel using hexanes and ethyl acetate as eluent to give the desirable chiral products **2**. The enantiomeric excesses were determined by chiral HPLC.

The full experimental details can be found in the Supporting Information.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202000409.

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