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Graphical Abstract

Cyclopentadiene-based Brønsted acid as a new generation of organocatalyst for transfer hydrogenation of 2-substituted quinoline derivatives

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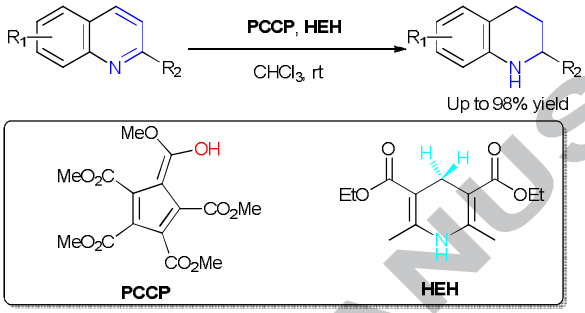

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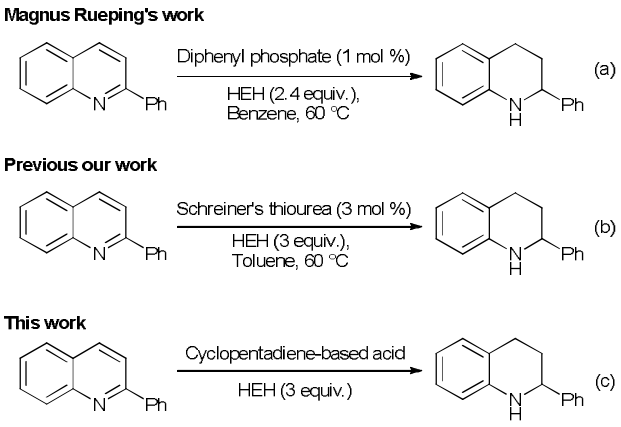
ABSTRACT

A simple and readily available cyclopentadiene-based Brønsted acid was employed to catalyze the transfer hydrogenation of 2-substituted quinolines using Hantzsch ester as the hydrogen source. This conceptually new designed organocatalyst demonstrates remarkably high efficiency for this transformation and a variety of substituted 1,2,3,4-tetrahydroquinoline derivatives were afforded in excellent yields under mild reaction conditions.

1,2,3,4-Tetrahydroquinoline-based frameworks are widely existed in biologically active natural products and pharmaceutics.[1] The regioselective reduction of quinoline derivatives for the synthesis of tetrahydroquinolines represents one of the most prevalent approaches, upon which a number of transition metal catalysts have been developed for this transformation in conjunction with hydrogen as the reducing agent.[2] Although most of these transition metals catalyzed processes showed high reactivity and selectivity, it is not free of problems, such as pollution and toxicity of transition metals as well as risk in handling high pressure of hydrogen gas. With increased consciousness of the environmental impact on current chemical processes, the development of sustainable synthetic methodologies has attracted much interest.[3] In this regard, nature has been regarded to be an uncompetitive master in mediating diverse redox transformations in biological systems with enzyme and organic hydride reduction cofactors, such as nicotinamide adenine dinucleotide (NAD(P)H) and flavin adenine dinucleotide ($FADH_2$).[4] Inspired by the mode of action that nature performs reductions, chemists have developed a plethora of biomimetic protocols for the reduction of quinolines employing Hantzsch ester (HEH) as NADH analogue in the presence of catalytic amount of organic molecules.[5]

Rueping and co-workers were among the first to report that Brønsted acids catalyze transfer hydrogenation of quinolines using diphenyl phosphate as the catalyst and Hantzsch ester as the hydrogen source (eq. a of Scheme 1).[6]



Scheme 1. Organocatalytic transfer hydrogenation of quinolines with Hantzsch ester.

Later on, this strategy was extended to the asymmetric transfer hydrogenation of quinolines catalyzed with chiral BINOL based (BINOL = [1,1'-binaphthalene]-2,2'-diol) phosphoric acids.[7] In continuation of our interest in the development of non-covalent organocatalytic transformations, we reported an example of transfer hydrogenation of quinolines promoted by an electron-

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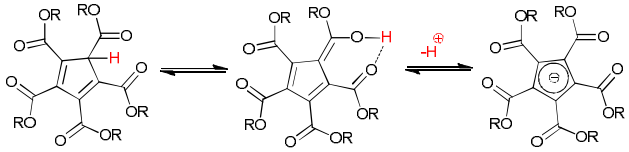
poor H-bond donor catalyst, i.e., *N*,*N*'-Bis[3,5-bis(trifluoromethyl)phenyl]thiourea (Schreiner's thiourea) via hydrogen bonding activation with Hantzsch ester as the hydrogen source (eq. b of Scheme 1).[8]



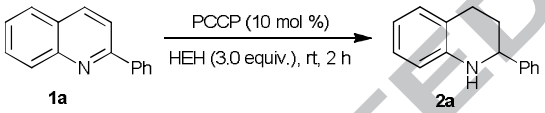
Scheme 2. Lambert's catalyst design.

Recently, a fundamentally new strategy on the design of Brønsted acid catalyst has been introduced by Lambert and co-workers.[9] The new catalyst class is based on 1,2,3,4,5-pentacarboxycyclopentadiene (PCCP), which preferably exists in the enol form and its deprotonation leads to the stable aromatic cyclopentadienyl anion and comparable acidity to mineral acids (Scheme 2). Further modification of the structure with chiral alcohols and amines give rise to a new type of chiral acid catalyst, which demonstrated high reactivity and selectivity for the enantioselective Mukaiyama-Mannich reaction.

In line with previous work and our observations, we reasoned that this new generation of Brønsted acid would also serve as an efficient organocatalyst for transfer hydrogenation of quinolines through activation of the substrate by protonation and subsequent hydride transfer from Hantzsch ester (eq. c of Scheme 1). This present work would not only be the first example of cyclopentadiene-based Brønsted acid catalyzed transfer hydrogenations, but also provide some preliminary guidance for the utilization of its chiral derivatives in asymmetric catalysis.

Table 1

Influence of the solvent on the PCCP catalyzed transfer hydrogenation of 2-phenylquinoline.



Entry[a]	Solvent	Yield[b] (%)
1	MeOH	33
2	EtOAc	86
3	DMF	48
4	THF	75
5	MeCN	73
6	$CHCl_3$	96
7	CH_2Cl_2	92
8	PhMe	90

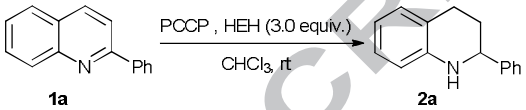
[a] All reactions were performed using 2-phenylquinoline **1a** (0.1 mmol) and HEH (3.0 equiv.) in 2 mL of solvent with PCCP (10 mol%) at room temperature for 2 h.

[b] Yield of isolated product after column chromatography.

We initiated our investigation by the synthesis of 1,2,3,4,5-pentacarboxycyclopentadiene (PCCP) according to the procedure reported.[10] Our initial study concentrated on solvent employed using 2-phenyquinoline as a model substrate. In the presence of 10 mol % of PCCP and 3 equiv. of HEH, we found that the reaction could proceed in all solvents tested at room temperature, but giving 1,2,3,4-tetrahydroquinoline in different yields at the same time interval (2 h) (Table 1). The reaction performed in nonpolar solvents such as chloroform, dichloromethane, and toluene shows superior rate and isolated yields (Table 1, entries 6–8), and chloroform appeared to be the best solvent for this transformation. The reaction in ethyl acetate, in agreement with Mukaiyama-Mannich reaction, also gives the product in high yield (Table 1, entry 2). Performing the reaction in other polar solvents results in inferior reactivity, probably due to the effect of competitive intermolecular hydrogen bonding interaction between polar solvents and PCCP (Table 1, entries 1, 3–5).

Table 2

Assessment of catalyst loading in PCCP-catalyzed transfer hydrogenation of 2-phenylquinoline.



Entry[a]	PCCP (mol %)	t (h)	Yield[b] (%)
1	5	2	96
2	4	2	96
3	3	2	96
4	2	2	97
5	1	2	97
6	0.1	24	trace
7[c]	0.1	48	92
8	0.01	24	trace
9[c]	0.01	63	86
10	0.001	24	trace
11[c]	0.001	74	77
12[c]	0	48	0

[a] All reactions were performed using 2-phenylquinoline (0.1 mmol) and HEH (3.0 equiv.) in 2 mL of $CHCl_3$ at room temperature.

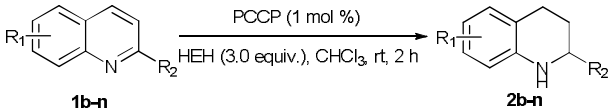
[b] Yield of isolated product after column chromatography.

[c] The reaction was performed at 60 °C.

Having established chloroform as the best solvent for transfer hydrogenation of 2-phenylquinoline **1a**, we next examined the catalyst loading (Table 2). Starting from 5 mol % of PCCP, the catalyst loading can be reduced to 1 mol % without obvious compromise of reactivity (Table 2, entry 5). When the catalyst loading was continued to decrease to the range of 0.1–0.001 mol %, only trace amount of product was obtained. However, after heating the reaction to 60 °C, the corresponding product **2a** can be isolated in good to excellent yield even with 0.001 mol % of catalyst loading (Table 2, entries 6–11). No reaction takes place without PCCP catalyst (Table 2, entry 12), indicating the crucial role of PCCP in promoting this transformation. For comparison, a control experiment with diphenyl phosphate (1 mol%) was also performed under identical reaction conditions, giving the product in 61% yield, which suggests that PCCP is somewhat superior over diphenyl phosphate for this title transformation.

Table 3

Substrate scope of the PCCP catalyzed transfer hydrogenation of 2-substituted quinolines.

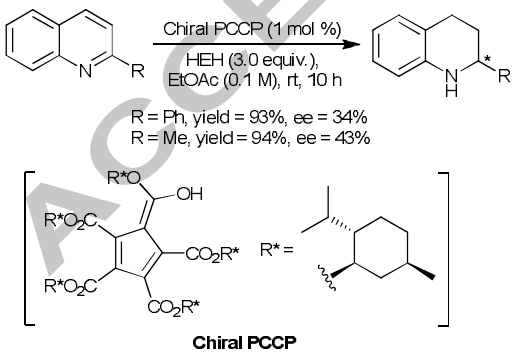


Entry[a]	R_1	R_2	Yield[b] (%)
1	H	4-Methylphenyl	77
2	H	2,4-Dimethylphenyl	92
3	H	4-Isopropylphenyl	97
4	H	4-Methoxyphenyl	93
5	H	1,1'-Biphenyl-4-yl	96
6	H	2-Fluorophenyl	84
7	H	4-Chlorophenyl	87
8	H	4-Bromophenyl	89
9	H	*n*-Butyl	96
10	H	Methyl	91
11	5-Me	Methyl	89
12	6-F	Methyl	98
13	6-Cl	Methyl	94

[a] All reactions were performed using quinolines (0.1 mmol), HEH (3.0 equiv.) and PCCP (1 mol %) in 2 mL of $CHCl_3$ at room temperature.

[b] Yield of isolated product after column chromatography.

With the optimized conditions in hand we explored the scope of PCCP catalyzed transfer hydrogenation of 2-substituted quinolines (Table 3). In general, differently 2-substituted quinolines bearing either with electron-donating or electron-withdrawing groups are compatible with this protocol, giving respective product in good to excellent yields (Table 3, entries 1–8). Notably, quinolines with aliphatic substituents such as 2-*n*-butyl and 2-methyl could also be reduced to afford the product in excellent yields (Table 3, entries 9–10). In addition, 5- and 6-substituted quinolines were also successfully reduced with this protocol (Table 3, entries 11–13).



Scheme 3. Asymmetric transfer hydrogenation of quinolines with chiral PCCP.

After identifying PCCP as a valuable alternative to the established Brønsted acids for transfer hydrogenation of 2-substituted quinolines, we decided to develop an asymmetric variant of this reaction utilizing its chiral derivative pentakis((*1R,2S,5R*)-2-isopropyl-5-methylcyclo hexyl) cyclo penta-1,3-diene-1,2,3,4,5-pentacarboxylate as the catalyst. In the presence of 1 mol% of chiral PCCP, 2-phenylquinoline and 2-methylquinoline furnished the corresponding product with 34% and 43% *ee*, respectively (Scheme 3). Further optimization of reaction parameters such as solvent, temperature, and concentrations did not show beneficial effect in the improvement of enantioselectivities.

Conclusions

In summary, we have successfully developed a highly efficient cyclopentadiene-based Brønsted acid catalyzed transfer hydrogenation of various 2-substituted quinolines with Hantzsch ester as the hydrogen source. This novel and alternative Brønsted acid catalytic reduction requires low catalyst loading and tolerates both 2-alkyl and aryl-substituted quinolines, giving the corresponding product in high to excellent yields. Furthermore, we were able to extend this valuable methodology to enantioselective reduction of 2-substituted quinolines. It should be highlighted that this organocatalytic procedure was the first to expand the application scope of cyclopentadiene-based Brønsted acid catalyst after its advent. The mild reaction conditions as well as the relatively low catalyst loading render this protocol an attractive approach to the synthesis of 1,2,3,4-tetrahydroquinoline derivatives. Further investigation will be directed toward the design of more efficient cyclopentadiene-based chiral derivatives for enantioselective transfer hydrogenations.

Acknowledgments

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Supplementary Material

Supplementary material associated with this article can be found in...

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First expanding application of cyclopentadiene-based Brønsted acid catalyst

Attractive approach with mild reaction conditions and low catalyst loading

Enantioselective reduction of 2-substituted quinolines