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Visible-Light Induction/Brønsted Acid Catalysis in Relay for the Enantioselective Synthesis of Tetrahydroquinolines

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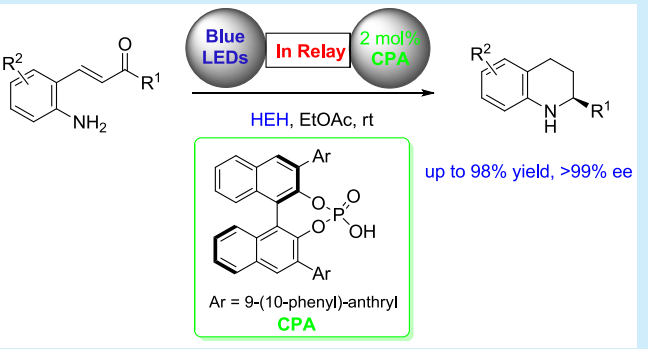
Supporting Information

ABSTRACT: An efficient method merging Brønsted acid catalysis with visible-light induction for the highly enantioselective synthesis of tetrahydroquinolines has been developed. This mild process directly transforms 2-aminoenones into 2-substituted tetrahydroquinolines with excellent enantioselectivities through a relay visible-light-induced cyclization/chiral phosphoric acid-catalyzed transfer hydrogenation reaction.

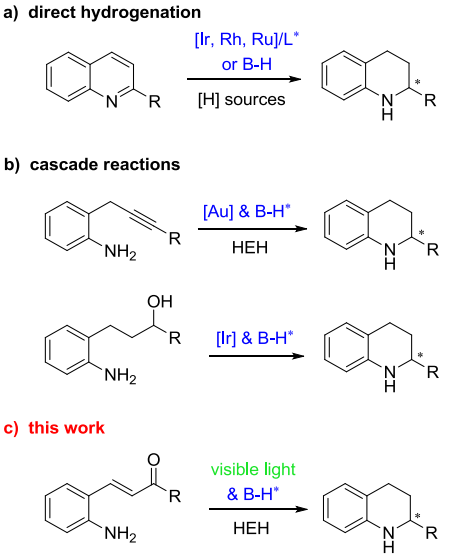


Visible-light photocatalysis has emerged as a powerful synthetic tool in modern organic chemistry.[1] Merging visible-light photochemistry with asymmetric catalysis for efficient assembly of chiral molecules is an intriguing and challenging field, and many successful catalytic systems have been developed in the past decade.[2] Among them, combining achiral photosensitizers and chiral organocatalysts in cooperative or relay catalysis has been widely regarded as an attractive and efficient strategy. However, the majority of these binary catalytic systems rely on chiral amines as organocatalysts for the effective control of stereoselectivity.[3] In contrast, catalytic systems with other types of chiral organocatalysts (e.g., carbenes, thiourea, Brønsted acids) for asymmetric visible-light photocatalysis have remained underdeveloped.[4]

Tetrahydroquinoline is an important structural unit frequently found in many chiral pharmaceutical molecules and natural alkaloids that exhibit diverse biological activities.[5] Given their significance, chiral tetrahydroquinolines have become an attractive synthetic target, and numerous catalytic asymmetric methods have been established, especially for 2-substituted ones.[6] Among them, direct asymmetric hydrogenation of quinolines offers the most straightforward and convenient access to chiral tetrahydroquinoline derivatives and has been well-explored by the development of various catalytic systems (Scheme 1a).[7] In addition, catalytic cascade reactions with readily prepared simple starting materials have been developed (Scheme 1b).[8] For example, Gong and co-workers[8a] reported an efficient tandem hydroamination/asymmetric transfer hydrogenation reaction catalyzed by gold complex/chiral phosphoric acid, transforming 2-(2-propynyl)aniline derivatives into tetrahydroquinolines with excellent enantioselectivities. Zhao's group[8c] employed amino alcohols as substrates and disclosed a highly enantioselective process through borrowing hydrogen under the cooperative catalysis of an achiral iridacycle and a chiral phosphoric acid. We envisaged that the combination of visible-light induction and chiral phosphoric acid catalysis may provide an efficient catalytic system that could convert 2-aminochalcones[9] into 2-substituted tetrahydroquinolines through a relay photocyclization/asymmetric transfer hydrogenation reaction (Scheme 1c).

We started to test our hypothesis with 2-aminochalcone (**1a**) as the model substrate and Hantzsch ester (HEH) as the

Scheme 1. Catalytic Enantioselective Synthesis of Tetrahydroquinolines



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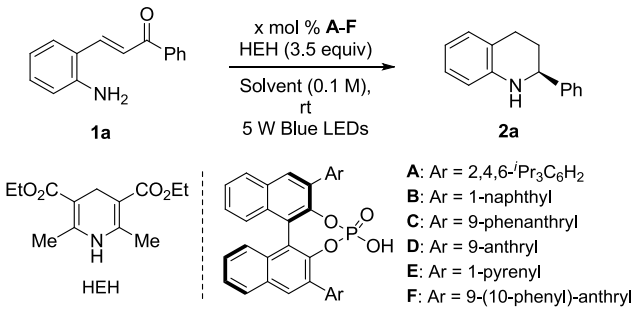
hydrogen source (Table 1). After trials, we found that the combination of light from blue LEDs and chiral phosphoric acids could enable this transformation.[10] In the presence of the representative chiral phosphoric acid **A** (TRIP) and 5 W blue LEDs, the cascade reaction proceeded cleanly in dichloromethane at room temperature to afford the desired tetrahydroquinoline **2a** with high efficiency and enantioselectivity (entry 1). It is noteworthy that the reaction is metal-free and requires no sensitizer. As far as we know, the majority of catalytic systems for the synthesis of tetrahydroquinolines involve metals, and removal of trace metals is usually a costly and tedious process, especially in the pharmaceutical industry. Subsequently, a series of chiral phosphoric acids **B**–**F** with different substituents were screened, and catalyst **F** was the best one, providing excellent enantioselectivity (entries 2–6). Excellent enantioselectivity was maintained with 2 mol % **F**, but further reducing the loading to 1 mol % decreased the enantioselectivity and yield (entries 7 and 8). Variation of the solvent had a limited impact on the outcome (entries 9–13). Ethyl acetate was the solvent of choice, and other common solvents all resulted in slightly diminished enantioselectivities. Further study of the loading of HEH and the reaction concentration identified the optimal conditions (3.0 equiv of HEH and 0.2 M concentration) with excellent efficiency and enantioselectivity (entries 14 and 15).

Having established the standard reaction conditions, we next examined the substrate scope of the cascade reaction (Table 2). A range of 2-aminochalcones with different electron-donating and -withdrawing groups reacted smoothly to afford the corresponding tetrahydroquinolines (**2b**, **2c**, **2e**–**l**, and **2s**–**v**) with high to excellent yields and enantioselectivities (90–99% ee) (entries 2, 3, 5–12, and 19–22). The electronic property of groups on the aromatic ring had a limited effect on the outcome, while the steric hindrance of the R^1 group greatly affected the efficiency. 2-Aminochalcone **1d** bearing a 2-methyl group displayed much lower reactivity, and just a moderate yield was achieved in a prolonged time (entry 4). 2-Aminochalcones with 1-/2-naphthyl groups worked with high efficiency, but the former gave lower enantioselectivity (87% ee) (entries 13 and 14). 2-Aminoenones with heteroaromatic and aliphatic groups were viable substrates, providing the desired tetrahydroquinolines **2o**–**r** in comparable yields but with diminished enantioselectivities (81–89% ee) (entries 15–18). The synthesis of 2,3-disubstituted tetrahydroquinolines was also realized using the catalytic method (Scheme 2). The 2,3-disubstituted tetrahydroquinoline **2w** was obtained in high yield with excellent diastereoslectivity, and **2x** was obtained in high yield but 78% ee. As shown in Scheme 3, a gram-scale catalytic reaction was performed well with almost no erosion in the yield (90%) and enantioselectivity (99% ee).

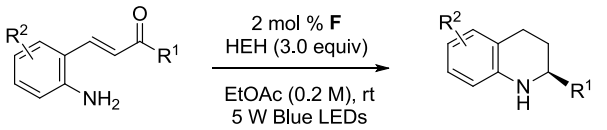
Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	x	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	**A**	5	DCM	12	>95	90
2	**B**	5	DCM	12	>95	53
3	**C**	5	DCM	12	>95	88
4	**D**	5	DCM	12	>95	78
5	**E**	5	DCM	12	>95	70
6	**F**	5	DCM	12	>95	97
7	**F**	2	DCM	24	95	98
8	**F**	1	DCM	36	80	90
9	**F**	2	DCE	24	>95	91
10	**F**	2	toluene	24	95	93
11	**F**	2	THF	24	>95	95
12	**F**	2	MeCN	24	95	93
13	**F**	2	EtOAc	24	>95	99
14[d]	**F**	2	EtOAc	48	95	>99
15[d,e]	**F**	2	EtOAc	36	>95	>99

[a]Reactions were performed with **1a** (0.10 mmol), Hantzsch ester (0.35 mmol), and the catalyst in the solvent (1.0 mL), irradiated with 5 W blue LEDs. [b]Determined by ^{1}H NMR analysis, with 100% conversion for all reactions. [c]Determined by HPLC analysis. [d]Run with 0.30 mmol of Hantzsch ester. [e]0.2 M concentration.

Table 2. Scope of the Enantioselective Synthesis of Tetrahydroquinolines[a]



entry	R^1/R^2 (in **2**)	time (h)	product	yield (%)[b]	ee (%)[c]
1	Ph/H	36	**2a**	93	>99
2	4-MeC_6H_4/H	36	**2b**	92	99
3	3-MeC_6H_4/H	15	**2c**	87	97
4	2-MeC_6H_4/H	120	**2d**	51	95
5	4-MeOC_6H_4/H	36	**2e**	89	99
6	3-MeOC_6H_4/H	12	**2f**	90	98
7	4-PhC_6H_4/H	18	**2g**	98	>99
8	4-FC_6H_4/H	18	**2h**	90	>99
9	4-ClC_6H_4/H	18	**2i**	90	>99
10	4-BrC_6H_4/H	40	**2j**	91	98
11	3-BrC_6H_4/H	12	**2k**	92	99
12	4-$CF_3C_6H_4$/H	40	**2l**	80	99
13	1-naphthyl/H	24	**2m**	96	87
14	2-naphthyl/H	18	**2n**	90	98
15	2-thienyl/H	48	**2o**	86	83
16	2-furyl/H	12	**2p**	91	84
17[d]	Me/H	36	**2q**	84	81
18[d,e]	$C_6H_5(CH_2)_2$/H	36	**2r**	86	89
19[f]	Ph/6′-Cl	60	**2s**	87	98
20[f]	Ph/6′-Br	48	**2t**	84	98
21[f]	Ph/7′-Br	22	**2u**	95	93
22[f]	Ph/7′-Ph	22	**2v**	96	90

[a]Reactions were performed with **1** (0.20 mmol), Hantzsch ester (0.60 mmol), and 2 mol % **F** in EtOAc (1.0 mL), irradiated with 5 W blue LEDs. [b]Yields of the isolated products. [c]Determined by HPLC analysis. [d]Run in two steps. [e]Run with 2 mol % catalyst **A**. [f]Run in DCM.

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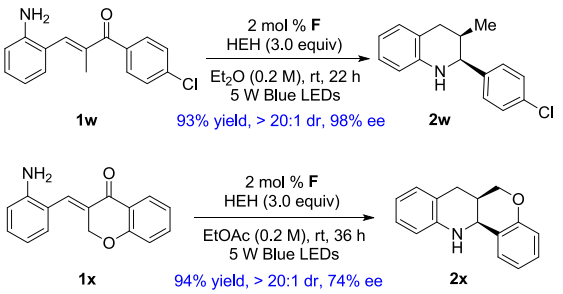
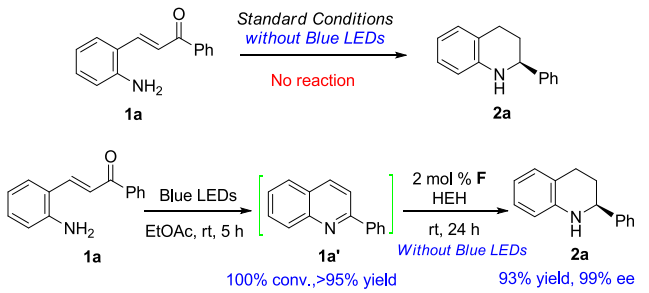
Scheme 2. Catalytic Enantioselective Synthesis of 2,3-Disubstituted Tetrahydroquinolines



Scheme 3. Gram-Scale Preparation

To understand the reaction mechanism, we carried out two simple control experiments (Scheme 4). Under otherwise

Scheme 4. Control Experiments



identical conditions, no reaction was observed without blue light. When 2-aminochalcone **1a** was subjected to a two-step one-pot procedure, almost the same result was obtained. In the first step, **1a** was efficiently converted into 2-phenylquinoline (**1a′**) with blue LEDs via visible-light-induced *E*/*Z* isomerization of chalcone. In the second step, **1a′** was transformed into the corresponding tetrahydroquinoline **2a** in the presence of catalyst **F** and Hantzsch ester. The above results indicated that the reaction proceeded via a relay catalytic process consisting of a visible-light-mediated intramolecular cyclization and a Brønsted acid-catalyzed asymmetric transfer hydrogenation. On basis of the configuration of **2a** and the observed results, a generally accepted reaction mechanism and a key transition state model were proposed (see the Supporting Information).

In summary, we have disclosed an efficient method for the direct transformation of 2-aminoenones into 2-substituted tetrahydroquinolines through a relay visible-light-mediated cyclization/Brønsted acid-catalyzed asymmetric transfer hydrogenation reaction. This protocol features metal-free catalysis, mild reaction conditions, and excellent efficiency and stereocontrol. It is a new and rare example of merging asymmetric Brønsted acid catalysis with visible-light chemistry. Further study of visible-light-mediated asymmetric organocatalysis is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01354.

Experimental details, copies of ^{1}H and ^{13}C spectra of new compounds, and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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