ORGANIC LETTERS

2012
Vol. 14, No. 15
4030–4033

Catalytic Radical Cation Salt Induced C_{sp^3}—H Functionalization of Glycine Derivatives: Synthesis of Substituted Quinolines

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Received July 10, 2012

ABSTRACT

A domino C_{sp^3}—H functionalization of glycine derivatives was achieved under catalytic radical cation salt induced conditions, producing a series of quinolines. The proposed mechanism shows that a peroxyl radical cation, which is generated by the coupling between O_2 and TBPA$^{+•}$, might be involved to initiate the catalytic oxidation.

Because of their ubiquity in organic compounds, the functionalization of C—H bonds has become an important synthetic strategy that allows the synthesis of useful compounds.[1] In recent years, cross-dehydrogenative coupling (CDC) has emerged as an attractive and challenging method in organic synthesis, and great progress has been achieved in this area.[2,3] Generally, one of the drawbacks of CDC reactions is that excess quantities of the oxidants are needed, which increases the amount of organic or inorganic byproducts, thus increasing the environmental impact as a result. An attractive alternative is the use of molecular oxygen as the terminal oxidant in CDC reactions, which leads to concomitant water loss. However, examples are still rare.[4]

It is known that triarylphosphine radical cations, which were generated in the ground or excited state,[5] can undergo radical coupling with O_2, producing a peroxyl radical cation.[5e,f] However, research related to the reaction between their analogues, triarylaminium radical cations, and O_2 remains rare, even if their persistent and isolable radical cation salts have been prepared over a centenary ago.[6] Based on our continuous interest in radical cation

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(1) For reviews, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(2) For reviews, see: (a) Li, C.-J. *Acc. Chem. Res.* **2008**, *42*, 335. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Scheuermann, C. J. *Chem.—Asian J.* **2010**, *5*, 436.

(3) Recent developments on CDC reactions: (a) Chandrasekharam, M.; Chiranjeevi, B.; Gupta, K. S. V.; Sridhar, B. *J. Org. Chem.* **2011**, *76*, 10229. (b) Park, S. J.; Price, J. R.; Todd, M. H. *J. Org. Chem.* **2012**, *77*, 949. (c) Zhao, M.; Wang, F.; Li, X. *Org. Lett.* **2012**, *14*, 1412. (d) Wang, P.; Rao, H.; Hua, R.; Li, C.-J. *Org. Lett.* **2012**, *14*, 902. (e) Correiaa, C. A.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1446. (f) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (g) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181.

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(5) (a) Yasui, S.; Shioji, K.; Ohno, A. *Tetrahedron Lett.* **1994**, *35*, 2695. (b) Nakamura, M.; Miki, M.; Majima, T. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1447. (c) Shioji, K.; Ohno, A.; Yoshihara, M. *J. Org. Chem.* **1995**, *60*, 2099. (d) Pandey, G.; Hajra, S.; Ghorai, M. K. *Tetrahedron Lett.* **1994**, *35*, 7837. (e) Yasui, S.; Tojo, S.; Majima, T. *J. Org. Chem.* **2005**, *70*, 1276. (f) Tojo, S.; Yasui, S.; Fujitsuka, M.; Majima, T. *J. Org. Chem.* **2006**, *71*, 8227.

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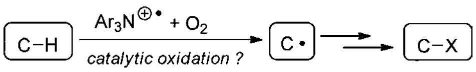
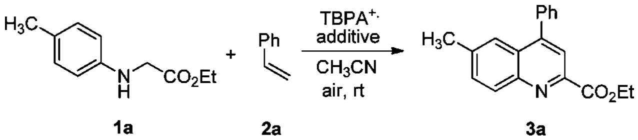


Figure 1. Radical cation salt initiated C–H functionalization.

chemistry,[7] we found that a commercially available persistent radical cation salt, tris(4-bromophenyl)aminium hexachloroantimonate (TBPA$^{+\bullet}$), is stable in the solid state but will be decomposed after 3 h in CH_3CN under an O_2 atmosphere.[8] This finding implies the coupling between O_2 and TBPA$^{+\bullet}$ would be possible. We wondered if such a peroxyl radical cation could react with a substrate to achieve C–H functionalization reactions, especially in a catalytic way (Figure 1). If our hypothesis is feasible, we will find a new class of catalyst to achieve CDC reactions.

With this idea in mind, we decided to test the reaction between glycine derivative **1a** and styrene **2a**, which has been achieved by the Mancheño and Hu group using an excess amount of TEMPO oxoammonium salt and di-*tert*-butylperoxide as oxidants, respectively.[9] We first examined the reaction of **1a** and **2a** using 1 equiv of TBPA$^{+\bullet}$. To our delight, **1a** was consumed only after 6 h, and the product **3a** was produced in 47% yield (Table 1, entry 1). A comparable yield was obtained (entry 2), when 5 mol % TBPA$^{+\bullet}$ was used, which implied catalytic oxidation prompted by a radical cation salt is feasible. These encouraging results prompted us to optimize the reaction conditions further (see Supporting Information).

Table 1. Optimization of Reaction Conditions



entry	TBPA$^{+\bullet}$ (mmol %)	additives	time (h)	yield (%)[a]
1	100	none	6	47
2	5	none	6	40
3	10	none	6	64
4	20	none	6	61
5	1	none	12	21
6	10	$FeCl_3$[b]	6	47
7	10	$BF_3\cdot Et_2O$[b]	6	42
8	**10**	**$InCl_3$**[b]	**6**	**90**
9	10	$InCl_3$[b]	24	<5%[c]

[a] Determined ^1H NMR analysis of the crude reaction mixture. [b] 10 mmol % Lewis acid added. [c] After stirring under argon for 24 h, the reaction solution was exposed to open air and an 82% yield of the desired product was obtained.

We first evaluated the catalyst loading. The best yield was obtained in the presence of 10 mol % TBPA$^{+\bullet}$ (entry 3). Reducing the catalyst loading to 1 mol % led to a remarkable decrease in the yield (entries 5), but a higher catalyst loading did not improve the yield (entry 4). Besides the desired product, some undesired byproducts were also generated.[10] Lewis acids were added to accelerate the Povarov reaction between styrene and glycine imine.[11] $FeCl_3$ and $BF_3\cdot Et_2O$ were ineffective, and mostly starting material was recovered in both cases, despite the side reaction being inhibited. The reaction was enhanced by the addition of 10% $InCl_3$, and the yield was increased to 90%. To confirm the participation of O_2, the reaction was performed under argon, and only a trace amount of product was detected by ^1H NMR analysis of the crude reaction mixture. Interestingly, after the solution was stirred for 24 h under argon and then exposed to air, the reaction occurred, giving the desired product in 82% yield, which suggests that O_2 is crucial in this reaction.

We subsequently studied the scope under optimal reaction conditions (Table 2). The experiments showed that electron-rich styrenes gave higher yields of the desired quinolines than electron-deficient styrenes. For example, **1a** reacted smoothly with both 4-methylstyrene and 4-methoxystyrene to give the quinoline products in 93% isolated yield in both cases, respectively (entries 2–3), while the use of 4-fluoro- or 4-chlorostyrene provided the corresponding quinolines in 67 and 79% isolated yield, respectively (entries 6–7). Steric hindrance also has a deleterious effect on reaction efficiency, as β- methylstyrene reacted to form the desired product in 50% yield (entry 4). Alkynes can also serve as dienophiles to participate in this reaction, but the yields are lower (entries 1–4). When indene was used in this reaction, a polycyclic quinoline was obtained in 82% yield (entry 8). Next, a variety of substituted glycines **1** was applied in the reaction with **2a**. The reactions of electron-rich glycine derivatives occurred smoothly, but electron-withdrawing groups make the reaction slower even in an O_2 atmosphere due to the lower stability of the iminium ion intermediate (entries 9–14). Free hydroxyl groups were also well tolerated, affording the desired product in 71% yield (entry 14).

We next turned our focus toward testing the intramolecular variant of this reaction. To our delight, the intramolecular reaction occurred smoothly even in the absence of $InCl_3$,

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(6) (a) Wurster, C.; Sendtner, R. *Ber.* **1879**, *12*, 1803. (b) Wurster, C. *Ber.* **1879**, *12*, 2071. (c) Wieland, H. *Ber.* **1907**, *40*, 426.

(7) (a) Jia, X.-D.; Wang, X.-E.; Yang, C.-X.; Huo, C.-D.; Wang, W.-J.; Ren, Y.; Wang, X.-C. *Org. Lett.* **2010**, *12*, 732. (b) Jia, X.-D.; Ren, Y.; Huo, C.-D.; Wang, W.-J.; Chen, X.-N.; Wang, X.-C. *Chin. Chem. Lett.* **2011**, *22*, 671. (c) Jia, X.-D.; Ren, Y.; Huo, C.-D.; Wang, W.-J.; Chen, X.-N.; Xu, X.-L.; Wang, X.-C. *Tetrahedron Lett.* **2010**, *51*, 6779. (d) Jia, X.-D.; Han, B.; Zhang, W.; Jin, X.; Yang, L.; Liu, Z.-L. *Synthesis* **2006**, 2831. (e) Jia, X.-D.; Lin, H.-C.; Huo, C.-D.; Wei, Z.; Lu, J.-M.; Yang, L.; Zhao, G.-Y.; Liu, Z.-L. *Synlett* **2003**, 1707.

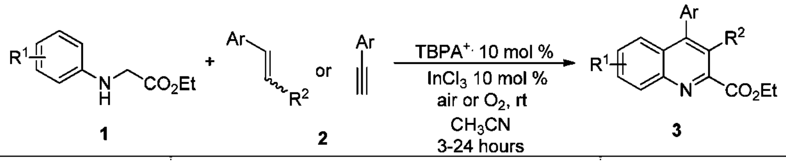
(8) The characteristic blue color of TBPA$^{+\bullet}$ will fade after 1 h, giving a brown solution. After 3 h, it will turn to a bright yellow solution.

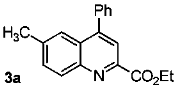
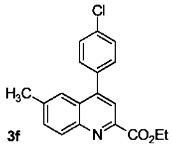
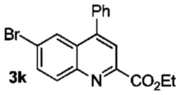
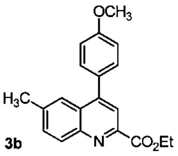
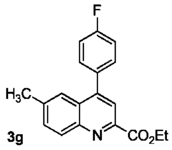
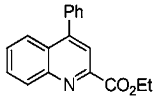
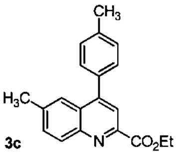
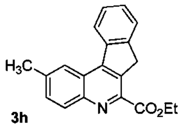
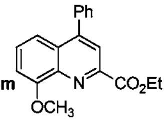
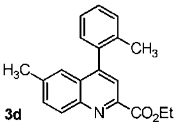
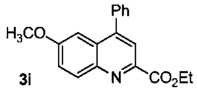
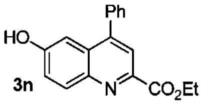
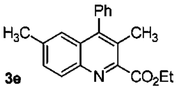
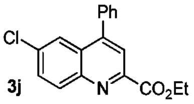
(9) (a) Richter, H.; Mancheño, O. G. *Org. Lett.* **2011**, *13*, 6066. (b) Liu, P.; Wang, Z.; Lin, J.; Hu, X. *Eur. J. Org. Chem.* **2012**, 1583.

(10) We found that, in the absence of styrene, the same byproducts were also produced, but if 10 mol % $InCl_3$ was added, these byproducts could not be detected. So $InCl_3$ may be just an inhibitor of the side reaction. Further investigation is underway in our laboratory.

(11) Review of Povarov reaction catalyzed by Lewis acid in synthesis of quinoline: Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721.

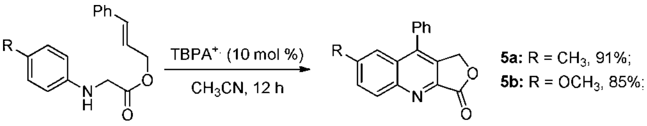
Table 2. Scope of Catalytic TBPA$^{+\bullet}$ Prompted C–H Functionalization[a]



entry	product	yield (%)	entry	product	yield (%)	entry	product	yield (%)
1	 **3a**	89%; 50%[b]	6	 **3f**	79%[c]	11	 **3k**	75%[c]
2	 **3b**	93%; 65%[b]	7	 **3g**	67%[c]	12	 **3l**	54%
3	 **3c**	93%; 61%[b]	8	 **3h**	82%[c]	13	 **3m**	35%
4	 **3d**	50%[b]	9	 **3i**	71%	14	 **3n**	71%
5	 **3e**	58%[c]	10	 **3j**	83%[c]			

[a] Reaction condition: substrate **1** (0.5 mmol), styrene **2** (1.25 mmol), $InCl_3$ (10 mol %), and TBPA$^{+\bullet}$ (10 mol %) in 5 mL of CH_3CN, under an atmosphere of air. All the yields are isolated yields. [b] Alkynes were used as dienophiles. [c] Under 1 atm of O_2 and 60 °C.

Scheme 1. Intramolecular Reaction Induced by Catalytic TBPA$^{+\bullet}$

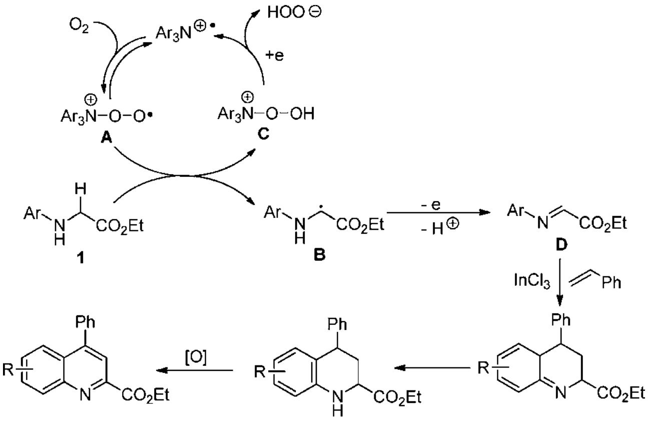


5a: R = CH_3, 91%;
5b: R = OCH_3, 85%;

giving the products in high yield (85–91%), where two rings and two C–C bonds were formed in a single step (Scheme 1). This intramolecular reaction may potentially open up a new synthetic route toward constructing the skeleton of *uncialamycin*, a new class of enediyne natural product.[12]

The key step of this chemistry is the formation of glycine imine (or iminium ion), which can smoothly add to styrenes to yield Povarov adducts.[11] We propose a possible mechanism to rationalize the formation of product, albeit the mechanism remains unclear (Scheme 2). First, oxygen couples with TBPA$^{+\bullet}$ in a reversible way, giving a peroxy

Scheme 2. Proposed Mechanism



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(12) (a) Davies, J.; Wang, H.; Taylor, T.; Warabi, K.; Huang, X. –H.; Andersen, R. J. *Org. Lett.* **2005**, *7*, 5233. (b) Desrat, S.; van de Weghe, P. *J. Org. Chem.* **2009**, *74*, 6728.

radical cation **A**, which abstracts a hydrogen atom from **1** to afford a free radical **B** stabilized by the adjacent nitrogen atom. After fragmentation of the peroxide intermediate **C**, $TBPA^{+\bullet}$ is regenerated to participate in the catalytic cycle. We also tried the reaction in the presence of 2 equiv of hydrogen peroxide, but the starting materials remained unchanged after stirring for 24 h, and no product was isolated, which implied that peroxides could not be the terminal oxidant. More details of the mechanism are currently under investigation.

In summary, we have developed a novel radical cation salt C–H functionalization of glycine derivatives, in which oxygen serves as the terminal oxidant. The proposed mechanism involves a triarylaminium radical cation, which can react with O_2 to induce C–H functionalization/oxidation reactions. We are currently focusing on applying this catalyst to other C–H functionalization reactions and further exploring the applications in the construction of more variable compounds. Further mechanistic studies of this reaction are also underway in this laboratory.

Acknowledgment. We thank NSFC (21002079) and Project 20096203120002 supported by the Ministry of Education of the People's Republic of China. We also thank the third Knowledge and Technological Innovation Project (NWNU-KJCXGC-03-75 and NWNU-KJCXGC-03-64) of Northwest Normal University for supporting our research.

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

The authors declare no competing financial interest.