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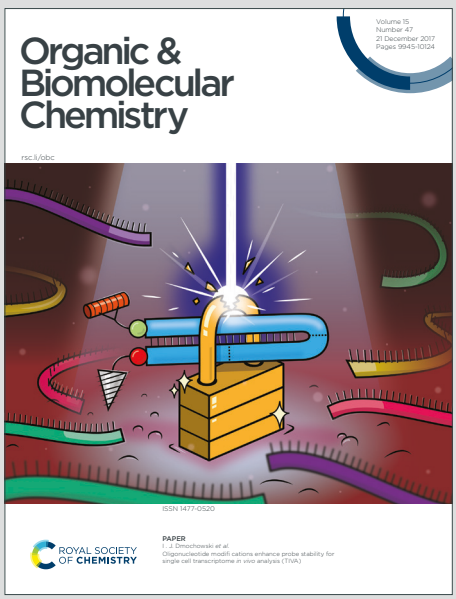

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ARTICLE

Boric acid catalyzed chemoselective reduction of quinolines

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Boric acid promoted transfer hydrogenation of substituted quinolines to synthetically versatile 1,2,3,4-tetrahydroquinolines (1,2,3,4-THQs) was described under mild reaction conditions using Hantzsch ester as a mild organic hydrogen source. This methodolgy is practical as well as efficient, where isolated yields are excellent and reducible functional groups are well-tolerated into the *N*-heteroarene moiety. The reaction parameters and tentative mechanistic pathways are demonstrated by various control experiments and NMR studies. The present work can also be scaled up to obtain gram quantities and the utility of the developed process is illustrated by the transformation of 1,2,3,4-THQs to a series of bilogically imporant moelcules including antiarrhythmic drug nicainoprol.

Introduction

Nature is the oldest laboratory, producing a wide series of molecules, that has the utmost diversity and utility, precisely in the identification of various medicines including antibacterial, antitumor, antifungal compounds.[1] These biologically active molecules are mostly cyclic molecules containing nitrogen atom in their active site.[2] In this context, saturated quinolines such as 1,2,3,4-tetrahydroquinolines (1,2,3,4-THQs) core are prevalent in nature and found in the numerous bioactive molecules.[3] A few examples[4] are listed in Figure 1. Since, these molecules have wider applications in the pharmaceuticals, agrochemicals industries and total synthesis of natural products, the scientific community is more involved in the synthesis of a wide library with easy and sustainable synthetic methodologies.[3,4] Nonetheless, there are several pathways known in the literature to construct the 1,2,3,4-THQs scaffold,[3] yet partial hydrogenation of *N*-heteroaromatics is a straightforward and practical method to produce these saturated nitrogen-containing heterocycles.[3a-b] Further, the hydrogenation reaction of quinolines is well explored with the precious as well as non-precious metal catalysts in presence of suitable hydrogen source.[5] Despite considerable progress these protocols still possess several disadvantages such as (a) metal contamination, (b) drastic conditions, (c) low substrate scope, (d) functional group intolerance, (e) expensive reagents etc.[5a-c,6]

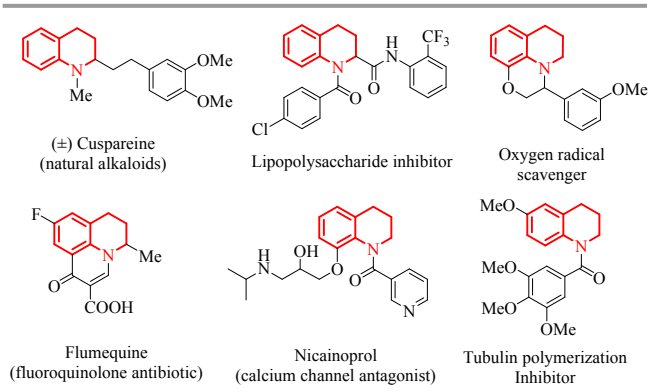

Fig. 1 Representative bioactive compounds containing 1,2,3,4-THQs framework.

Occasionally, this reaction is also reported *via* metal-free Lewis acid-catalyzed pathway[7-10] through hydrogenation,[7] hydroborylation,[8] and hydrosilylation[9] as well, and very recently iodine catalyzed route has been reported[10] (Scheme 1). Despite their excellent work where the above-said issues were somehow resolved, there are several other limitations such as (a) additional step requires in hydroboration and hydrosilylation pathway (for reduction); (b) barely compatible with sensitive reducible functional groups; (c) loss in atom-economy (generates stoichiometric amount of boron-or silicon-containing byproduct); (d) practical methodology that requires less sophisticated techniques; (e) economical reagents etc., therefore, an improved methodology is deemed desirable.

Hantzsch ester (1,4-dihydropyridines), a close analog of biological NAD(P)H, is an organic hydride source and a mild reducing agent[11] can easily reduce the appropriate

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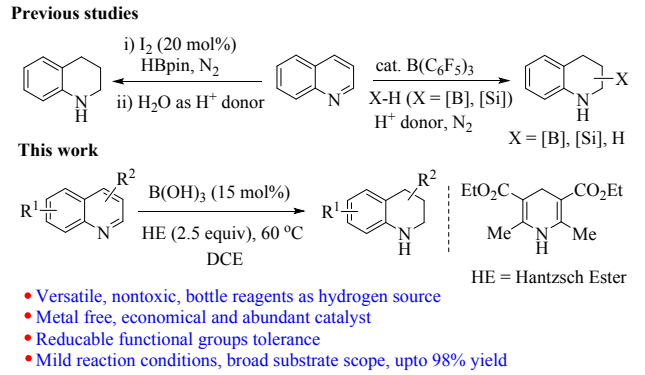
†Electronic Supplementary Information (ESI) available: Experimental details, analytical data, and copies of NMR-spectroscopic characterisation of all the compounds. Single crystal X-ray structure analyses of **3f** (CCDC 1946184). CIF and crystallographic data in ESI or other electronic format See DOI: 10.1039/x0xx00000x



Scheme 1 Metal-free Lewis acid induced the catalytic reduction of quinolines to 1,2,3,4-THQs.

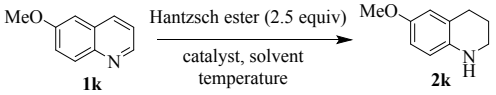
N-heteroaromatics under proper catalytic system.[11,12-15] Reuping et al. reported[12] pioneering biomimetic transfer hydrogenation of quinolines using chiral phosphoric acid as the catalyst and Hantzsch ester as the hydrogen source. Subsequently, various research groups independently reported the racemic as well as asymmetric catalytic system for this particular transformation, by using different Brønsted acids[13] as well as metal based-Lewis acids[14] as the catalysts. Nonetheless, more practical and efficient method specially in terms of functional group tolerance in the quinoline moiety, (which is not well discussed in the literature) is a worthwhile effort. Therefore, the development of a chemoselective and regioselective synthetic protocol is highly desirable in this context.

With these brief background survey, we report herein the transfer hydrogenation of various substituted quinolines with commercially available boric acid ($B(OH)_3$) as a catalyst. Further, the reaction parameters and a plausible mechanistic pathways are demonstrated by various control experiments and NMR studies to gain more insight. The protocol is extended to gram-scale studies and transform to synthetically versatile various tetrahydroquinolines products and finally, we have shown their synthetic utility in pharmaceutical purpose. Overall, the catalytic protocol is practical as well as efficient for the synthesis of 1,2,3,4-THQs by transfer hydrogenation pathway over the previously reported literature.

Results and Discussion

In literature, we identify that the quinoline ring contains two fragments; (a) activated ring containing nitrogen atom; and (b) unactivated fused benzene ring. The activated ring can be further activated/ polarised by mild Lewis acid. Thus, we sought to use commercially available $B(OH)_3$, which possesses soft acidity and helps in the selective/ partial reduction of quinolines in the presence of other reducible functional groups. Initially, we started the catalytic transfer hydrogenation with 6-methoxyquinoline **1k** as a model substrate, 15 mol% boric acid (catalyst), 2.5 equiv. of Hantzsch ester and 2 mL of DCE (solvent). After 3 h, the crude compound was analyzed and found the desired product **2k** with 70% yield. Fortified by the preliminary results, next we try to establish the optimized condition and started by varying the different boronic acid catalyst (Table 1, entries 1-3). While comparing the different boronic acid such as boric acid, phenylboronic acid, and 4-methoxyphenylboronic acid, the reaction proceeds relatively in a faster in the case of phenylboronic acid. This could be due to maximum electron deficiency on the boron atom as compared with other catalysts. However, the result with boric acid (70%) is not very discouraging and hence we sought to proceeds with commercially available and economical boric acid as a catalyst for further studies. Then after, we have scrutinized the catalyst loading and solvent effect (entries 4-14). While increasing the catalyst loading from 5 to 15 mol% (Table 1, entries 1, 4-9), the best yield was achieved with 15 mol% catalyst within 7 h at 60 °C. Notably, the reaction was failed in the absence of a catalyst, as well as at room temperature, suggesting both factors was very crucial to achieve the desired product (Table 1, entries 7, 11). Further, a variety of solvents were investigated. It was found that chlorinated solvent (DCE) as the appropriate solvent for the present protocol (Table 1, entries 6 and 12-16). Thus, the optimized condition is 15 mol% of $B(OH)_3$ as catalyst and DCE as a reaction medium for this particular reduction.

Table 1 Optimization studies for the transfer hydrogenation of 6-methoxyquinoline.[a]



entry	catalyst	catalyst (mol%)	solvent	yield (%)
1[b]	$B(OH)_3$	15	DCE	70
2[b]	$PhB(OH)_2$	15	DCE	90
3[b]	4-OMePhB(OH)_2	15	DCE	75
4	$B(OH)_3$	5	DCE	16
5	$B(OH)_3$	10	DCE	58
6	$B(OH)_3$	15	DCE	95
7[c]	$B(OH)_3$	15	DCE	nd
8[d]	$B(OH)_3$	15	DCE	63
9[e]	$B(OH)_3$	25	DCE	94
10[f]	$B(OH)_3$	15	DCE	88
11	-	-	DCE	nd
12	$B(OH)_3$	15	DMC	10
13	$B(OH)_3$	15	toluene	37
14	$B(OH)_3$	15	THF	10
15	$B(OH)_3$	15	CH_3CN	46
16	$B(OH)_3$	15	CH_3OH	7

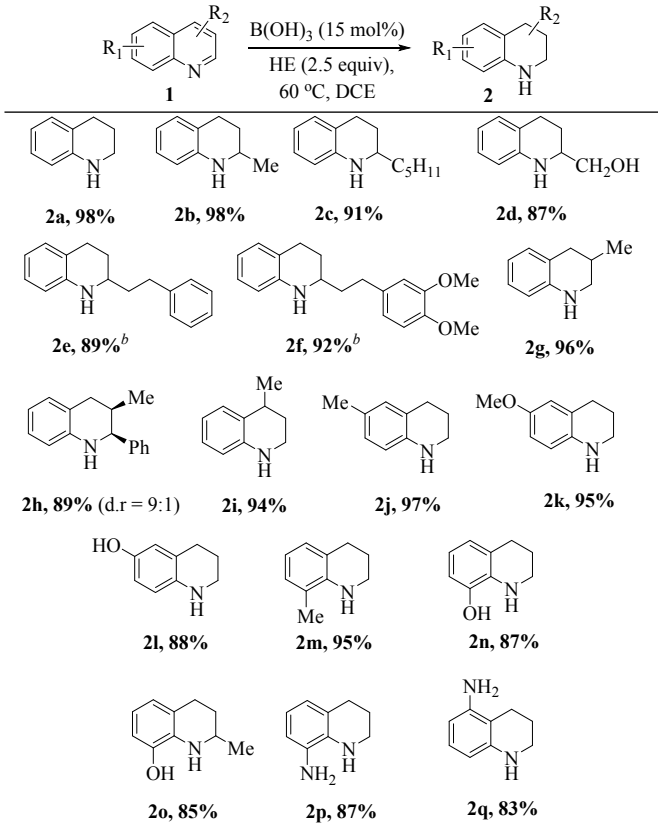
[a] Reaction conditions: 6-methoxyquinoline (0.5 mmol), catalyst (mol%), Hantzsch ester (2.5 equiv.) in solvent (2 mL) at 60 °C for 7 h; isolated yields are reported. [b] For 3 h at 60 °C. [c] At 27 °C for 7 h. [d] At 45 °C for 7 h. [e] At 60 °C for 6 h. [f] At 75 °C for 7 h. nd = not detected. DMC = dimethyl carbonate.

With these optimized conditions in hand, we explored the transfer hydrogenation of various substituted quinolines. For that, we have chosen substitution on both sides, nitrogen-containing ring as well as fused benzene ring and the results were described in the Table 2-3. The quinolines bearing alkyl, aryl, styryl, methoxy, amine, and hydroxy groups at the various position were efficiently reduced to give their corresponding THQs **2a-q** in high product yield (Table 2). In styryl substrates, it

reduces both the quinoline as well as the conjugated double bond and leads to the saturated molecule **2f**. The 2-phenyl-3-methylquinoline was reduced to its corresponding product **2h** with excellent cis-selectivity (diastereomeric ratio = 9:1). It should be noted that molecules "**2a-c**, **2f**, **2i**, **2k-l**" are important building blocks for various bioactive compounds (see ESI, Table S1).[3b,4] Likewise, substituted tetrahydroquinolin-8-ols (**2n** and **2o**) possess unique activity e.g. chelation with metal ions, and medicinal activity.[3b]

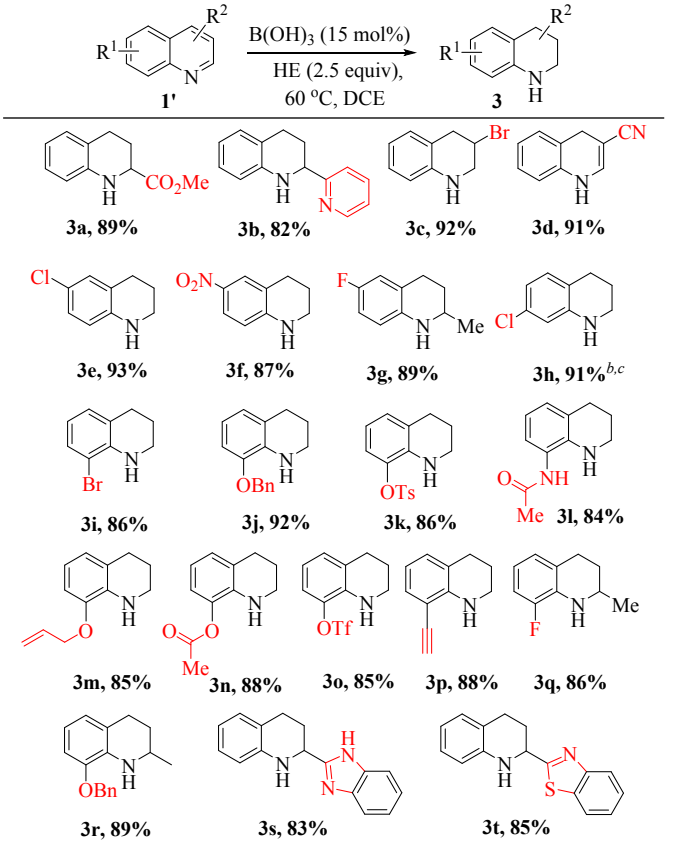
Then, we have attempted to explore chemoselective transfer hydrogenation of substituted quinolines where reducible groups are present on activated and/or un-activated rings of fused *N*-heteroarenes (Table 3). In this context, we have examined the various substituted quinolines containing ester, fluoro, chloro, bromo, nitro, nitrile, alkyne, amide, *O*- protected benzyl, tosyl, triflate and allyl groups. Interestingly, all the substituted quinolines were efficiently reduced to their corresponding THQs with the retention of their functional groups in good yields (**3a**, and **3c-r**). To our delight, the molecular structure of **3f** provides evidence for the formation of THQ core and intact the nitro unit. The X-ray crystal structure of compound **3f** is depicted in Figure 2.

Table 2 Catalytic transfer hydrogenation of basic quinolines.[a]



[a] Reaction conditions: Substituted quinoline (0.5 mmol), $B(OH)_3$ (15 mol%), Hantzsch ester (2.5 equiv.) in DCE (2 mL) at 60 °C for 7 h, stirring speed: 400 rpm; isolated yields are reported. [b] 3.5 equiv. HE was used.

Table 3 Chemoselective transfer hydrogenation of substituted quinolines and other *N*-heteroarenes.[a]



[a] Reaction conditions: Substituted quinoline (0.5 mmol), $B(OH)_3$ (15 mol%), Hantzsch ester (2.5 equiv.) in DCE (2 mL) at 60 °C for 7 h, stirring speed: 400 rpm; isolated yields are reported. [b] 4,7-dichloroquinoline was used as the substrate [c] 3.5 equiv. HE was used.

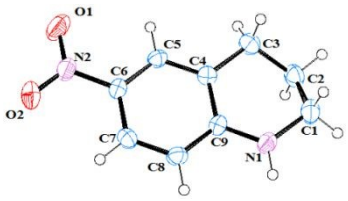


Fig. 2 Molecular structure of compound **3f** (thermal ellipsoid 40% probability level).

Notably, 3-bromoquinoline is efficiently reduced to the corresponding product **3c** with excellent yield. In contrast the reduction of 3-cyanoquinoline, led to 3-cyano-1,4-dihydro quinoline **3d** with the retention of cyano group, which can be attributed to the inherent stability by π-electron delocalization. 4,7-dichloroquinoline interestingly preceded to dehalogenated THQ product **3h** in good yield (proposed pathway is given in Scheme S9). In the case of quinoline-6-carbaldehyde, both quinoline ring and carbaldehyde unit were reduced to yield 6-methyl-1,2,3,4-tetrahydroquinoline **2j** (Scheme 2) *via* intermediate 6-methylene-2,3,4,6-tetrahydroquinoline (proposed reaction pathway is included in Scheme S8). Moreover, we have analyzed C8-substituted *O*- and *N*-atom

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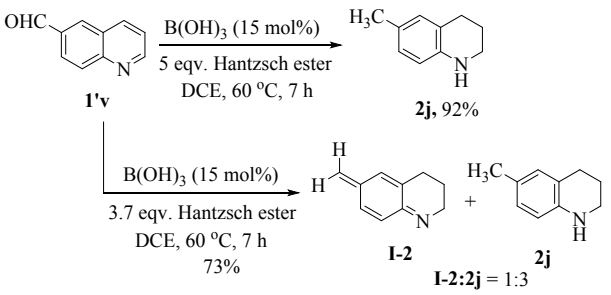


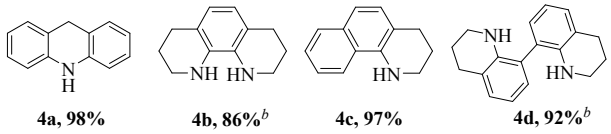
Scheme 2 Catalytic reduction of quinoline-6-carbaldehyde.

functionalize quinolines **3j-o**, and **3r** to know the effect of steric hindrance near the active site. Excitingly, these quinolines were also hydrogenated quantitatively and suggested that the catalytic protocol was not only chemoselective but also tolerate the bulky functional groups. It is worthy to mention that the present reduction approach is well tolerated for the alkyne functional group into the quinoline moiety (product **3p**).

Further, we have examined 2,8-disubstituted quinolines to know the effect of steric hindrance near the active site. To our delight, these were also well compatible and provided the desired products (**3q**, and **3r**) in good yields. In order to probe the selective reduction of *N*-hetero arenes we have also examined C-2 position heteroaromatic pyridyl group (**1'b**) and benzo-fused heterocycles (**1't-u**) with quinoline moiety. It should be noted that these substrates with more than one reaction center also reduced quantitatively with excellent (100%) regioselectivity (**3b**, **3s-t**).

A series of other *N*-heteroarenes like acridine, 1,10-phenanthroline, 7,8-benzoquinoline and 8,8'-biquinoline were also examined under the optimized conditions (Table 4). These were also smoothly proceeded with good yields (**4a-d**). Overall, this mild catalytic protocol was excellent to showcase the variety of substrates with very good chemoselectivity.

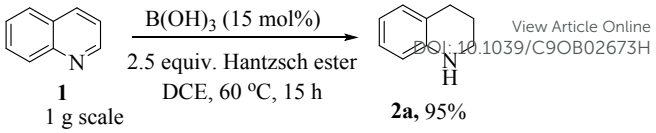
Table 4 Selective transfer hydrogenation of substituted quinolines and other *N*-heteroarenes.[a]



4a, 98% **4b, 86%**[b] **4c, 97%** **4d, 92%**[b]

[a] Reaction conditions: Substituted quinoline (0.5 mmol), $B(OH)_3$ (15 mol%), Hantzsch ester (2.5 equiv.) in DCE (2 mL) at 60 °C for 7 h, stirring speed: 400 rpm; isolated yields are reported. [b] 5 equiv. HE was used.

We have examined the efficiency of the process by scaling up the reaction in a gram scale so that it has some bulk utilization. For this, we have performed the reaction with 1 g of quinoline using an optimized condition. The reaction takes somewhat more time to complete (15 h), however ends with the full conversion with 95% yield (Scheme 3). Moreover, the by-product of Hantzsch ester was further regenerated (see ESI), so that it cannot treat as waste and makes our process more efficient and practical.



Scheme 3 Gram-scale transfer hydrogenation of quinoline.

To gain more clarity about the reaction pathway, first, we relook the substrate scope studies, particularly **3c**, **3d**, and **3h** (Scheme S10). Among these, the product 3-cyano-1,4-dihydroquinoline (**3d**), indicates that the reaction possibly proceeded *via* 1,4 addition of hydride into quinoline moiety. To ensure the above results and gain further insight into this transfer hydrogenation process thereby, we have performed the series of ^{1}H and ^{11}B experiments as shown in Figure 3. [N.B-NMR experiments were performed with quinoline as a substrate and phenylboronic acid as a catalyst (compare to boric acid) since it has very good solubility in $CDCl_3$]. For the bare quinoline in $CDCl_3$, the ^{1}H chemical shift for H2 and H4 appears at δ 8.92–8.93 ppm, and δ 8.11–8.13 ppm respectively which shifted to downfield while interacting with $PhB(OH)_2$ due to

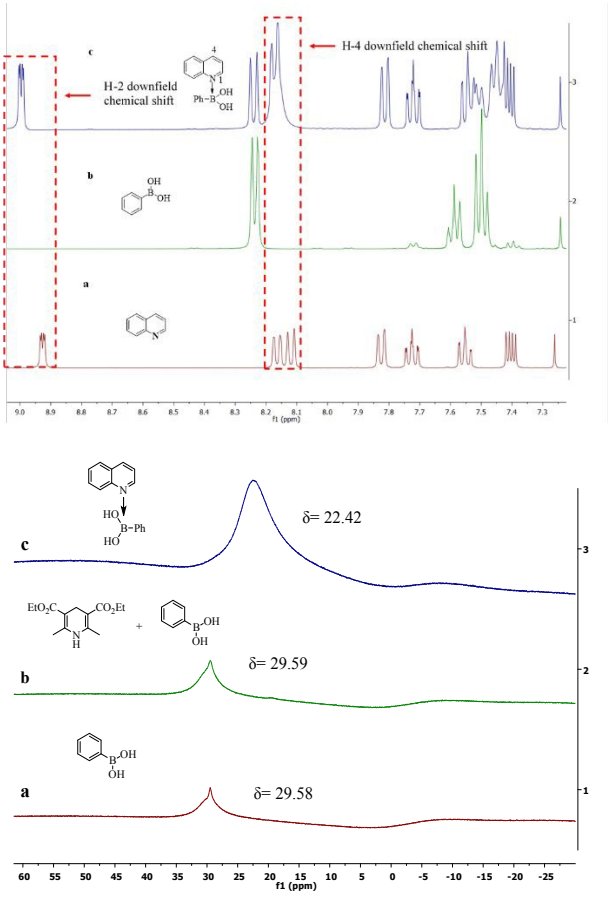


Fig. 3 Comparative study: (in the top) ^{1}H NMR spectra of (a) quinoline; (b) phenylboronic acid; and (c) combination of both quinoline and phenylboronic acid. (in the bottom) ^{11}B NMR spectra of (a) phenylboronic acid; (b) combination of phenylboronic acid with Hantzsch ester; (c) combination of phenylboronic acid with quinoline. The reaction condition is given in supporting information.

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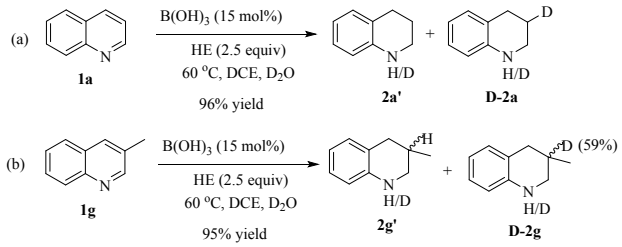
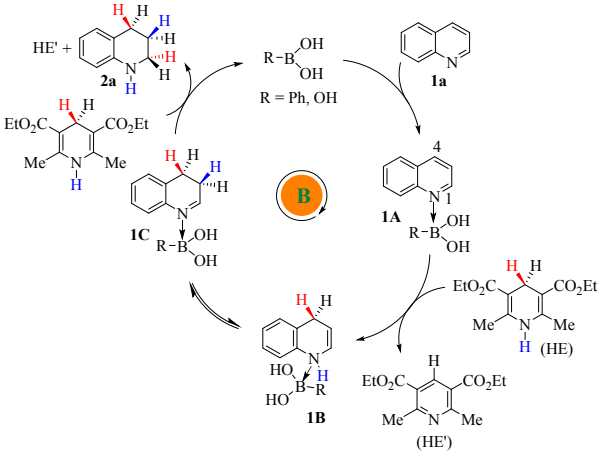
coordinate bond of nitrogen to boron results decreasing of electron density over nitrogen atom. A similar effect can be shown in the ^{11}B NMR of bare phenylboronic acid and combination of phenylboronic acid and quinoline. Due to the coordinate bonding electron density on boron increases and it shifted towards upfield (Figure 3). Hence, the NMR study demonstrates that a weak adduct was formed with quinoline and arylboronic acid,[16] however there was not any interaction with Hantzsch ester and arylboronic acid (see ESI, Figure S4).

To locate the hydridic proton and acidic proton in this transformation, the deuterium-labelled experiments were performed with **1a** and **1g** independently in the presence of D_2O, 59% deuterium atom was incorporated in both cases at C-3 position of the THQ moiety *via* exchangeable proton of Hantzsch ester and D_2O (Scheme 3). From all the results obtained from the catalytic reactions and NMR studies, we reason that 1,4-position of quinoline ring gets activated by interaction with boron based Lewis acid[16] (**1A**). Consequently, the hydride atom attacks at C-4 position and generate 1,4-dihydroquinoline[17] (**1B**), which gets isomerized to 3,4-dihydro quinoline (**1C**) and subsequent 1,2-hydride transfer occurs.[5f,11,12a] A plausible reaction mechanism is depicted in Scheme 4.

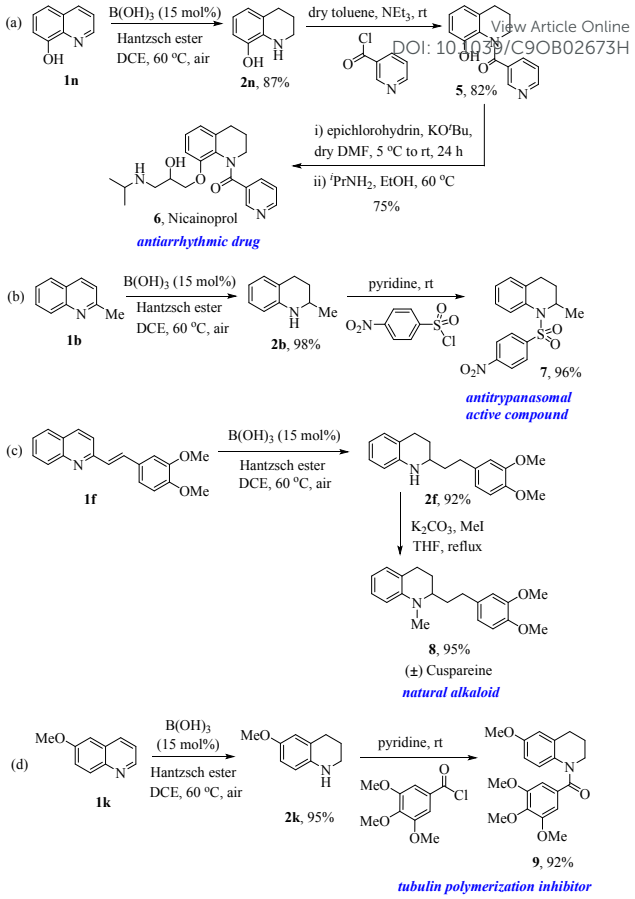


Scheme 4 Deuterium-labelled experiment for quinoline and 3-methyl quinoline.



Scheme 5 Probable mechanistic pathway.

As, THQ's are the key intermediate for numerous biological active molecules, therefore the synthetic utility of the present protocol was also explored towards few of the target bioactive molecule such as antiarrhythmic drug nicainoprol (**6**), antitrypanasomal active compound (**7**), natural alkaloid (±) cuspareine (**8**), and TB inhibitor (**9**) (Scheme 5). The desired



Scheme 6 Application in the synthesis of the nicainoprol and other bioactive compounds.

molecules can be easily prepared in a multi-step process from the readily available starting precursor. The molecule nicainoprol,[4e, 18] an antiarrhythmic drug has been synthesized in multi-steps, starting from commercially available 8-hydroxyquinoline (**1n**) which was transformed to **2n**, subsequently converted to *N*-amidation derivative **5** with 82% yield, compound **5** was then reacted with epichlorohydrin, followed by an overnight reflux with isopropyl amine to yield the desired product **6** with 75% yield. Building block **2b** was explored for the synthesis of biologically active compound i.e., antitrypanasomal.[5a,19] The desired compound was readily available by the transfer hydrogenation of 2-methylquinoline using the present protocol. A subsequent reaction with 4-nitrobenzenesulfonyl chloride give 96% isolated yield of molecule **7**. Furthermore, natural alkaloid (±) cuspareine (**8**)[4a-b] has been prepared with 95% isolated yield from the synthesized precursor **2f**, followed by methylation with methyl iodide. Moreover, we have also synthesized a bioactive compound (**9**) having activity tubulin polymerization inhibitor starting from 6-methoxyquinoline in just two step route.[4g,5a,10] The first step was the boron mediated transfer hydrogenation with Hantzsch ester and the final step was a coupling of 6-methoxy tetrahydroquinoline with 3,4,5-trimethoxy benzoyl chloride in the presence of pyridine to the desired product with 92% isolated yield. Besides this, we have presented few other active

molecules in Table S1 which can be synthesized in multiple steps from the obtained THQs.

Experimental Section

General procedure for transfer hydrogenation reaction: In a pyrex tube (15 mL), substituted quinoline (0.5 mmol), Hantzsch ester (2.5 equiv.), $B(OH)_3$ (15 mol%) and solvent (2 mL) was charged. The reaction tube was closed without the exclusion of air and placed in a preheated oil bath (60 °C) with continuous stirring. The reaction was monitored by thin layered chromatography (TLC) in *n*-hexane and ethyl acetate solvent system. After completion of the reaction, the crude compound was purified by column chromatography on silica gel for the pure compound.

Conclusions

In summary, the catalytic reduction of quinolines with boric acid and Hantzsch ester is reported. The present protocol works under mild reaction conditions with excellent yield and good chemoselectivity. The mechanistic studies demonstrate that transformation proceeds through a stepwise 1,4/1,2-hydride addition to the quinoline moiety, activated by metal-free air stable boron-based Lewis acid. The synthetic utility of the 1,2,3,4-tetrahydroquinoline derivatives is demonstrated by the synthesis of several bio-active molecules, including antiarrhythmic drug nicainoprol. Overall, this approach is promising especially from industrial perspective because it's an operationally simple, highly efficient, environment-friendly, scalable, economical, and abundant boric acid used as the catalyst.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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