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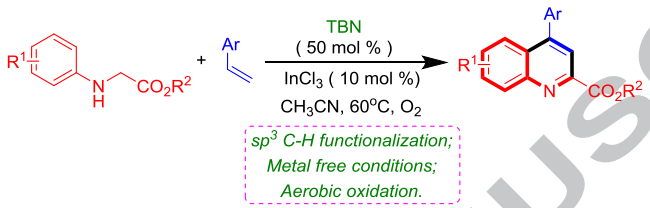

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ABSTRACT

As a metal-free reagent, *tert*-butylnitrite (TBN) initiated aerobic sp^3 C-H bond oxidation of glycine esters was achieved, providing a series of quinoline-2-carboxylates in good yields. The mechanistic investigation revealed that in the presence of molecular oxygen, TBN derived radicals were involved in the C-H bond oxidation and the terminal aromatization.

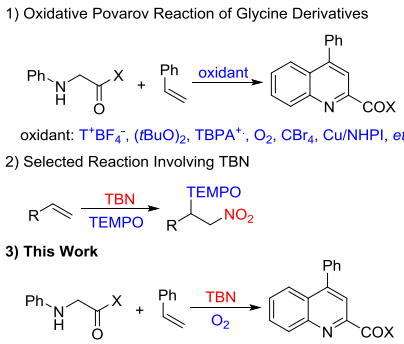
Recently, with the development of activation of inert chemical bonds, such as C−C, [1] C−N [2] and C−O [3] bonds, C-H bond activation has become one of the hottest topic in organic chemistry, and numerous methods were established for the synthesis of complex molecules from readily accessible starting materials. [4] Besides sp^2 and sp C-H bond activation, the direct sp^3 C-H bond functionalization might be one of the most challenging and exciting goals. In particular, the oxidative functionalization of glycine derivatives has attracted considerable attention for the construction of structurally diverse □-amino acids and related derivatives. [5, 6, 7]

In 2008, the first example of direct sp^3 C-H functionalization of glycine esters with alkynes was reported by Li and co-workers, in which Cu(I) was employed in the presence of TBHP as the stoichiometric oxidant. [5a] Since then, various nucleophiles were applied to this reaction, such as carbonyl compounds, [5b-c] indoles, [5d-j] β-keto esters, [5a, k-l] arylboronic acids, [5n, 6c] methylquinolines [5m] and so on. Beyond the development of nucleophiles, a large number of oxidation systems were established to promote this direct functionalization of glycine derivatives, in which the TBHP/metal catalyst system was widely employed. [5a-c, e,] Albeit this catalyst system exhibited wide applicability and high reaction efficiency, some shortcomings inevitably exist. For example, in some cases, the C-H functionalization of glycine amides occurred smoothly, while the corresponding analogues, glycine esters, were not compatible. More importantly, the over use of a stoichiometric amount of TBHP, an explosive peroxide, might cause serious security issues, especially in large amount.

To solve this problem, milder and greener oxidants were discovered by several research groups. [5d, f-j, l, m] Mancheño's group reported an oxidative Povarov reaction of glycine derivatives, using $T^+BF_4^-$ (2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate) as the stoichiometric oxidant, constructing quinoline-2-carboxylate skeleton in high efficiency (Figure 1, eq 1). [6a-b] This oxidant exhibited good functional group tolerance, and could also be applied to arylation of glycine derivatives in the presence of arylboronic acids. [5n] However, $T^+BF_4^-$ is not commercially available, and needs prepreparation. In the search of commercially available catalysts, Liu and co-workers reported that N-hydroxyphthalimide (NHPI) could also initiate this oxidative Povarov reaction in the presence of copper and molecular oxygen. [6c] Since 2012, we developed a new catalyst system to initiate the reaction between glycine derivatives and styrenes, in which a catalytic amount of triarylamine radical cation salt was employed to promote the aerobic oxidation of glycines. [6d-h] This catalyst can initiate various sp^3 C-H bond functionalization, and exhibited broad functional group tolerance. However, only one triarylamine radical cation salt is commercially available (tris(4-bromophenyl)aminium hexachloroantimonate, $TBPA^{+\cdot}$), and preparation of other analogues needs $SbCl_6$, [7] which is hygroscopic and toxic. Based on the economical and environmental issues, the development of more convenient, efficient, and general oxidants is still highly desirable in the direct transformations of glycine derivatives. As part of our continuous interests on direct transformation of C-H bond, the use of molecular oxygen as a clean source of oxidant was focused on. Since oxygen itself does not oxidize glycines effectively, the help of an appropriate catalyst to promote the aerobic oxidation is

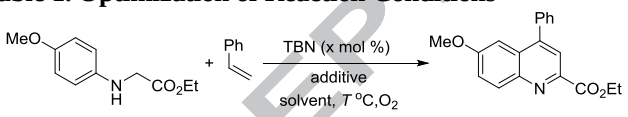
generally necessary. Consequently, we hope to find a new catalyst system to activate dioxygen, achieving more valuable transformations.

Figure 1. Design for TBN-initiated Functionalization of Glycines.



As a metal-free reagent, TBN (*tert*-butyl nitrite) is inexpensive and commercially available, possesses good solubility in common solvents, and is widely applied to organic synthesis. Generally, it acts as a surrogate of nitric oxide (NO) and nitrous acid to participate in nitrosation reactions. [8] In the presence of molecular oxygen, it can also be used as a nitration reagent, avoiding the use of high acidic and oxidizing reagents, nitric acid. [9] Recently, several difunctionalization of C=C unsaturated bond was achieved by TBN/TEMPO catalyst system (Figure 1, eq 2). [10] Albeit a great innovation, the report using TBN as an oxidant remains rare. [11] Among these elegant reactions, the reaction between TBN and dioxygen attracted our attention. There is ample evidence that TBN can react with molecular oxygen, giving the peroxynitrite and tert-butoxyl radical smoothly, [9b-e] and these oxidizing radicals could probably act as single electron oxidant and radical initiator. So we questioned whether TBN/O_2 could act as a new catalyst system to initiate sp^3 C-H bond functionalization of glycine derivatives. Herein, we report a practical oxidative Povarov reaction using commercially available TBN and molecular oxygen as oxidant (Figure 1, eq 3).

Table 1. Optimization of Reaction Conditions [a]



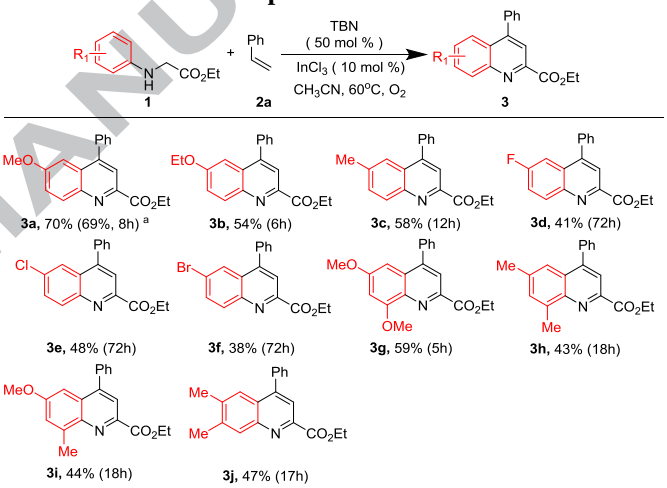
1a 2a 3a

Entry	TBN (mol %)	Additive (10 mol %)	Solvent	Yield (%) [b]
1	20	none	MeCN	36
2	30	none	MeCN	52
3	50	none	MeCN	67
4	100	none	MeCN	55
5	150	none	MeCN	55
6	50	none	DCE	21
7	50	none	$CHCl_3$	40
8	50	none	DCM	17
9	50	$InCl_3$	MeCN	75
10	50	$BF_3{\cdot}OEt_2$	MeCN	68
11	50	$InCl_3$	MeCN	41 [c]
12	50	$InCl_3$	MeCN	25 [d]
13	50	$InCl_3$	MeCN	45 [e]
14	0	$InCl_3$	MeCN	trace [f]

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.1 mmol), **2a** (0.2 mmol) in the presence of TBN, and anhydrous solvent (1.0 mL). [b] Determined by crude products1H NMR, using 1,3,5-trimethoxylbenzene as the internal standard; [c] At 40 °C; [d] At room temperature; [e] At 80 °C; f In the absence of TBN.

To test the possibility of TBN initiated aerobic oxidation of glycine derivatives, we commenced our studies by attempting the glycine ester **1a** with styrene **2a** under different reaction conditions, and the results were compiled in Table 1. Fortunately, in the presence of 20 mol % TBN under molecular oxygen atmosphere, the expected reaction occurred smoothly, yielding the desired quinoline **3a** in 36% yield (entry 1). Increasing the amount of TBN lead to higher yields (entries 2-5), and 50 mol % TBN gave the best result (entry 3). Then the solvent screen were performed (entries 6-8), and MeCN was identified as the optimal choice (entry 3). Lewis acid additives proved to be beneficial to improve the reaction efficiency, providing the desired product in 75% yield (entry 9). Evaluation of the reaction temperature revealed that increasing and decreasing the temperature reduced the yields (entries 11-13). It is worth noting that in the absence of TBN, only trace amount of the quinoline product was detected (entry 14), implying that dioxygen could not effectively initiate this sp^3 C-H bond oxidation.

Scheme 1. Reaction Scope of Anilines



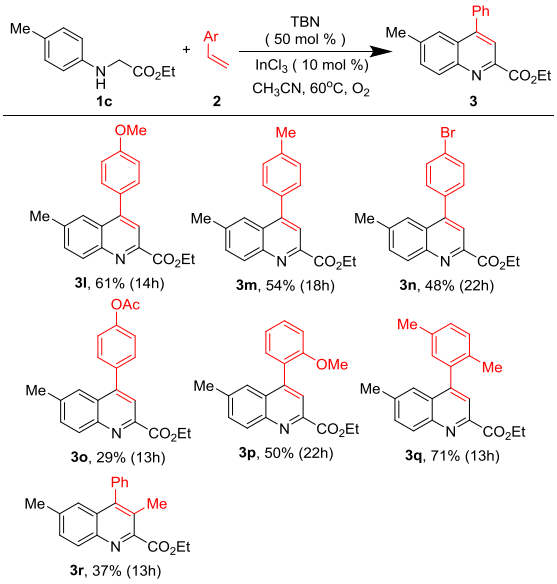
[a] The yield in the parentheses is obtained in 10 mmol scale.

With the best reaction conditions established, the reaction scope was then investigated. The substituents on aniline was firstly varied to evaluate the reaction generality, and the results are displayed in Scheme 1. Both electron-donating methoxy and ethoxy groups gave the corresponding products **3a** and **3b** in good yields. Electron-withdrawing groups, such as 4-F, 4-Cl, and 4-Br, slightly decreased the reaction efficiency, offering the desired quinoline-2-carboxylates in 41%, 48%, and 38% yield, respectively. The 2,4-disubstituted substrates with higher steric hindrance did not exert negative effect on this oxidative Povarov reaction, giving the desired products in comparable yields (**3g-3i**). When 3,4-dimethylaniline derived glycine ester was involved, the cyclization occurred selectively on the ortho-position (**3j**), probably due to the steric reasons. To test the practical application of this catalyst system, the reaction of **1a** was performed on 10 mmol scale, and the desired **3a** was obtained in 69% yield, suggesting potential in industrial applications.

Next, the scope of this reaction was extended to various styrenes, which reacted smoothly in the standard conditions (Scheme 2). Styrenes with electron-donating groups, such as OMe, Me, gave higher yields than electron-withdrawing groups (**3l** to **3n**). The acetoxyl group could also be tolerated, providing the corresponding quinoline **3o** in lower yield. Styrenes with ortho-groups did not decrease the reaction efficiency, and the desired products **3p** and **3q** were isolated in 50% and 71% yields,

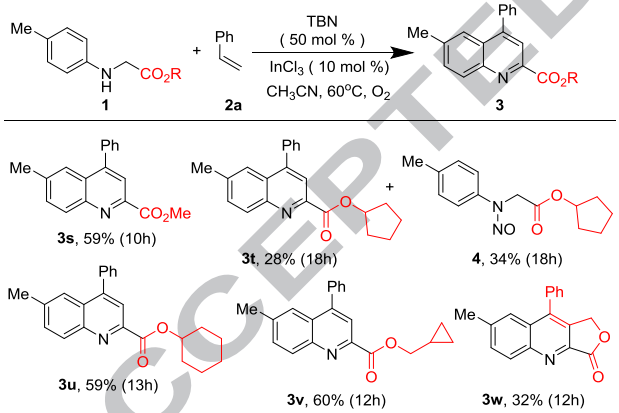
respectively. When β-methylstyrene was employed, the highly substituted quinoline **3r** were obtained in 37% yield.

Scheme 2. Reaction Scope of Styrenes



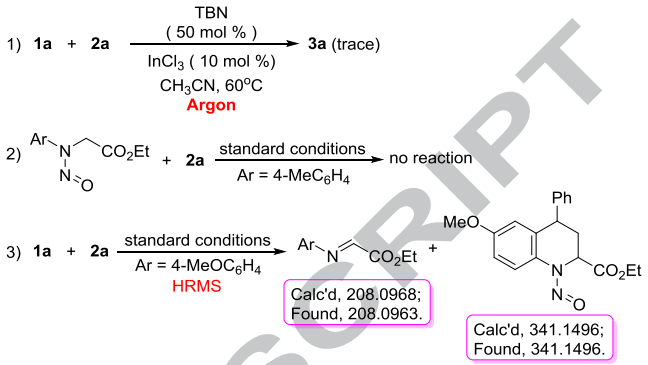
Furthermore, glycine derivatives with various ester groups were also compatible in this reaction (Scheme 3), and in the presence of sensitive cyclopropyl ring, the reaction efficiency did not decrease, generating the expected product **3v** in good yield. When cyclopentyl ester existed, the quinoline **3t** was obtained in lower yield, together with isolation of 34% *N*-nitroso glycine ester. The intramolecular oxidative Povarov reaction was also tested, and the desired quinoline-fused lactone **3w** was obtained in 32% yield.

Scheme 3. Reaction Scope of Esters



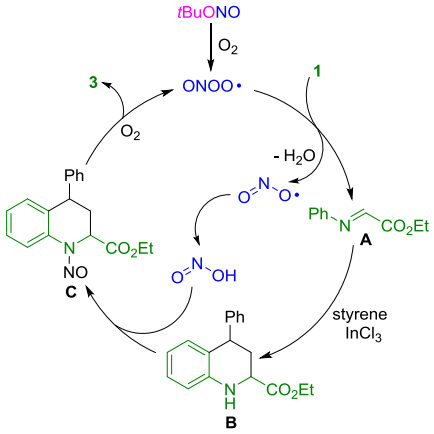
To probe the reaction mechanism, several control experiments were carried out under the standard conditions (Scheme 4). In the absence of molecular oxygen, only trace amount of the product **3a** was detected, implying that dioxygen is crucial to initiate this reaction, and TBN derived peroxynitrite and *tert*-butoxyl radical, whose generation is supported by literatures, [9-10] might be involved in the C-H bond oxidation step. Since secondary amines can readily be transformed to *N*-nitrosoamines in the presence of TBN/O_2, the reaction of *N*-nitrosoglycine ester was tested under the standard reaction conditions. However, no reaction occurred, which ruled out the participation of N-nitrosoglycine ester as the reaction intermediate. To detect the active intermediate and gain more information of the mechanism, a HRMS experiment of the reaction mixture was performed. To our delight, a glycine imine intermediate at m/z 208.0963 (calcd for $C_{11}H_{13}NO_3$ + H^+, 208.0968) was detected, verifying that the glycine ester was oxidized by TBN/O_2, followed by InCl3 catalyzed Povarov cyclization. Furthermore, a N-nitrosotetrahydroquinoline intermediate (calcd for $C_{19}H_{20}N_2O_4$ + H^+, 341.1496; found, 341.1496) was also detected. This intermediate, which was derived from *N*-nitrosation of the corresponding tetrahydroquinoline, might be involved in the aromatization process, providing the quinoline product.

Scheme 4. Control Experiments



Although the exact mechanism remains obscure, a possible reaction pathway was proposed for this TBN/O_2 initiated C-H bond functionalization of glycine esters, based on experimental evidence and literature precedent (Scheme 5). [9-10] Initially, a peroxynitrite radical was formed by aerobic cleavage of the N-O bond of TBN. Then, the glycine ester was oxidized by this peroxynitrite radical, generating an imine intermediate **A**. [12] In the presence of Lewis acid $InCl_3$, a classical Povarov cyclization occurred, affording the tetrahydroquinoline intermedaite **B**. After the subsequent *N*-nitrosation, a N-nitrosotetrahydroquinoline **C** was formed. Through further aerobic aromatization, the desired quinoline **3** was yielded together with the regeneration of the peroxynitrite radical closing the catalytic cycle.

Scheme 5. Proposed Mechanism



In summary, we developed a new catalyst system to achieve the oxidative Povarov reaction of glycine esters, in which TBN as an efficient organic catalyst exhibits good reactivity. A series of quinoline-2-carboxylates were synthesized with good functional group tolerance. Compared with the reported methods to functionalize glycines, this reaction is featured by accessible catalyst system, good efficiency, and transition metal free conditions. More importantly, this work revealed that TBN can not only be widely applied to tranditional nitrosation and nitration reactions, but also be used as an efficient organic oxidant to initiate the aerobic oxidation of C-H bond. Further applications and more variants of TBN initiated reaction are still underway in our laboratory.

Acknowledgments

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12. According to one reviewer's suggestion, the glycine ester might be oxidized to imine by *tert*-butoxyl radical generated from TBN, followed by the Povarov reaction.

Supplementary Material

Copies of all ^{1}H NMR and ^{13}C NMR spectra of the products.

1. TBN (*tert*-butyl nitrite) as commercially available and green oxidant.
2. Aerobic sp^3 C-H oxidation of glycine esters under metal-free conditions.
3. Efficient synthesis of quinoline-2-carboxylate esters.