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Enantioselective Organocatalytic Transfer Hydrogenation of 1,2-Dihydroquinoline through Formation of Aza-*o*-xylylene

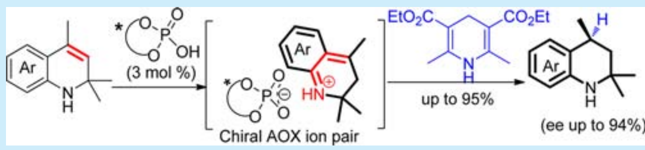
Guangxun Li,*,† Hongxin Liu,† Gang Lv,† Yingwei Wang,‡ Qingquan Fu,† and Zhuo Tang*,†

†Natural Products Research Center, Chengdu Institution of Biology Chinese Academy of Science Chendu, Sichuan 610041, China

‡College of Chemical Engineering, Sichuan University, Chendu Sichuan 610041, China

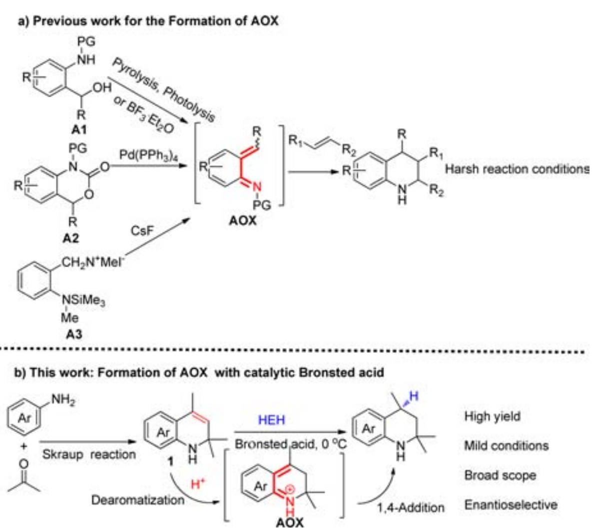
Ⓢ *Supporting Information*

ABSTRACT: A new way of forming the aza-*o*-xylylene with easily accessible 1,2-dihydroquinolines as precursor has been developed. The presence of an electron-donating group at the proper position of 1,2-dihydroquinoline was crucial for protonation of the alkene through dearomatization with a simple Brønsted acid. The in situ forming reactive intermediate was trapped with Hantzsch ester to afford tetrahydroquinolines in excellent yield and enantioselectivity.



Aza-*o*-xylylene and *o*-quinone methide imine (**AOX**) (Scheme 1a) are highly reactive and unstable species, with the first documented occurrence in 1966.[1] Owing to their high reactivity, they could be trapped with an olefin and proceed through cycloaddition or electrocyclization reactions to produce a wide variety of heterocycles.[2] These highly unstable and reactive intermediates are generally formed in situ with different methods according to the precursor. For example, pyrolysis or photolysis of various precursors such as *o*-aminobenzyl alcohols or their (*tert*-butoxycarbonyl)amino derivatives were applied previously (**A1**) (Scheme 1a),[2a,c] and then more and more precursors such as dihydro-l, 3-benzoxazine-2-one,[2g] 2,1-benzisothiazoline 2,2-dioxide,[2h] 2-azidoindoles,[2d] and *N*-phenylbenzoazetine[1] were used for producing these useful intermediates more efficiently.

Scheme 1. Paths for the Formation and Application of AOX



However, these precursors were inefficient due to the strict reaction conditions. Other methods for formation of **AOX** under milder reaction conditions such as dehydroxylation with $BF_3 \cdot Et_2O$ at room temperature (**A1**) (Scheme 1a),[21] fluoride-induced 1,4-elimination of [*o*-[(trimethylsilyl)alkylamino]-benzyl]trimethylammonium iodide (**A2**) (Scheme 1a),[2b] and palladium-mediated decarboxylation (**A3**) (Scheme 1a)[3] were restricted to special substrates which were difficult to obtain. As a result, a lack of efficient and mild synthetic methods to manipulate **AOX** likely contributed to the paucity of applications of these species.

1,2-Dihydroquinoline **1** was quite easy to obtain through the modified Skraup reaction with simple aromatic amine and ketone (Scheme 1b).[4] Our interest in this underexplored species stemmed from 1,2-dihydroquinoline **1** that might form **AOX** through dearomatization with catalytic Brønsted acid under mild conditions (Scheme 1b). We reasoned that increasing the nucleophilicity of the alkene moiety would allow the substrate to be protonated even by mild Brønsted acid based on the fact that dihydroquinoline **1** has been used as electrophile to react with benzene by catalytic $AlCl_3$.[5] Adding an electron-donating group to the aromatic ring of **1** would easily improve the nucleophilicity of the alkene.

Moreover, a chiral Brønsted acid mediated **AOX** ion pair might be used as the electrophile to efficiently prepare chiral tetrahydroquinolines, which are very important skeletons found in numerous biologically active natural products and pharmacologically relevant therapeutic agents[5,6] (Figure 1). Herein, we report a mild strategy for dearomatization of 1,2-dihydroquinolines to **AOX** in situ with catalytic amounts of Brønsted acid, which were then applied as efficient electrophiles to react with Hantzsch diethyl ester (**HEH**) to prepare chiral tetrahydroquinolines.

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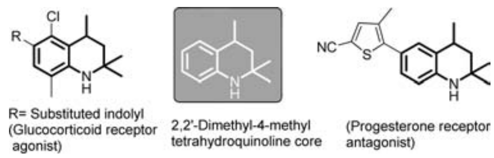
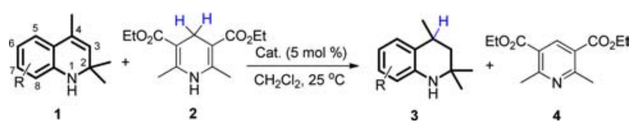


Figure 1. Pharmaceutical active tetrahydroquinolines.

As a model reaction to evaluate this concept, we chose the Hantzsch diethyl ester (**HEH**) as hydride source to reduce this active intermediate.[7] As a result, several 2,2,4-trimethyldihydroquinolines with different substituents on the phenyl ring were prepared and subjected to **HEH** with catalytic TsOH in $CHCl_3$ (Table 1). Neither dihydroquinoline **1a** without substituent (Table 1, entry 1) nor dihydroquinolines **1b** or **1c** with electron-withdrawing groups such as 6-Cl or 6-CF_3 (Table 1, entries 2 and 3) could undergo the transfer hydrogenation to give the corresponding tetrahydroquinolines. The same results were found for dihydroquinoline **1d** with a weak electron-donating group on the phenyl ring (Table 1, entry 4).

Table 1. Screening of Appropriate Dihydroquinolines



entry[a]	1, R	cat.	yield[b] (%)
1	**1a**, R = H	TsOH	
2	**1b**, R = 6-Cl	TsOH	
3	**1c**, R = 6-CF_3	TsOH	
4	**1d**, R = 6-Me	TsOH	
5	**1e**, R = 7-OCH_3	TsOH	95
6	**1f**, R = 6-OCH_3	TsOH	
7	**1g**, R = 6,8-di-OCH_3	TsOH	
8	**1e**, R = 7-OCH_3	TFA	94
9	**1e**, R = 7-OCH_3	$Yb(OTf)_3$	93
10	**1e**, R = 7-OCH_3	$MgBr_2$	85

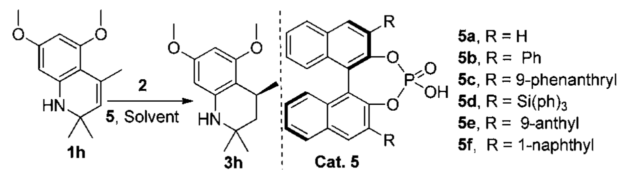
[a]Reaction conditions: 0.2 mmol of **1**, 0.24 mmol of **2**, cat. (5 mol %), 2 mL of $CHCl_3$ at 25 °C, nitrogen atmosphere. [b]Isolated yield from **1**.

The above results were ascribed to the failure of formation of the **AOX** intermediate. We hypothesized that increasing the electron density of the phenyl ring by using a stronger electron-donating group would make the dihydroquinoline substrate form an **AOX** intermediate by dearomatization.[8] As expected, dihydroquinoline **1e** with a 7-methoxy on the phenyl ring could be efficiently transformed to the corresponding tetrahydroquinoline **3e** (Table 1, entry 5). Nevertheless, dihydroquinolines **1f** and **1g** with 6-methoxy or 6,8-dimethoxy could not afford the corresponding product (Table 1, entries 6 and 7), which indicated that the substitution pattern of the electron-donating group on the proper position of the dihydroquinoline substrate was crucial for the dearomatization.

We then continued to investigate the reaction with different types of catalysts including Brønsted acid TFA (Table 1, entry 8), Strong Lewis acid $Yb(OTf)_3$ (Table 1, entry 9) or mild Lewis acid $MgBr_2$ (Table 1, entry 10). The results revealed that all of these catalysts could catalyze the reaction with excellent yield. Meanwhile, using chiral Brønsted acid as catalyst would allow the formation of an ionic pair between **AOX** and an optically active phosphoric anion,[9] which could be trapped with **HEH** to provide chiral 2,2,4-trisubstituted tetrahydroquinolines. Therefore, we systematically investigated the asymmetric reduction of the dihydroquinolines with binol-derived chiral phosphoric acids **5**.

At the beginning, we optimized the reaction by screening different chiral catalysts with CH_2Cl_2 as solvent at room temperature. The reaction results revealed that catalyst **5c** was more efficient considering the enantioselectivity (enties 1−6, Table 2). We then screened the reaction solvent and found that toluene was more efficient in which the product was obtained with 75% ee (entries 7−10, Table 2). Decreasing the reaction temperature to 0 °C could greatly improve the enantioselectivity to 80% (entry 11, Table 2). Finally, addition of 4 Å molecular sieves could improve the enantioselectivity and yield (entry 12, Table 2). Further decreasing the reaction temperature to −10 °C did not improve the enantioselectivity but decreased the enantioselectivity and yield (entry 13, Table 2). Meanwhile, the catalyst loading was screened, which demonstrated that 3 mol % was better considering the yield and enantioselectivity (entries 14−15, Table 2). These preliminary studies revealed that the best conditions for the transfer hydrogenation of dihydroquinoline **1h** were 1.2 equiv of dihydropyridine **2** and 3 mol % of catalyst **5c** at 0 °C in toluene for 48 h with 4 Å molecular sieves as additive.

Table 2. Optimizing the Reaction Conditions



entry[a]	cat. 5 (mol %)	solvent	temp (°C)	ee[b] (%)	yield[c] (%)
1	**5a** (5)	CH_2Cl_2	25	11	98
2	**5b** (5)	CH_2Cl_2	25	11	96
3	**5c** (5)	CH_2Cl_2	25	68	95
4	**5d** (5)	CH_2Cl_2	25	30	89
5	**5e** (5)	CH_2Cl_2	25	10	88
6	**5f** (5)	CH_2Cl_2	25	40	92
7	**5c** (5)	toluene	25	75	94
8	**5c** (5)	THF	25	65	92
9	**5c** (5)	TBME	25	68	85
10	**5c** (5)	*m*-xylene	25	74	92
11	**5c** (5)	toluene	0	80	93
12[d]	**5c** (5)	toluene	0	88	95
13 [d]	**5c** (5)	toluene	−10	86	85
14 [d]	**5c** (3)	toluene	0	88	92
15 [d]	**5c** (1)	toluene	0	86	80

[a]General conditions: 1 equiv of **1h** and 1.2 equiv of **4**. [b]Enatioselectivity was determined by HPLC with chiral AD-H. [c]The reaction yield were determined after purification by flash column; 4 Å molecular sieves were added.

Under these optimized conditions, we explored the scope of the Brønsted acid catalyzed transfer hydrogenation of dihydroquinoline based on the in situ formed **AOX** (Scheme 2). Tetrahydroquinoline with one methoxy group (**3e**), two methoxy groups (**3h,i**), and three methoxy groups (**3j**), tetrahydroquinolines with different 7-alkoxy (**3n−r**), and even tetrahydroquinolines with 7-methoxy and different halogens at C-6 (**3k−m**) were obtained under the optimal reaction

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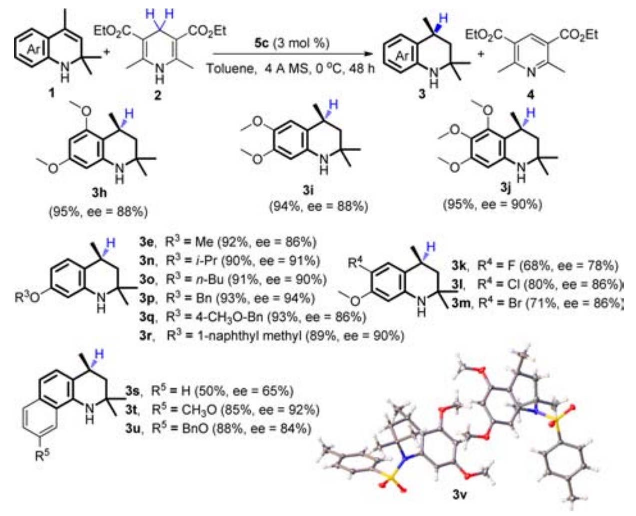
Scheme 2. Scope of the Transfer Hydrogenation Reaction



conditions in good yields (68−95%) and excellent enantioselectivities (78−94%).

Meanwhile, different 7,8-benzotetrahydroquinolines without electron-donating groups (**3s**) or with alkoxy groups (**3t−u**) could be obtained with moderate to good yield (50−88%) and ee (65−92%). The absolute configuration of the product was detected by transfer **3e** to **3v** and assigned as 4*S* by X-ray crystallographic analysis (see the Supporting Information).

In summary, we succeeded in developing a new method for transferring 1,2-dihydroquinoline to the reactive **AOX** intermediate through dearomatization with catalytic Brønsted acid. The resulting intermediate formed in situ could be efficiently transfer hydrogenated with HEH. This method offers an opportunity to form an **AOX** intermediate under mild reaction conditions while avoiding the use of metals as well as tedious synthesis of substrate. Meanwhile, this method was validated in the presence of catalytic chiral Brønsted acid. The resulting chiral **AOX** was transfer hydrogenated with **HEH** to produce tetrahydroquinolines with excellent yield and enantioselectivity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02025.

Full experimental details and analytical data including NMR spectra and chiral HPLC analysis (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ligx@cib.ac.cn.

*E-mail: tangzhuo@cib.ac.cn.

Notes

The authors declare no competing financial interest.

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