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Oxidative Povarov Reaction via sp^3 C−H Oxidation of *N*-Benzylanilines Induced by Catalytic Radical Cation Salt: Synthesis of 2,4-Diarylquinoline Derivatives

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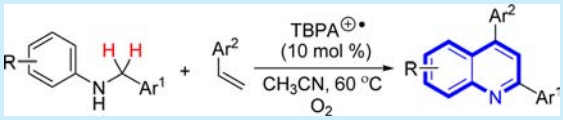
Supporting Information

ABSTRACT: Oxidative Povarov reaction of *N*-benzylanilines was realized under catalytic radical cation salt induced conditions. The mechanism studies revealed that a radical intermediate was involved in this catalytic oxidation. This method provides a new way to synthesize 2,4-diarylquinoline derivatives.



Direct C−H functionalization is a widely utilized method for the efficient and selective formation of C−C bonds. Since the pioneering work of Murahashi[1] and Li,[2] cross-dehydrogenative coupling (CDC) has attracted considerable interest among synthetic organic chemists because it does not require prefunctionalization of substrates and is more atom economic and environmentally friendly. Inspired by this new concept, more and more CDC reactions have emerged. Among these reactions, the oxidative coupling of tetrahydroisoquinolines has been studied extensively. In 2004, Li reported the first example of a CDC reaction between *N*-phenyltetrahydroisoquinoline and phenylacetylene catalyzed by a copper complex.[2a] The author proposed a reasonable mechanism to rationalize the formation of products in which the generated iminium intermediate is intercepted by a nucleophile, affording a Mannich-type addition product. Since then, the study of CDC reactions has primarily concentrated on the functionalization of tetrahydroisoquinoline derivatives, and a variety of different nucleophiles have been employed (Figure 1, reaction 1).[3] Recently, this area still remains hot, and some new nucleophiles have been developed.[4] For example, Wang and co-workers used DDQ/quinine catalysis-promoted oxidative coupling of tetrahydroisoquinoline with α,β-unsaturated γ-butyrolactam to achieve asymmetric CDCs.[4a] Xiao's group reported an unprecedented Ir-catalyzed intramolecular dehydrogenative coupling to construct a C=C bond.[4b] Zhou's group achieved a novel version of the CDC reaction in which diazo compounds were employed as nucleophiles under photoredox catalysts, providing a series of β-amino-α-diazo adducts.[4c] Moreover, some new catalyst systems have been developed to initiate CDC reactions. The CDC reaction between tertiary amines and nitroalkanes was realized by Wu and co-workers under an oxygen atmosphere in water simply by using graphene-supported RuO_2 as the catalyst.[4d] Molecular iodine could also be used to catalyze CDCs in the presence of hydrogen peroxide.[4e] In 2014, Lou et al. employed triphenylcarbenium perchlorate (Ph_3CClO_4) as an efficient oxidant to activate an sp^3 C−H bond adjacent to a nitrogen atom.[4f] Despite the use of different nucleophiles and new catalysts, the development of new types of CDC reactions is still in high demand.

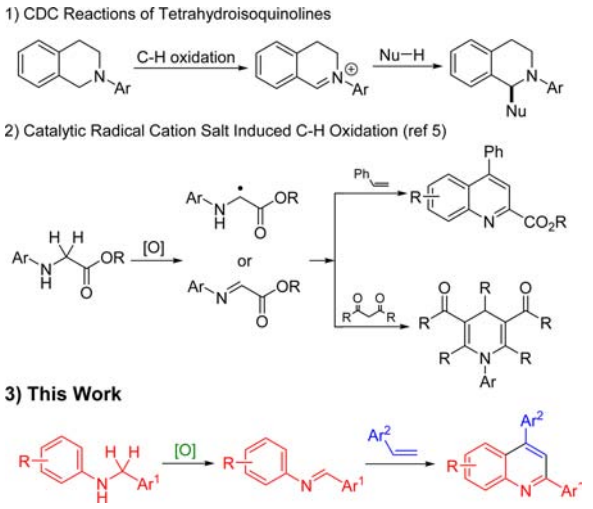


Figure 1. Different variants of CDC reactions.

As part of our ongoing research program,[5] we focused on two aspects: (1) developing new catalysts to achieve catalytic oxidation of sp^3 C−H bonds while avoiding over use of a stoichiometric oxidant and (2) not only constructing new C−C bonds via C−H functionalization but also building useful and important heterocyclic skeletons. On the basis of these goals, we reported in 2012 the first example of C−H activation of an sp^3 C−H bond prompted by catalytic radical cation salts in the presence of O_2, providing a series of quinoline derivatives (Figure 1, reaction 2).[5a] Furthermore, if 1,3-dicarbonyls were used as the acceptor of the generated α-amino radical, 1,4-dihydropyridines (1,4-DHPs) could be constructed through a

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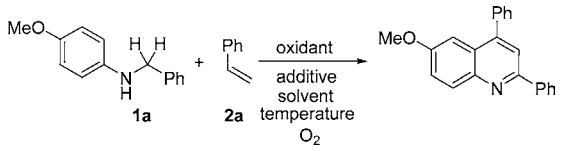
fragment-reassembly process (Figure 1, reaction 2).[5d] Inspired by these results, we questioned whether the sp^3 C−H oxidation of tertiary amines could also be prompted by radical cation salts. Tetrahydroisoquinolines show good reactivity toward C−H functionalization and were studied extensively. However, in most cases, *N*-aryl groups were needed to stabilize the iminium intermediate in which the *N*-aryl group acts as an auxiliary group instead of a functionalized group to participate in CDC reactions. Thus, we wanted to know that if its linear analogues, *N*-benzylanilines, have similar reactivity under oxidative conditions and if an *N*-aryl group can not only be a stabilizer but also participate in a CDC reaction. Therefore, when *N*-benzylaniline was oxidized smoothly, an imine (or iminium) intermediate would be generated, which is a good aza-diene to undergo a Povarov reaction with dienophiles (Figure 1, reaction 3). If our hypothesis is feasible, an oxidative Povarov reaction could be achieved via sp^3 C−H oxidation induced by catalytic radical cation salt to realize the synthesis of quinoline derivatives.

With these ideas in mind, we used the reaction of *N*-benzyl-4-methoxylaniline **1a** with styrene **2a** as a model reaction to test the possibility of an oxidative Povarov reaction (Table 1). As

Table 1. Optimization of Reaction Conditions[a]



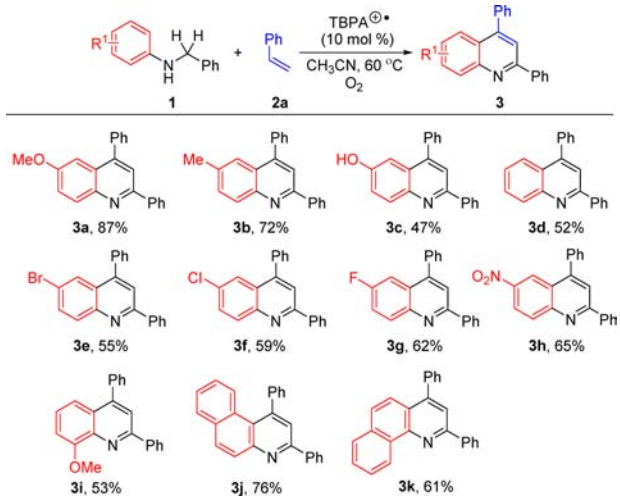
entry	$TBPA^{+\cdot}$ (mol %)	additive (mol %)	solvent	temp (°C)	yield (%)[b]
1	10	$InCl_3$(10)	CH_3CN	60	41
2	20	$InCl_3$(10)	CH_3CN	60	90
3	20[c]	$InCl_3$(10)	CH_3CN	60	39
4	20[d]	$InCl_3$(10)	CH_3CN	60	88
5	**10**	**none**	**CH_3CN**	**60**	**95 (87)**[e]
6	5	none	CH_3CN	60	22
7	2	none	CH_3CN	60	22
8	10	none	CH_2Cl_2	60	NR
9	10	none	$CHCl_3$	60	NR
10	10	none	$ClCH_2CH_2Cl$	60	trace
11	10	none	CH_3CN	80	36
12	10	none	CH_3CN	60	9[f]

[a]Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol) and **2a** (0.15 mmol) in the presence of $TBPA^{+\cdot}$ and anhydrous solvent (1.0 mL) for 72 h. [b]Yield of crude product by 1H NMR using 1,3,5-trimethoxylbenzene as an internal standard. [c]CAN (20 mol %) was added to the reaction solution in the presence of tri(4-bromophenyl)amine (20 mol %). [d]CAN (20 mol %) and tri(4-bromophenyl)amine (20 mol %) were premixed for 15 min then added to the reaction solution. [e]Yield of the isolated product. [f]Reaction was performed under argon.

desired, the 2,4-diarylquinoline product was obtained in 41% yield in the presence of 10 mol % tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+\cdot}$) and 10 mol % $InCl_3$ (entry 1). When 20 mol % $TBPA^{+\cdot}$ was added, the yield was increased to 90% (entry 2). As reported previously, cerium(IV) ammonium nitrate (CAN) can also trigger aerobic oxidation in the presence of catalytic tris(4-bromophenyl)aminium (TBPA),[5e] in which the TBPA radical cation was generated in situ. We tried this catalyst system in two ways: If CAN was added to the reaction solution in the presence of 20 mol % TBPA, 39% yield was obtained (entry 3). When TBPA and CAN were premixed, a characteristic dark blue solution was afforded, indicating the formation of the corresponding radical cation. Then, when the blue solution was added dropwise to a mixture of **1a** and **2a**, the quinoline product was afforded in 88% yield (entry 4), which suggested generation of the radical cation was crucial to prompt efficient transformation. Because $TBPA^{+\cdot}$ can efficiently induce a Povarov reaction between imines and alkenes,[6] we tried the reaction in the absence of $InCl_3$. The oxidative Povarov reaction occurred smoothly, giving **3a** in excellent yield (entry 5). Further optimization of the conditions showed that the reaction was significantly affected by catalyst loading and diminished yields were obtained (entries 6 and 7). Next, a solvent screen revealed that halogenated solvents were deleterious to this reaction (entries 8−10). Higher temperature resulted in complicated products, and the desired product was given in lower yield (entry 11). To test the role of dioxygen, the reaction was conducted under argon atmosphere, but only 9% yield was obtained by crude product ^1H NMR. This result implied that O_2 was pivotal to oxidation of the sp^3 C−H bond.

Under the optimized reaction conditions, we then investigated scopes of the oxidative Povarov reaction by using various *N*-arylbenzylamines and styrenes. We first examined the substituent effect on the benzene ring connected to the nitrogen atom in the *N*-arylbenzylamines (Scheme 1). The

Scheme 1. Reaction of *N*-Benzylanilines with Styrene[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), $TBPA^{+\cdot}$ (10 mol %), MeCN (2 mL), 60 °C under O_2 for 24 h, isolated yield.

substrates bearing electron-donating groups, such as 4-methoxyl and 4-methyl, underwent smooth reactions with styrene and afforded the desired products **3a** and **3b**, respectively, in good yields (87 and 72%, respectively), probably due to their higher electron-donating ability to stabilize the electron-poor intermediate. A free phenolic hydroxyl group could be tolerated under the oxidative conditions, resulting in the corresponding product **3c** in 47% yield. Unsubstituted aniline also shows good reactivity (**3d**), and no coupling product on the *p*-position of aniline was isolated. Introduction of an electron-withdrawing group, such as 4-bromo, 4-chloro, 4-floro, and 4-nitro led to the desired products **3e−3h** in marginally reduced yields (55−65%). We were pleased to find that the substrate with the strong electron-withdrawing group, the nitro group, could also undergo an

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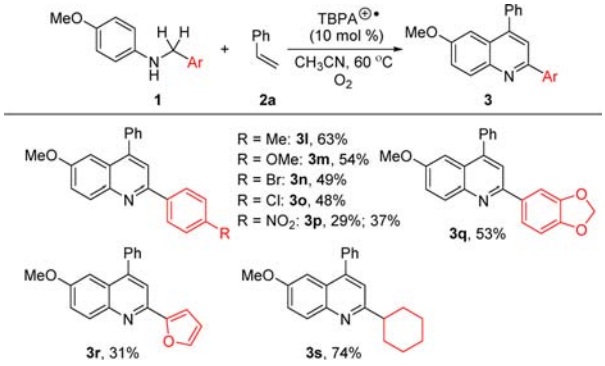
oxidative Povarov reaction with styrene, resulting in the quinoline product in acceptable yield (**3h**). In another case, when 1- and 2-naphthylamine were used, a benzoquinoline skeleton can be formed in good yields (**3j** and **3k**, respectively).

Next, different benzyl groups were varied to evaluate the effect of a substituent on the benzyl group (Scheme 2). In general, electron-donating groups gave higher yields of the desired products due to higher stability of the radical intermediate (**3l**, **3m**, and **3q**). When electron-withdrawing groups, such as 4-bromo and 4-chloro, were connected under Ar, the oxidative Povarov reaction was less efficient, providing the quinoline products in lower yields (**3n** and **3o**). The nitro group exerts a negative effect, and the yield of **3p** was decreased to 29% together with isolation of 4-nitrobenzaldehyde in 37% yield. The formation of 4-nitrobenzaldehyde was attributed to oxidation of *N*-benzylaniline to imine followed by hydrolysis. This byproduct also supported the Povarov reaction pathway. The furan-derived substrate is also applicable; however, a low yield was obtained (**3r**). Notably, radical cation-prompted aerobic oxidation can also be applied to oxidation of *N*-alkylaniline, yielding the Povarov product **3s** in 74% yield.

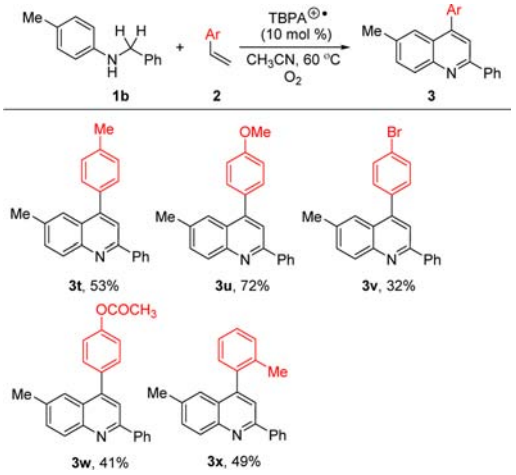
To further demonstrate the scope of the reaction, we extended the present protocol to substituted styrenes, and the results are compiled in Scheme 3. Overall, electron-rich styrenes gave better results than electron-poor ones, which supports the participation of an electron-deficient intermediate (**3t**−**3w**). 2-Methylstyrene shows slightly lower reactivity than 4-methylstyrene, giving the quinoline product **3x** in 49% yield. To avoid terminated aromatization, we employed α-methylstyrene as a dienphile to test if 1,2,3,4-tetrahydroquinoline could be obtained (Scheme 4). To our great surprise, the reaction was inefficient, and a novel product **5** was isolated in 19% yield together with some unidentified products. A plausible pathway to rationalize the formation of product **5** is that α-methylstyrene first reacted with the generated imine, and a 1,2,3,4-tetrahydroquinoline intermediate was generated, but was followed by further oxidation to imine **A**. Under the aerobic oxidation conditions, α-hydrogen of imine **A** was oxidized, and a radical intermediate was formed, which was trapped by dioxygen. Finally, the generated peroxide underwent elimination of water, leading to product **5**. The poor yield of **5** suggests that aromatization might be an important driving force for terminating the reaction.

Scheme 2. Reaction of *N*-Benzyl-4-methoxylanilines with Styrene[a]



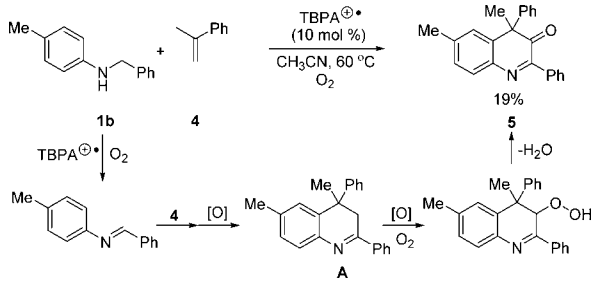
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), $TBPA^{+\cdot}$ (10 mol %), MeCN (2 mL), 60 °C under O_2 for 24 h, isolated yield

Scheme 3. Reaction of *N*-Benzyl-4-methylanilines with Substituted Styrenes[a]



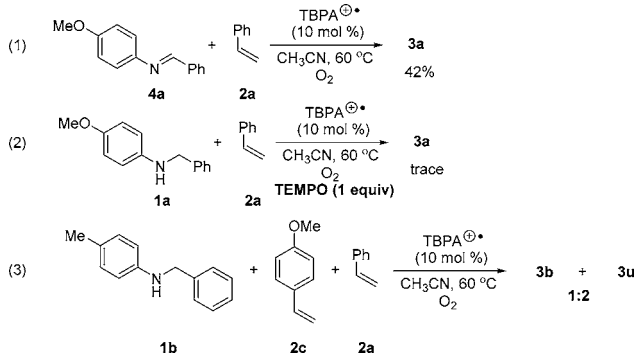
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), $TBPA^{+\cdot}$ (10 mol %), MeCN (2 mL), 60 °C under O_2 for 24 h, isolated yield.

Scheme 4. Reaction of *N*-Benzyl-4-methylanilines with α-Methylstyrene



To illuminate the reaction mechanism, we performed several control experiments (Scheme 5). The reaction between imine and styrene was conducted under the standard reaction conditions, and the quinoline product was isolated in 42% yield (Scheme 5, reaction 1). This result suggested that an imine might be the intermediate involved in the oxidative Povarov reaction. The lower yield compared to that of the reaction of **1a** and **2a** was due to the decomposition of imine, which is in high concentration under the radical cation-induced condition.[6a] In the presence of one equiv of the radical inhibitor TEMPO, the reaction was completely inhibited (Scheme 5, reaction 2). A competition reaction was performed between **2a**

Scheme 5. Control Experiments



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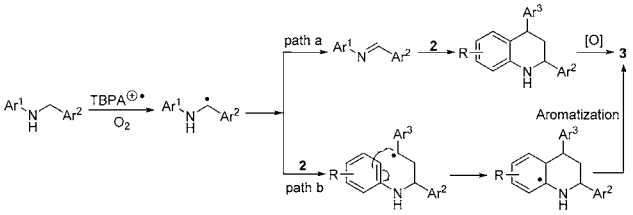
and **2c**. From the crude product ^{1}H NMR, the ratio of the product mixture is ~1:2. This result supports the idea that an electron-deficient intermediate is involved in the reaction, and an electron-rich dienophile is more reactive in the process of Povarov cyclization.

On the basis of the experimental results and literature reports, a radical intermediate-mediated mechanism was proposed (Scheme 6). The *N*-benzylaniline was oxidized by

Scheme 6. Proposed Mechanism of a Radical Cation-Prompted Oxidative Povarov Reaction



the radical cation salt TBPA$^{+\cdot}$ in the presence of dioxygen, yielding a radical intermediate, which was oxidized to the corresponding imine (Scheme 6, path a). Then, a TBPA$^{+\cdot}$-induced Povarov reaction occurred, resulting in the formation of 1,2,3,4-tetrahydroquinoline. After further aromatization, the desired quinoline product was generated. However, another pathway might also be possible (Scheme 6, path b). The radical intermediate adds to the double bond of styrene directly, followed by radical addition to the phenyl group. After further oxidation and aromatization, the quinoline derivative was afforded. At this stage, one of these two pathways cannot fully be ruled out.

In conclusion, we demonstrated an efficient sp^3 C–H oxidation of *N*-benzylaniline derivatives under aerobic conditions prompted by a catalytic radical cation salt. This method provides a new way of conducting CDC reactions to achieve not only C–C bond formation but also construction of useful quinoline skeletons. Further applications of this reaction and synthesis of heterocycles are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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