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Iodine-Mediated Intramolecular Electrophilic Aromatic Cyclization in Allylamines: A General Route to Synthesis of Quinolines, Pyrazolo[4,3-*b*]pyridines, and Thieno[3,2-*b*]pyridines

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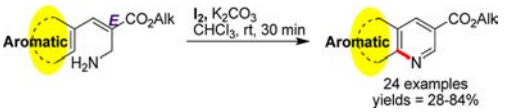
ABSTRACT



An unprecedented synthesis of aromatic ring annulated pyridines from suitably substituted primary allylamines via intramolecular electrophilic aromatic cyclization mediated by molecular iodine under mild conditions is described.

In recent times, organic transformations catalyzed by molecular iodine have attracted considerable attention. A mild Lewis acid and electrophilic in nature, molecular iodine is inexpensive, readily available and nontoxic. It has been successfully employed in reactions involving activation of π-system, which proceeds either through a charge transfer complex or via an iodoiranium/iodoirenium intermediate followed by attack of a nucleophile either in an endo or exo fashion leading to the preparation of a variety of heterocycles.[1] Such iodine-catalyzed reactions not only complement several metal-catalyzed processes but are also considered environmentally benign.

Although allylamines are considered to be basic units in synthetic chemistry, they are apposite precursors to a variety of aza-heterocycles.[2] In one of our research programs we are exploring the potential of allylamines, synthesized from the Morita–Baylis–Hillman (MBH) adducts, as the starting substrates for diverse nitrogen heterocycles. In this context we have reported recently the synthesis of pyrazolo[4,3-*b*]pyridines, 1,3-thiazines, 5-aminotetrazoles and pyrimido[2,1-*b*]quinazolines.[3] Influenced by various reports about iodine-promoted iodocyclization of tethered heteroatom-containing alkenyl or alkynyl systems resulting into heterocyclic compounds,[4]

(1) (a) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Chem.—Eur. J.* **2012**, *18*, 5460–5489and references cited therein. (b) Mphahlele, M. J. *Molecules* **2009**, *14*, 4814–4837and references cited therein. (c) Wu, H.-C.; Yang, C.-W.; Hwang, L.-C.; Wu, M.-J. *Org. Biomol. Chem.* **2012**, *10*, 6640–6648. (d) Dai, B.; Duan, Y.; Liu, X.; Song, L.; Zhang, M.; Cao, W.; Zhu, S.; Deng, H.; Shao, M. *J. Fluorine Chem.* **2012**, *133*, 127–133. (e) Kamat, D. P.; Tilve, S. G.; Kamat, V. P. *Tetrahedron Lett.* **2012**, *53*, 4469–4472. (f) Khan, A. T.; Das, D. K.; Islam, K.; Das, P. *Tetrahedron Lett.* **2012**, *53*, 6418–6422. (g) Yin, G.; Fan, L.; Ren, T.; Zheng, C.; Tao, Q.; Wub, A.; She, N. *Org. Biomol. Chem.* **2012**, *10*, 8877–8883. (h) Reddy, G. R.; Reddy, T. R.; Joseph, S. C.; Reddy, K. S.; Pal, M. *RSC Adv.* **2012**, *2*, 3387–3395. (i) Verma, A. K.; Shukla, S. P.; Singh, J.; Rustagi, V. *J. Org. Chem.* **2011**, *76*, 5670–5684. (j) Chen, C.-C.; Yang, S.-C.; Wu, M.-J. *J. Org. Chem.* **2011**, *76*, 10269–10274. (k) Chen, D.; Song, G.; Jia, A.; Li, X. *J. Org. Chem.* **2011**, *76*, 8488–8494. (l) Sharma, S. K.; Mandadapu, A. K.; Kumar, B.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 6798–6805. (m) Zora, M.; Kivrak, A.; Yazici, C. *J. Org. Chem.* **2011**, *76*, 6726–6742. (n) Huo, Z.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2010**, *75*, 1266–1270. (o) Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691–7703. (p) Just, Z. W.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 2662–2667. (q) Zhang, X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 236–244. (r) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2005**, *8*, 243–246.

(2) (a) Nag, S.; Batra, S. *Tetrahedron* **2011**, *67*, 8959–9061and references cited therein. (b) Zhong, W.; Liu, Y.; Wang, G.; Hong, L.; Chen, Y.; Chen, X.; Zheng, Y.; Zhang, W.; Ma, W.; Shen, Y.; Yao, Y. *Org. Prep. Proced. Int.* **2011**, *43*, 1–66.

(3) (a) Nayak, M.; Batra, S. *RSC Adv.* **2012**, *2*, 3367–3373. (b) Bhowmik, S.; Mishra, A.; Batra, S. *RSC Adv.* **2011**, *1*, 1464–1470. (c) Bhowmik, S.; Mishra, A.; Batra, S. *RSC Adv.* **2011**, *1*, 1237–1244. (d) Nag, S.; Bhowmik, S.; Gauniyal, H. M.; Batra, S. *Eur. J. Org. Chem.* **2010**, 4705–4702. (e) Nag, S.; Mishra, A.; Batra, S. *Tetrahedron* **2008**, *64*, 10162–10171.

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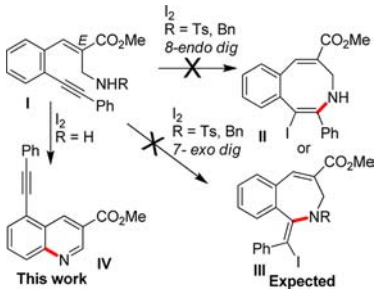
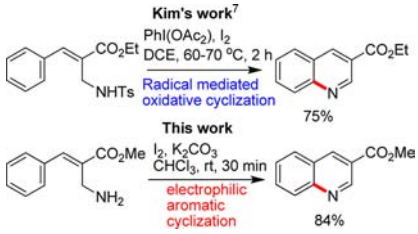


Figure 1. Iodine-mediated unexpected formation of quinoline from allylamine.

Scheme 1. Different Pathways for the Iodine-Mediated Quinoline Formation from Allylamines



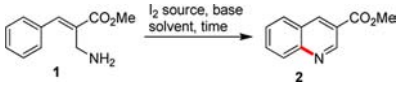
we sought to investigate intramolecular iodocyclization in substituted secondary allylamine prepared from adduct of the MBH reaction of 2-(phenylethynyl)benzaldehyde with alkylacrylate. Since the allylamine originating from the MBH reaction of acrylate bears E-stereochemistry, it was reasoned to be suited for the envisaged reaction.[5] In principle, iodine-mediated intramolecular electrophilic cyclization in substrate **I** is anticipated to proceed either via 8-*endodig* fashion to afford dihydrobenzoazocine **II** or via 7-*exodig* fashion to yield dihydrobenzazepine **III**. To test the feasibility of the strategy, we treated substituted *N*-tosylamide (**I**, R = Ts) or *N*-benzylamine (**I**, R = Bn) with iodine, but our attempts to achieve the desired iodocyclization failed. Unexpectedly however, when a similar reaction was performed with appropriately substituted primary allylamine (**I**, R = H), it resulted in 5-phenylethynyl quinoline **IV** in good yields (Figure 1).

Literature revealed that the iodine-catalyzed reactions leading to quinolines either proceed via electrophilic cyclization in aniline derivatives or via imino-Diels–Alder reaction in a multicomponent protocol where aniline is one of the substrates.[6] In 2002, although Kim and co-workers reported the synthesis of quinolines via iodine/$PhI(OAc)_2$ catalyzed intramolecular cyclization of allyl *N*-tosylamides, their reaction was believed to proceed via a free radical mechanism (Scheme 1).[7] In a preliminary experiment, however, we found that reacting allyl *N*-tosylamide with molecular iodine under basic conditions resulted in no reaction.

Given the relevance of quinoline motif in natural products and bioactive compounds,[8] we were encouraged to study the reaction in greater details. Herein we disclose our results toward developing an iodine-mediated efficient synthesis of quinolines, pyrazolo[4,3-*b*]pyridines and thieno-[3,2-*b*]pyridines from suitably substituted primary allylamines under mild conditions, which is presumed to proceed via an intramolecular electrophilic aromatic cyclization.

In order to ascertain that the protocol works with primary allylamine having unsubstituted phenyl ring, we started by probing the reaction of amine (**3**) prepared from the MBH adduct of benzaldehyde with iodine in the presence of K_2CO_3 in MeCN at room temperature; to our delight, the quinoline (**2**) was obtained in 80% yield within 30 min. Next, to investigate if we can achieve better yields of quinoline via this strategy, we considered optimizing the reaction conditions with respect to base, iodine source and solvent, and the results of the study are summarized in Table 1. Initial experimentation to examine the

Table 1. Optimization of the Reaction Conditions for the Iodine-Mediated Intramolecular Electrophilic Aromatic Cyclization in Substituted Allylamine



entry[a]	base (equiv)	iodine source (equiv)	solvent	time	yield (%)[b]
1	Na_2CO_3 (3)	I_2 (3)	MeCN	24 h	
2	**K_2CO_3 (3)**	**I_2 (3)**	**MeCN**	**30 min**	**80**
3	K_2CO_3 (2)	I_2 (3)	MeCN	12 h	58
4	K_2CO_3 (1)	I_2 (3)	MeCN	12 h	10
5	Cs_2CO_3 (3)	I_2 (3)	MeCN	24 h	
6	$NaHCO_3$ (3)	I_2 (3)	MeCN	12 h	10
7	Et_3N (3)	I_2 (3)	MeCN	24 h	
8	DBU (3)	I_2 (3)	MeCN	24 h	
9	K_2CO_3 (3)	ICl (3)	MeCN	15 h	35
10	K_2CO_3 (3)	NIS (3)	MeCN	15 h	39
11	K_2CO_3 (3)	I_2 (2)	MeCN	12 h	40
12	K_2CO_3 (3)	I_2 (1)	MeCN	12 h	15
13	K_2CO_3 (3)	I_2 (3)	CH_2Cl_2	5 h	39
14	**K_2CO_3 (3)**	**I_2 (3)**	**$CHCl_3$**	**30 min**	**84**
15	K_2CO_3 (3)	I_2 (3)	H_2O	24 h	19

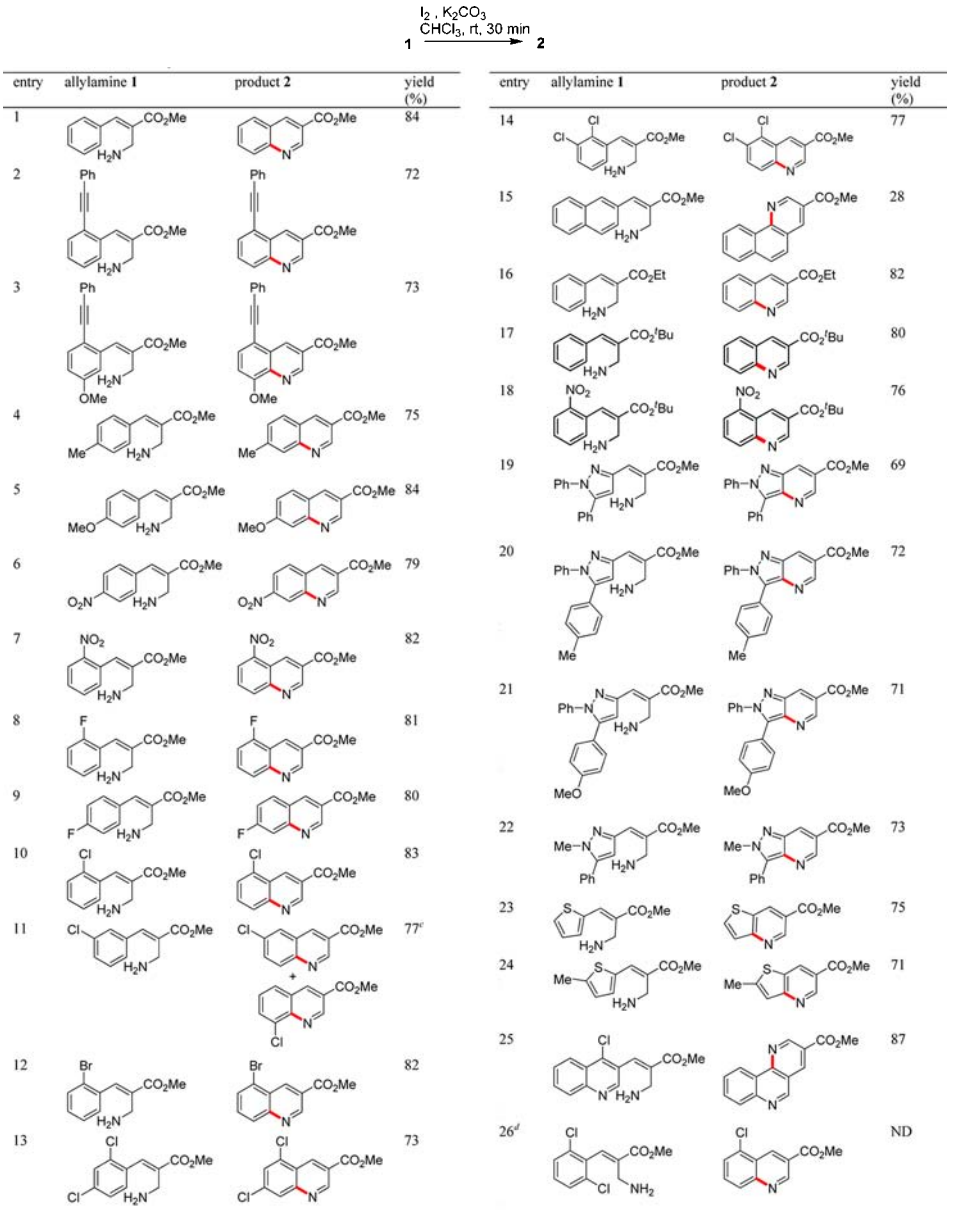
[a] All reactions were performed on a 100 mg (0.52 mmol) scale of the allylamine at room temperature in 5 mL of solvent. [b] Isolated yields of chromatographically pure product.

(4) (a) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937–2980and references cited therein. (b) Hummel, S.; Kirsch, S. F. *Beilstein J. Org. Chem.* **2011**, *7*, 847–859and references cited therein.

(5) Pathak, R.; Singh, V.; Nag, S. N.; Kanojiya, S.; Batra, S. *Synthesis* **2006**, *5*, 813–816.

(6) (a) Ali, S.; Zhu, H.-T.; Xia, X.-F.; Ji, K.-G.; Yang, Y.-F.; Song, X.-R.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 2598–2601. (b) Zhang, X.; Yao, T.; Campo, A. M.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177–1187. (c) Ali, S.; Zhu, H.-T.; Xia, X.-F.; Ji, K.-G.; Yang, Y.-F.; Song, X.-R.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 2598–2601. (d) Li, X.; Mao, Z.; Wang, Y.; Chen, W.; Lin, X. *Tetrahedron* **2011**, *67*, 3858–3862. (e) Wang, X.-S.; Li, Q.; Wu, J.-R.; Tu, S.-J. *J. Comb. Chem.* **2009**, *11*, 433–437. (f) Zhao, Y.-L.; Zhang, W.; Wang, S.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 4985–4988. (g) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243–246. (h) Zhang, M.-M.; Wang, W.; Li, T.-J.; Yao, C.-S.; Wang, X.-S. *Tetrahedron Lett.* **2006**, *47*, 3127–3130. (i) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763–766. (j) Xia, M.; Lu, Y.-D. *Synlett* **2005**, *15*, 2357–2361.

Table 2. Substrate Scope for the Iodine-Mediated Intramolecular Electrophilic Aromatic Cyclization in Substituted Allylamines



[a] Reactions were performed with substituted allylamine **1** (1 equiv), iodine (3 equiv), and K_2CO_3 (3 equiv) in $CHCl_3$ for 30 min at rt. [b] Yields after column chromatography. [c] Products were obtained as 1:1 mixture of regioisomers (on the basis of ^1H NMR), which were not separated. [d] No reaction takes place even after 12 h (ND: not detected).

most suitable base revealed that the reaction is specific to the use of K_2CO_3 since Na_2CO_3, Cs_2CO_3, Et_3N and DBU failed to initiate any reaction (entries 1−5, 7, 8), whereas $NaHCO_3$ (entry 6) gave low yields only. Reducing the amount of K_2CO_3 to 2 or 1 equiv also significantly affected the formation of the product (entries 3, 4). Changing the iodine source from molecular iodine to ICl or NIS not only decreased the yield of the quinoline but also increased the reaction time considerably (entries 9, 10). Even decreasing the amount of molecular iodine from 3 to 1 equiv resulted in the formation of product in lower yields (entries 11, 12).

Finally we discovered that the best result can be obtained by carrying out the reaction in chloroform at room temperature (entry 14). Solvents such as methylene chloride and water were found to be unsuitable for the protocol, as they yield the quinoline in inferior yields (entries 13 and 15).

To investigate the scope of the protocol, a variety of differently substituted allylamines **1** prepared from the MBH adducts of aromatic aldehydes were treated with iodine under the optimized conditions. The corresponding quinoline derivatives **2** were obtained in very good yields (Table 2). As evident, the protocol works nicely with both electron-donating and electron-withdrawing groups at ortho and para position of the phenyl ring. However for

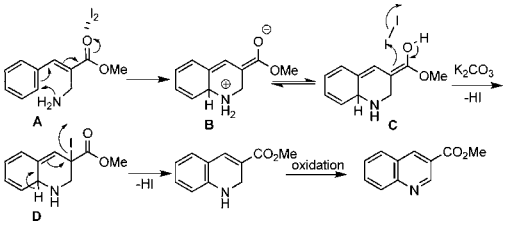
(7) Kim, J. N.; Chung, Y. M.; Im, Y. J. *Tetrahedron Lett.* **2002**, *43*, 6209–6211.

the allylamine carrying a meta substituted phenyl ring, no regioselectivity was observed, and the product although obtained in good yields was a 1:1 mixture of 6- and 8-substituted quinolines (entry 11). On the other hand, the allylamine synthesized from MBH adduct of 2-naphthaldehyde resulted in regioselective cyclization at 1-position albeit in low yields (entry 15). Changing the methyl ester to ethyl ester or *tert*-butyl ester in the allylamine did not influence the formation of the product (entries 16–18).

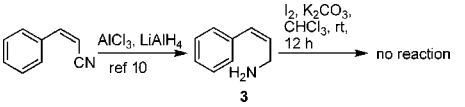
Following successful synthesis of quinolines from the substrates prepared from benzaldehydes, we decided to examine the substituted primary allylamines generated from heterocyclic aldehydes in order to enhance the scope of our methodology. Therefore appropriate primary allylamines were prepared from the MBH adducts of 3-pyrazolecarbaldehydes, 2-thiophenecarbaldehydes and 4-chloro-3-quinolinecarbaldehyde and were treated with iodine under the optimized conditions. It was pleasing to note that the pyrazole and the thiophene derivatives gave the expected products in good yields (entries 19–24). Interestingly however the quinoline derivative, instead of the expected product, afforded a naphthyridine derivative presumably via S_NAr reaction (entry 25). As a consequence, we considered investigating the reaction of allylamine prepared from the MBH adduct of 2,6-dichlorobenzaldehyde with iodine. But we found that this allylamine failed to afford the expected product even after 12 h of reaction time (entry 26).

In order to rationalize these results, we propose a plausible mechanism summarized in Figure 1, wherein the iodine initially activates the carbonyl group to form intermediate **A** (Scheme 2). This initiates an electrophilic cyclization via a nucleophilic attack of the amino group onto the aromatic ring leading to a zwitterionic intermediate **B**, which may stabilize to **C**. Subsequently in the presence of iodine and base, the iodinated intermediate **D** is formed, which is then deiodinated to furnish the dihydroquinoline. Oxidation of the dihydroquinoline under reaction conditions yield the quinoline. Since we were unable to isolate any intermediate, we presume that the product is formed via a concerted mechanism.[9] To manifest the essentiality of alkoxycarbonyl group for the protocol, we considered probing similar reaction with the allylamine **3** bearing E-stereochemistry. The required allylamine **3** prepared by the reported method[10] on treatment with iodine failed to yield the required quinoline (Scheme 3).

Scheme 2. Proposed Reaction Mechanism



Scheme 3. Unsuccessful Attempt to Cyclize Allylamine **3** via the Optimized Protocol



In conclusion, we have developed a unique route to the synthesis of aromatic ring annulated pyridines via an unprecedented intramolecular electrophilic aromatic cyclization in suitably substituted primary allylamines. This method not only allows installing desired functional groups at C-5 and C-7 in quinoline, but also gives the option to readily prepare C-5–C-6, C-5–C-7 and C-5–C-8 disubstituted quinolines with preferred substitutions. Further, the versatility of the protocol is evident from the synthesis of substituted pyrazolo[4,3-*b*]pyridines and thieno-[3,2-*b*]pyridines. The readily available starting reagents, no use of metal catalyst, and mild conditions are some of the additional features of this protocol.

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Supporting Information Available. Experimental procedures and spectroscopic data for new compounds and copies of ^1H and ^{13}C NMR spectra for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(8) (a) Alajarín, R.; Burgos, C. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, Germany, 2011; pp1527–1630. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166–187. (c) Wagman, A. S.; Wentland, M. P. In *Comprehensive Medicinal Chemistry II*; Taylor, J. B., Triggle, D. J., Eds.; Elsevier, Ltd.: Oxford, UK: 2006; Vol. 7, pp 567–596. (d) Goncalves, V.; Brannigan, J. A.; Whalley, D.; Ansell, K. H.; Saxty, B.; Holder, A. A.; Wilkinson, A. J.; Tate, E. W.; Leatherbarrow, R. J. *J. Med. Chem.* **2012**, *55*, 916–919. (e) Hudson, S. A.; McLean, K. J.; Surade, S.; Yang, Y.-Q.; Leys, D.; Ciulli, A.; Munro, A. W.; Abell, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 9311–9316. (f) Rusconi, C.; Vaiana, N.; Casagrande, M.; Basilico, N.; Parapini, S.; Taramelli, D.; Romeo, S.; Sparatore, A. *Bioorg. Med. Chem.* **2012**, *20*, 5980–5985. (g) Sabatini, S.; Gosetto, F.; Manfroni, G.; Tabarrini, O.; Kaatz, G. W.; Patel, D.; Cecchetti, V. *J. Med. Chem.* **2011**, *54*, 5722–5736. (h) Wang, Y.; Ai, J.; Wang, Y.; Chen, Y.; Wang, L.; Liu, G.; Geng, M.; Zhang, A. *J. Med. Chem.* **2011**, *54*, 2127–2142. (i) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245–3264.

(9) A successful iodine-mediated cyclization of (*E*)-methyl 2-(aminomethyl)-3-phenylacrylate to corresponding quinoline in the presence of radical scavengers including chloranil, benzoquinone or oxygen (balloon) ruled out the possibility of a radical mechanism. Unfortunately, however, the starting amine was decomposed, and no product could be isolated when the similar reaction was attempted in the presence of TEMPO.

(10) Li, M.-B.; Wang, Y.; Tian, S.-K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2968–2971.