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What Happens When the Terminal Aromatization is Blocked? Construction of 1,2-Dihydroquinoline Derivatives by sp^3 C–H Bond Oxidation of *N*-Arylalaninates

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Abstract: Using an aromatization-blocked strategy, the 1,2-dihydroquinoline skeleton was efficiently constructed by sp^3 C–H bond oxidation of *N*-arylalaninates under catalytic radical cation salt-promoted conditions. Investigation of the reaction scope shows broad generality and good functional group tolerance. This method provides a new way to synthesize 1,2-dihydroquinoline derivatives from easily accessible starting materials.

Keywords: aromatization-blocked strategy; *N*-arylalaninates; sp^3 C–H oxidation; 1,2-dihydroquinolines; radical cation salts

The partially hydrogenated quinoline skeleton is a key structural motif in various natural products, pharmaceuticals, and synthetic intermediates,[1] in which dihydroquinolines are known to display a broad range of biological activities and have potential pharmaceutical applications, such as antioxidative,[2] anti-inflammatory,[3] psychotropic,[4] anti-allergenic,[5] and estrogenic activities.[6] For example, ethoxyquin (6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline) is an FDA-approved antioxidant commonly used as a preservative in the food processing industry.[7] Furthermore, some derivatives of dihydroquinoline were found to display outstanding antitrypanosomal activities.[8]

Due to their great importance, considerable efforts have been devoted to the synthesis of the dihydroquinoline skeleton and numerous methods have been developed to access to this family of compounds.[9] Since the pioneering work of Skraup in 1880s,[10] the Skraup reaction and its variants have been commonly utilized in the synthesis of dihydroquinolines.[11] Recently, efficient methodology directed toward the synthesis of dihydroquinolines has focused on a catalytic version. Based on the transition metal (Pd,[12] Ru,[13] Ag[14] and Au[15]) catalyzed reactions between anilines with alkynes, polysubstitiuted 1,2-dihydroquinolines can be produced in good yields. You and co-workers reported an elegant route to enantiomerically enriched 1,2-dihydroquinoline derivatives by Ru-catalyzed ring-closing metathesis (RCM) reaction of *N*-allyl-2-vinylanilines.[16] Using an intramolecular allylic amination strategy, the Chan and Sun groups achieved a synthesis of substituted dihydroquinolines under $AuCl_3/AgSbF_6$ (5 mol%/15 mol%) and $FeCl_3{\cdot}6H_2O$ (2 mol%) catalyzed conditions, respectively.[17] The reaction between carbonyl-containing compounds is also an efficient method to construct 1,2-dihydroquinolines, which was generally prompted by acids.[18] Besides these general substrates and their transformations, some other methods can also be used to build the dihydroquinoline framework.[19] However, some remarkable limitations still exist in these procedures, such as low yields, harsh reaction conditions, narrow substrate scope, inaccessible catalysts, and poor functional group tolerance. Therefore, a simple and facile method for constructing dihydroquinolines, especially highly functionalized ones, is still desirable and has practical benefits.

Recently, C–H activation mediated by radical intermediates has attracted much attention, and a variety of methodologies have been established.[20] Since the first example of aerobic C–H oxidation of an sp^3 C–H bond prompted by catalytic radical cation salts in the presence of O_2,[21a] we have reported a series of syntheses of heterocyclic compounds, such as quinolines, quinoline fused lactones and lactams, pyridines, 1,4-dihydropyridines.[21] In these reactions, two aspects were focused: (i) use of triarylamine radical cation to achieve catalytic oxidation of sp^3 C–H bonds avoiding over use of a stoichiometric oxidant and (ii) construction of important heterocyclic skeletons based on C–

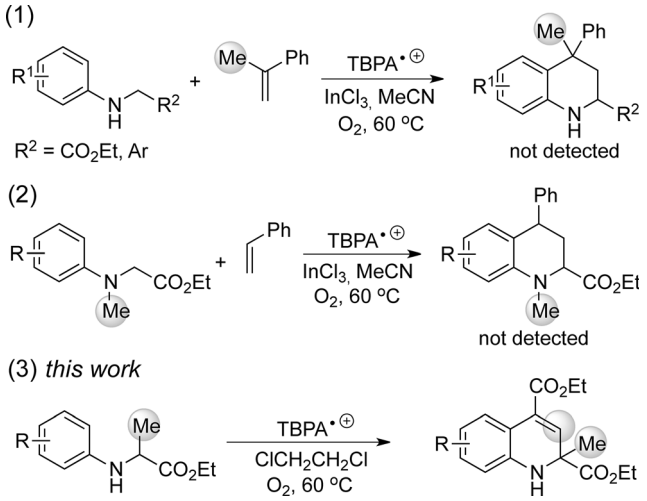


Figure 1. Reactions designed with the aromatization-blocked strategy.

H functionalization. During this research, we found that late stage aromatization was an important driving force to achieve an efficient transformation. For example, if α-methylstyrene was used to react with *N*-arylglycine esters and *N*-benzylanilines, respectively, in which the terminal aromatization was blocked by the methyl group, the reaction efficiency decreased and none of the expected 1,2,3,4-tetrahydroquinoline (THQ) was detected [Figure 1, Eq. (1)]. Similarly, if a methyl group was installed on the nitrogen of *N*-arylglycine esters, no THQ was found, either [Figure 1, Eq. (2)]. So we questioned if blocking the terminal aromatization could be a strategy to find new reactions and make some new compounds. Herein, we report an interesting construction of 1,2-dihydroquinolines with a tertiary center by aerobic oxidation of *N*-arylalaninates induced by $TBPA^{+\bullet}$ [Figure 1, Eq. (3)].

To investigate the aromatization-blocked strategy, the reaction between **1a** and styrene was tried under $TBPA^{+\bullet}$ [(tris(4-bromophenyl)aminium hexachloroantimonate] induced conditions.[22] To our surprise, the intermolecular cyclization of **1a** and styrene was totally inhibited, and **2a** was isolated in 40% yield, instead (Figure 2). From retrosynthetic disconnections, the synthesis of this 1,2-dihydroquinline is inaccessible through the corresponding alkyl acrylates or alkyl propiolate, for 2-azadienes are generally electron-poor, and only react with electron-rich dienophiles. However, the tautomer of the imine, an enamine, exhibited good reactivity towards 2-azadienes, which could be easily provided by oxidation of *N*-arylalaninates. Furthermore, the termination C–N bond cleavage could be achieved under radical cation salt-induced conditions.[23] Inspired by the above result, we used the reaction of **1a** as a model reaction to screen the best reaction conditions (Table 1). Initially, in the presence of 5 mol% $TBPA^{+\bullet}$, the desired product was obtained in 46% yield (entry 1). On increasing the amount of $TBPA^{+\bullet}$ to 10 mol%, the yield was improved to 64% (entry 2).

If 20 mol% of $TBPA^{+\bullet}$ was added, the reaction became complicated, and the expected dihydroquinoline was isolated in lower yield (entry 3). Next, the reaction temperature was screened. At room temperature, the reaction became slow, and only trace of the product was detected by TLC after 13 h (entry 4). With use of higher temperatures, the yields were increased (entries 5 and 6). Further optimization of the solvents showed that DCE was the best solvent, and the desired product was isolated in 72% yield (entry 7). Addition of acids was tried to increase the yield, but no positive effect on the reaction was found (entries 10–13). To confirm the need for dioxygen, the oxidative reaction was performed under an argon atmosphere; however, no reaction occurred (entry 14), implying that O_2 was crucial to sp^3 C–H bond oxidation. Under an air atmosphere, the reaction of **1a** was also unsuccessful, and only a trace of the desired product was detected by TLC (entry 15).

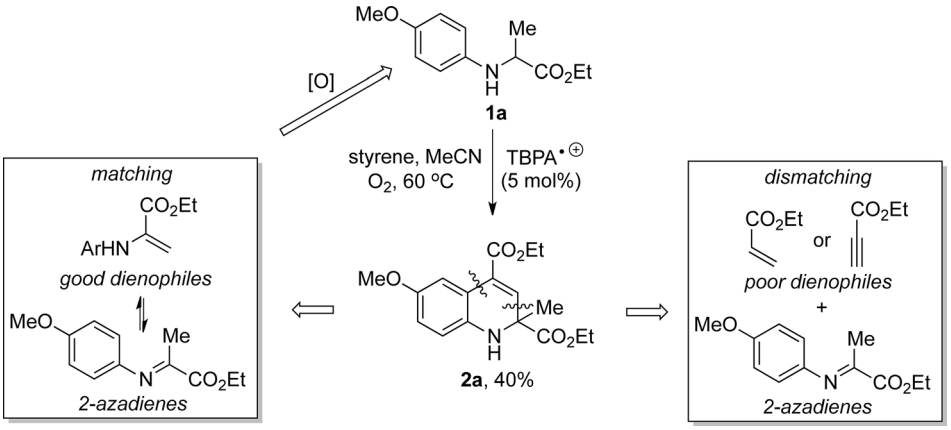
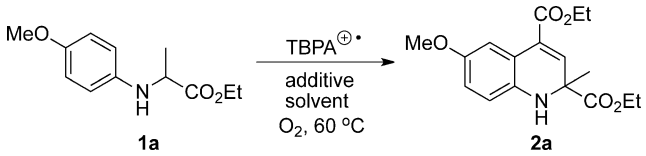


Figure 2. Reaction of **1a** induced by the radical cation salt.

Table 1. Optimization of the reaction conditions.[a]



Entry	$TBPA^{+\cdot}$ (mol%)	Additive (mol%)	Solvent	Temperature [°C]	Time [h]	Yield [%][b]
1	5	no	CH_3CN	60	8	46
2	10	no	CH_3CN	60	8	64
3	20	no	CH_3CN	60	8	50
4	10	no	CH_3CN	r.t	13	tace
5	10	no	CH_3CN	40	10	42
6	10	no	CH_3CN	80	6	72
7	**10**	**no**	**DCE**	**60**	**8.5**	**85 (72)[c]**
8	10	no	CH_3CN	60	8.5	57
9	10	no	$CHCl_3$	60	8.5	66
10	10	$BF_3{\cdot}O(Et)_2$	DCE	60	15	trace
11	10	TsOH	DCE	60	12	57
12	10	$InCl_3{\cdot}4\,H_2O$	DCE	60	12	58
13	10	CuCl	DCE	60	12	54
14	10	no	DCE	60	24	N.R.[d]
15	10	no	DCE	60	48	trace[e]

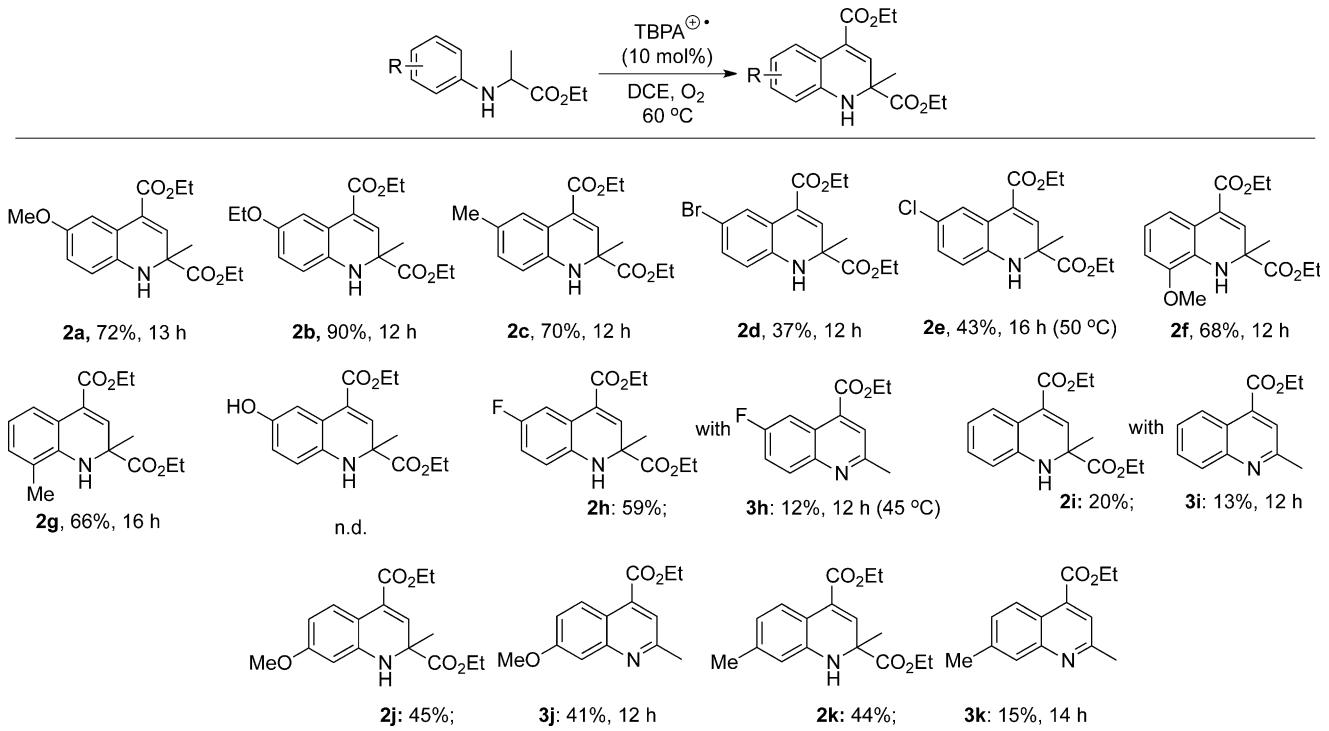
[a] Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol) in the presence of $TBPA^{+\cdot}$, and anhydrous solvent (1.5 mL).
[b] Yield of crude product by ^1H NMR using 1,3,5-trimethoxylbenzene as internal standard, and the yield was calculated based on 0.05 mmol of **1a**.
[c] Yield in the parentheses is the isolated yield.
[d] The reaction was performed under argon.
[e] The reaction was performed under an air atmosphere.

With the best conditions established, we then investigated scope of synthesis of 1,2-dihydroquinolines. Firstly, the substituent effect on anilines was examined, and the results are compiled in Scheme 1. The substrates with electron-donating groups gave better results than those with electron-withdrawing groups (**2a–2c** compared with **2d** and **2e**). The reason is attributed to their higher electron-donating ability to stabilize the radical intermediate of alaninates. In our previous papers, we reported that a free phenolic hydroxy group could be tolerated under the oxidative conditions, but in this case, no desired product was isolated when ethyl (4-hydroxyphenyl)alaninate was involved. Introduction of *ortho*-groups did not result in a decrease of the reaction efficiency, and the corresponding dihydroquinolines were obtained in good yields (**2f–2g**). Interestingly, if *meta*-group-substituted anilines were employed, the cyclization selectively occurred on the *para*-position (**2j** to **2k**). It is worth noting that, in some cases, decarboxylation products of dihydroquinoline, 2-methylquinoline-4-carboxylates, were isolated in certain amount (**3h–3k**). The exact reason remains unknown.

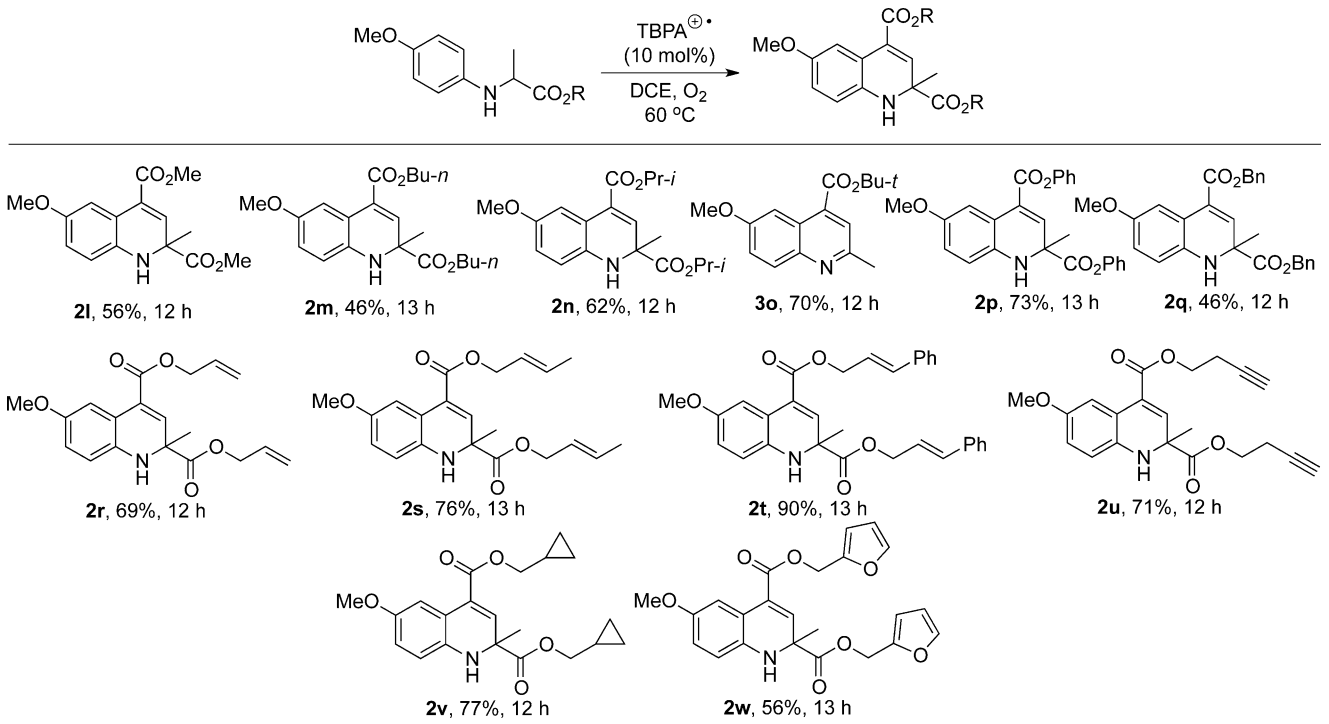
Next, different esters were examined to evaluate the tolerance of various functional groups (Scheme 2). In general, alkyl esters did not affect the reaction efficiency and the desired dihydroquinolines were afforded in good yields (**2l–2n**). Only the decarboxylation product was isolated when *tert*-butyl ester was used in the standard reaction conditions (**3o**). The phenyl ester could also be tolerated, giving 73% yield (**2p**). A lower yield was provided when the benzyl ester was involved, probably due to the existence of another active benzyl sp^3 C–H bond, which might disturb the oxidation process (**2q**). We were pleased to note that carbon-carbon unsaturated bonds such as those in allyl, 2-butenyl, cinnamyl and but-3-yn-1-yl groups could be well tolerated, yielding the desired products in 69–90% yields (**2r–2u**). Even the fragile cyclopropylmethyl group remained unchanged under the oxidative conditions (**2v**), showing good functional group tolerance. The furfuryl ester was also tested, and the product was obtained in a slightly lower yield (**2w**).

To evaluate the practical application of our method, the reaction of *N*-arylalaninates has been performed on a large scale. And to our delight, no yield loss was observed (Scheme 3).

To elucidate the reaction process, several control experiments were conducted under the standard conditions (Scheme 4). In the presence of the radical inhibitor, TEMPO (1 equiv.) or BHT (2 equiv.), the reaction was totally inhibited, which means that the re-

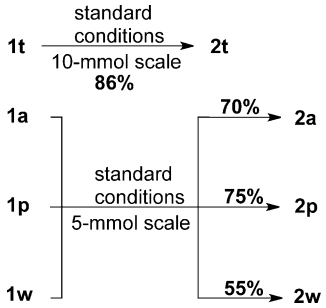


Scheme 1. Reaction of ethyl *N*-arylalaninates. *Reaction conditions:* **1** (1 mmol), $TBPA^{+\bullet}$ (10 mol%), DCE (5 mL), 60 °C under O_2, isolated yield (the yields were calculated based on 0. 5 mmol of **1**).

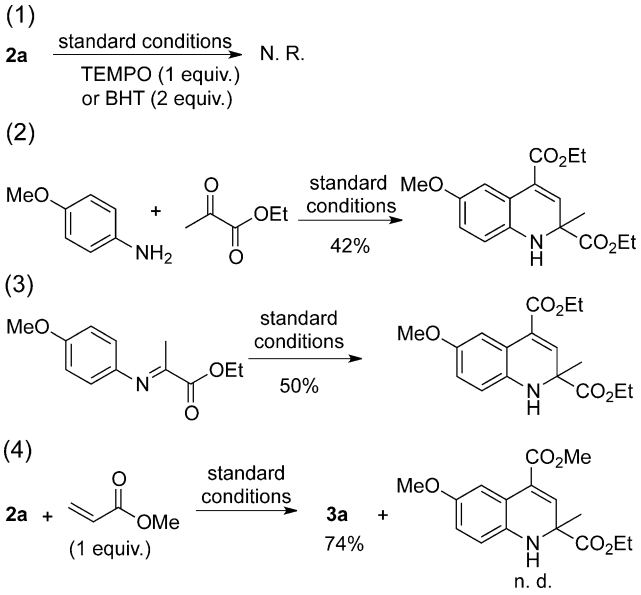


Scheme 2. Reaction of alkyl *N*-arylalaninates. *Reaction conditions:* **1** (1 mmol), $TBPA^{+\bullet}$ (10 mol%), DCE (5 mL), 60 °C under O_2, isolated yield (the yields were calculated based on 0. 5 mmol of **1**).

action was mediated by a radical intermediate. According to literature reports, anilines can react with alkyl pyruvate under Lewis acid-catalyzed conditions, providing the corresponding dihydroquinolines.[19] So



Scheme 3. Preparation of DHQs in a large scale.

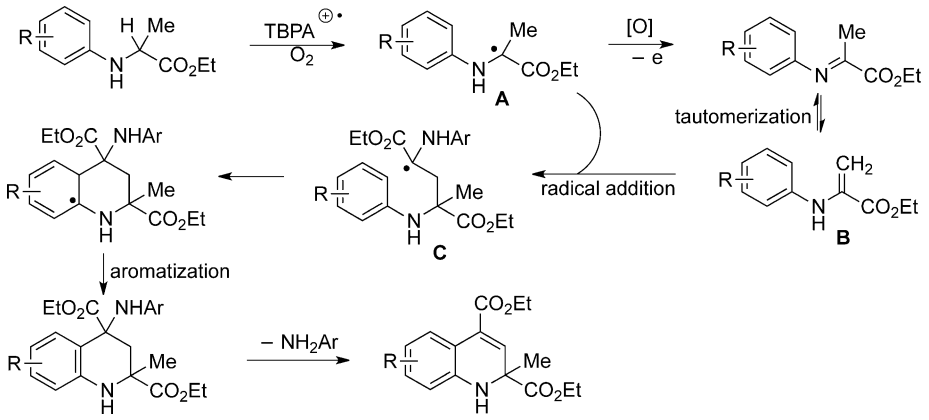


Scheme 4. Control experiments.

the reaction between 4- methoxyaniline and ethyl pyruvate was tried under these radical cation salt-induced conditions, and the desired product was only isolated in 42% yield. This result shows that the acid-prompted Mannich-type reaction was not the dominant reaction pathway. If alkyl pyruvate imine was used instead of *N*-arylalaninate, the reaction efficiency was also decreased, giving the corresponding product **2a** in 50% yield, which implied that the reaction pathway might be different from the reported acid-catalyzed process. To rule out other mechanisms, we tested the reaction of **1a** in the presence of methyl acrylate, which has a different ester group, but after the product analysis, none of the anticipated methyl acrylate was found. It is understandable that methyl acrylate is a poor substrate in 2-aza-[4+2] cycloaddition.

Based on the results described above, a possible mechanism is proposed to rationalize the formation of the products (Scheme 5). The sp^3 C–H bond of an *N*-arylalaninate was oxidized by the radical cation salt, in the presence of dioxygen, yielding a radical intermediate **A**. Then an imine intermediate was provided whose tautomerization leads to enamine **B**, a good radical acceptor. Attack on the enamine **B** by radical **A** results in the formation of a new radical **C**. After intramolecular radical cyclization and further aromatization, the tetrahydroquinoline skeleton is assembled. Finally, elimination of aniline leads to a 1,2-dihydroquinoline. However, at this stage, the acid-prompted process cannot be totally ruled out, although the control experiments showed that it was not the dominant reaction pathway.

In conclusion, based on this aromatization-blocked strategy, an efficient sp^3 C–H oxidation of *N*-arylalaninate derivatives was achieved, synthesizing a series of 1,2-dihydroquinolines. The scope examination shows good substrate generality and functional group tolerance. This method provides a new way to construct the biologically relevant dihydroquinoline skeleton. Further applications of this reaction and studies on the synthesis of partially hydrogenated quinolines are underway in our laboratory.



Scheme 5. Proposed mechanism for DHQ formation.

Experimental Section

General Procedure

A solution of **1** (1 mmol) in DCE (15 mL) was mixed fully and flushed with O_2, then $TBPA^{+\cdot}$ $SbCl_6^-$ (10 mol%) was added dropwise under an oxygen atmosphere. The reaction solution was stirred at 60 °C. After completion as monitored by TLC (UV visualization), the reaction was quenched by addition of saturated Na_2CO_3. The mixture was poured into a separatory funnel with the addition of excess DCM (10 mL), and then the crude organic solution was extracted three times with water to remove inorganic salts. The organic phase was then dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was separated by silica gel column chromatography eluted with petroleum ether/acetone (v/v 20:1) to afford the products.

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