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Cite this: DOI: 10.1039/c0xx00000x

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Communication

Thiourea as an efficient organocatalyst for the transfer hydrogenation of 2-substituted quinoline derivatives

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

This study reports on the first transfer hydrogenation of 2-substituted quinolines promoted by a thiourea catalyst with Hantzsch ester as the hydrogen source. A wide range of quinoline derivatives, including 2-alkylquinolines, 2-arylquinolines as well as 2-hetereoaryl quinolines were efficiently reduced to give 1,2,3,4-tetrahydroquinolines with good to excellent yields. The operational simplicities and conveniences of this reaction pathway render this protocol considerably promising in the preparation of biologically active tetrahydroquinoline derivatives.

2-Substituted-1,2,3,4-tetrahydroquinoline architectures are widely found in numerous biologically active natural products and pharmaceutical compounds.[1] For example (Fig. 1), this framework is universal in many natural occurring alkaloids, i.e. angustureine, galipinine, cuspareine, etc..[2] As far as chemotherapeutic potential is concerned, 2-substituted tetrahydropyridine derivatives have been also reported to possess a variety of biological activities such as antiarrhythmic (oxamniquine), high-density lipoprotein cholesterol-lowering (torcetrapib) and antibiotic (virantmycin) activities.[3]

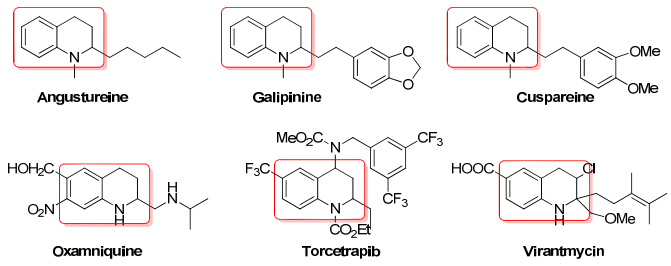


Fig. 1 Selected natural occurring and biologically active 1,2,3,4-tetrahydroquinoline derivatives

Direct hydrogenation of quinoline derivatives, which are easily prepared from readily available starting materials[4], represents a concise approach to tetrahydroquinoline compounds.[5] However, these methods are currently dominated by the use of precious metal catalysts in conjunction with molecular hydrogen, which are often carried out under relatively rigorous operation conditions, i.e. in air- and moisture-free as well as high-pressure resistant apparatus.[6] From the viewpoint of operational simplicity, the development of an easily manageable synthetic protocol is therefore highly desirable.

At the beginning of this century, the chemical transformations promoted by metal-free organic molecules started to shed light into the synthetic world and serve as an alternative method to metal- and biocatalysis.[7] In this context, transfer hydrogenation of unsaturated compounds such as imines, olefins as well as carbonyls catalyzed by organocatalysts in combination with organic hydride donors has resulted in new paradigm in the reduction of unsaturated compounds.[8] As one of the most widely used organic hydride donors, Hantzsch ester (HEH), since its advent[9], has been employed as a biomimetic mimics to NAD(P)H in a series of redox reactions.[10] Recently, Rueping and other research groups have developed a number of Brønsted acid-catalyzed transfer hydrogenation of quinolines with HEH as reducing agent.[11] Similar to well-developed Brønsted acid-based catalysts, thiourea derivatives have also been widely employed as efficient catalysts in a variety of chemical transformations.[12] As part of our ongoing research interests in the development of H-bond mediated transfer hydrogenation methods, we have reported the reduction of aldimines (Fig. 2, eq. 1) and nitroolefins (Fig. 2, eq. 2) in the presence of privileged thiourea catalyst **T1**[13] using HEH as the hydrogen source.[14] Inspired by these observations, we reasoned that the interaction of thiourea **T1** with the nitrogen atom contained in the quinoline through hydrogen bonding may dramatically reduce the barrier energy and consequently promote the tandem hydride transfer from HEH to the nitrogen-containing part of quinolines, thereby furnishing the tetrahydroquinolines (Figure 2, eq. 3). Herein, in continuation to our early work, we describe the first example of thiourea as H-bond catalyst for the transfer hydrogenation of quinolines using HEH as the corresponding reductant.

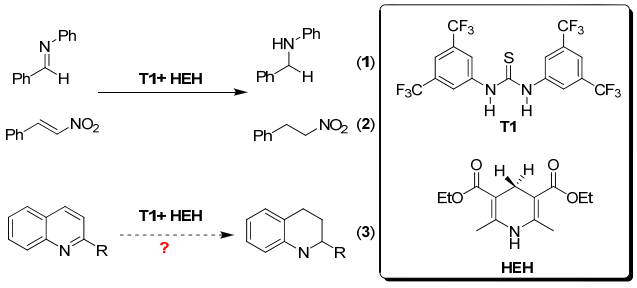
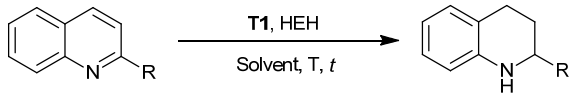


Fig. 2 T1-catalyzed transfer hydrogenations with HEH

Our initial study began with the investigation of the feasibility of our strategy. In the presence of 10 mol% of **T1** and 2.2 equiv. of

HEH, the transfer hydrogenation of 2-phenylquinoline was selected as the standard reaction for the optimization of reaction conditions. As shown in Table 1, only trace amount of product was observed when the reaction was performed at ambient temperature in CH_2Cl_2 (Table 1, entry 1). The reaction proceeded smoothly in toluene when the reaction temperature increased to 6o °C, giving the product in 70% conversion at 24 h (Table 1, entry 3). To our delight, the conversion can be further improved when increasing the amount of HEH to 3.0 equiv., whereby the slight excess of HEH is probably due to its partial oxidation at air. Note that the catalyst loading of **T1** can be reduced to 3 mol% without obvious compromise of the conversion (Table 1, entry 6). The polarities of the solvents also had a significant effect on the reaction outcome. When polar solvents such as EtOAc, MeCN, DMF, MeOH, THF were used (Table 1, entries 8–12), the conversion of this reaction decreased dramatically, which is in agreement with the deleterious effect of polar solvents to H-bond formation during the transition state. Apolar solvents generally suitable for this catalytic pathway, among others, toluene has been proved to be the best reaction media. Control experiments revealed that no reaction happened in the absence of **T1** catalyst (Table 1, entry 13).

Table 1 Optimization of the thiourea-catalyzed transfer hydrogenation



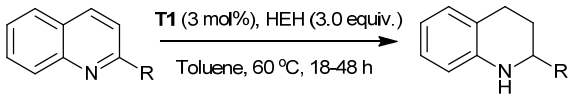
Entry[a]	**T1** (mol %)	HEH (equiv.)	Solvent	T (°C)	*t* (h)	Conversion (%)[b]
1	10	2.2	CH_2Cl_2	r.t.	72	trace
2	10	2.2	CH_2Cl_2	40	24	15
3	10	2.2	Toluene	60	24	70
4	10	3.0	Toluene	60	24	97
5	5	3.0	Toluene	60	24	97
6	3	3.0	Toluene	60	24	90
7	3	3.0	$CHCl_3$	60	24	75
8	3	3.0	EtOAc	60	24	48
9	3	3.0	MeCN	60	24	49
10	3	3.0	DMF	60	24	3
11	3	3.0	MeOH	60	24	23
12	3	3.0	THF	60	24	7
13	0	3.0	Toluene	60	24	0

[a] All reactions were performed using 2-phenylquinoline (0.20 mmol) and HEH in 1 ml of solvents in the presence of **T1** as the catalyst.

[b] Determined by GC analysis with tridecane as the internal standard.

Under the optimal reaction conditions, the substrate scope of this **T1**-catalyzed transfer hydrogenation of quinolines was examined. As shown in Table 2, various substituents on the phenyl ring of 2-substituted quinolines did not have much influence on the catalytic efficiency. Both electron-donating groups (Me, OMe, Ph etc.) (Table 2, entries 2–6) and the electron-withdrawing groups (F, Cl, Br) (Table 2, entries 7–9) are well applicable to this protocol, furnishing the corresponding tetrahydroquinolines in good to excellent yields. Moreover, it is worthy of noting that 2-alkyl substituted quinolines also proceed smoothly, affording the corresponding products with yield of 97% and 77% (Table 2, entries 10–11), respectively.

Table 2 Thiourea-catalyzed reduction of various quinolines



Entry[a]	R	Time (h)	Yield (%)[b]
1	phenyl	24	90
2	4-methylphenyl	18	95
3	2,4-dimethylphenyl	24	77
4	4-isopropylphenyl	24	79
5	4-methoxyphenyl	36	96
6	1,1'-biphenyl-4-yl	24	87
7	2-fluorophenyl	24	69
8	4-chlorophenyl	24	82
9	4-bromophenyl	48	90
10	n-butyl	36	97
11	isopropyl	36	77

[a] All reactions were performed using quinoline (0.20 mmol) and HEH (0.60 mmol) at 60 °C in 1 ml of toluene in the presence of 3 mol% of **T1**.

[b] Isolated yield after chromatography.

Conclusions

In summary, we have developed a thiourea-catalyzed transfer hydrogenation of 2-substituted quinolines with HEH as the hydrogen source, which gives direct access to a variety of 2-aryl- and 2-alkyl-substituted tetrahydroquinolines with good to excellent yields. This organocatalytic process not only further expands the application scope of thiourea **T1**, but also demonstrates for the first time that the hydride transfer from HEH to quinolines can be successfully promoted via H-bond interaction. The mild reaction conditions as well as the relatively low catalyst loading make this transformation an attractive approach to tetrahydroquinoline derivatives. Further work will be directed toward the application of chiral thiourea catalyzed enantioselective transfer hydrogenation of quinolines to enantioenriched tetrahydroquinoline derivatives as well as other heteroaromatic systems.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 21376212, 21222601), Doctoral Fund of Ministry of Education of China (No. 20120101120107) and the Natural Science Foundation of Zhejiang Province, China (No. LY13B060001).

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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