Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201500574

An Unexpected Construction of 2-Arylquinolines from *N*-Cinnamylanilines through sp^3 C–H Aerobic Oxidation Induced by a Catalytic Radical Cation Salt

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Received: June 14, 2015; Revised: October 8, 2015; Published online: January 18, 2016

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500574.

Abstract: An unexpected reaction of cinnamylanilines was achieved through the radical cation salt-induced aerobic oxidation of sp^3 C–H bonds, providing a series of 2-arylquinolines. The mechanistic study shows that the cinnamylaniline was oxidized to an imine, which was attacked by the aniline generated through decomposition of the corresponding imine. After further intramolecular cyclization and aromatization, 2-arylquinolines were obtained. This reaction provides a new method to construct 2-arylquinolines from readily accessible starting materials.

Keywords: aerobic oxidation; 2-arylquinolines; *N*-cinnamylaniline; radical cation salts

The quinoline skeleton, which is widespread in natural products and drugs, plays important roles in organic and pharmaceutical chemistry. Their derivatives exhibit a wide range of biological activities, such as antimalarial,[1] anti-inflammatory,[2] antibacterial[3] and others.[4] Because of their great importance, considerable efforts have been devoted to the synthesis of quinoline derivatives, including the Conrad–Limpach–Knorr synthesis,[5] the Skraup–Doebner–Von Miller synthesis,[6] the Friedländer synthesis,[7] and other methods.[8] It is worth noting that the [4+2] cycloaddition of *N*-arylaldimines with dienophiles (Povarov reaction) is also a powerful approach to construct the quinoline skeleton.[9]

Besides these intermolecular approaches, the intramolecular cyclization of aniline derivatives has also been attempted to construct the quinoline skeleton.[10] For example, Wang's group reported an iron-catalyzed annulation of homoallylic alcohol substituted anilines,[10a] in which a leaving group (such as a hydroxy group) is necessary to achieve the terminal aromatizition. The combination of *O*-alkynylisocyanobenzene with an appropriate nucleophile has also been achieved both with and without a basic promoter.[10c,d] Cyclization of propargyl-substituted aniline derivatives through Friedel–Crafts-type reactions could also be used to forge the quinoline skeleton.[8b] In these elegant synthetic strategies, the substrates must be pre-functionalized in order to construct the quinoline motif.

Recently, MacMillan provided an artful direct β-alkylation of aldehydes *via* photoredox organocatalysis, in which the allyl C–H bond of an enamine was oxidized to an allyl free radical, followed by radical addition to the C=C double bond.[11] This methodology inspired us to investigate if similar free radicals could be generated by oxidation of *N*-allylaniline, it could then undergo intramolecular or intermolecular radical addition to the C=C double bond to achieve C–C bond formation. If our hypothesis is feasible, the quinoline skeleton could be formed through an intramolecular radical addition pathway [Figure 1, Eq. (4)].

Recently, we reported, for the first time, that the catalytic radical cation salt, [tris(4-bromophenyl)aminium hexachloroantimonate, $TBPA^+$], could efficiently initiate C–H oxidation of sp^3 C–H bonds adjacent to nitrogen to build heterocyclic skeletons.[12] This method represented a new approach to CDCs (cross-dehydrogenative couplings), avoiding use of excess quantities of the oxidants (such as DDQ, peroxides and so on). The catalytic oxidation of *N*-benzylanilines was also achieved under radical cation salt-induced conditions, providing a series of 2,4-diarylquinolines in high yield [Figure 1, Eq. (1)].[12e] Based on these results, we questioned if the analogues of *N*-benzylanilines, the *N*-allylanilines, couzld also be oxi-

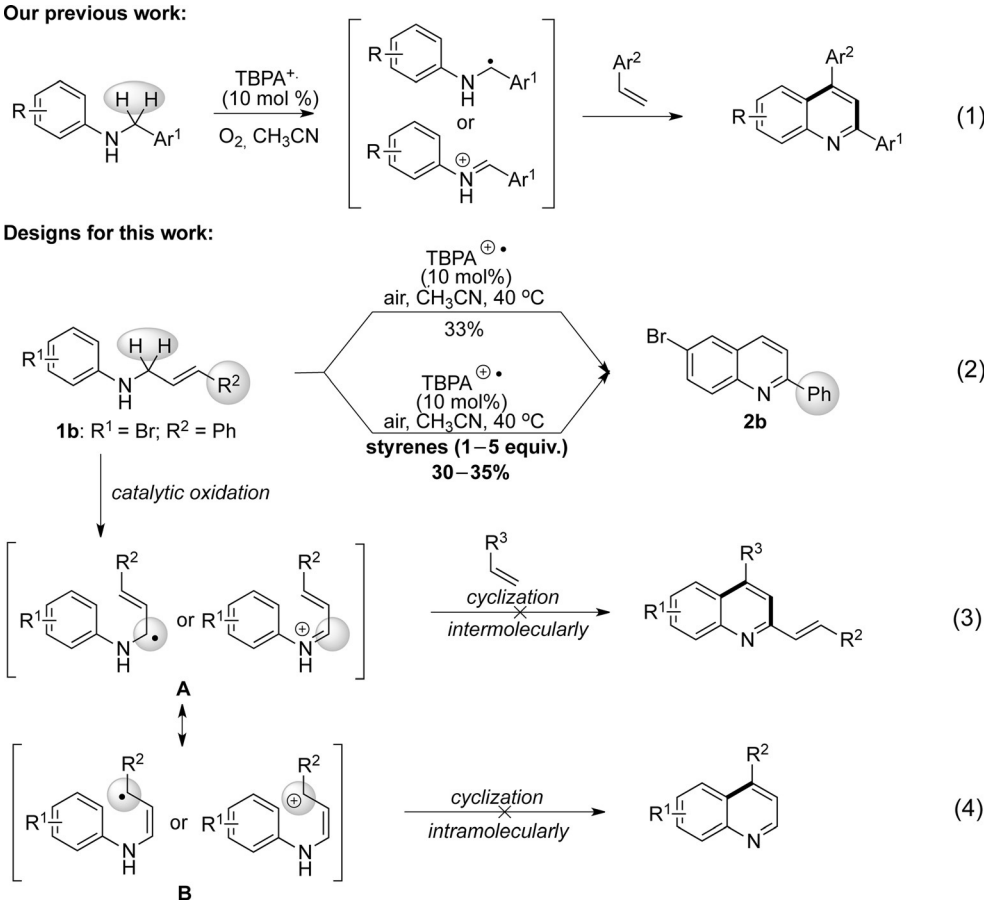


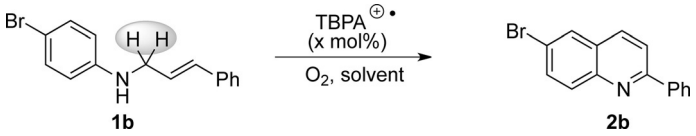
Figure 1. Radical cation salt-induced sp^3 C–H oxidation.

dized to the corresponding free radical (Figure 1, intermediate **A**) which is stabilized by the adjacent nitrogen and C=C double bond. Since the radical intermediate **A** can resonate to **B**, two different reactions would be possible. In the presence of a radical acceptor, such as alkenes, intermolecular addition might occur *via* [4+2] cycloaddition to yield 2-vinyl-1,2,3,4-tetrahydroqinolines [Figure 1, Eq. (3)]. If the radical **B** was more stable, intramolecular cycloaddition might be dominant and 1,4-dihyroquinolines could be generated [Figure 1, Eq. (4)]. Since the aromatization of 1,2,3,4-tetrahydroqinolines and 1,4-DHPs can also be achieved under radical cation salt-induced aerobic oxidation, it is predictable that quinoline derivatives would be provided through tandem aromatization.[13]

With these ideas in mind, we used the *N*-cinnamylaniline **1b** as a model substrate to test the possibility of the intermolecular and intramolecular reactions [Figure 1, Eq. (2)]. The reactions occurred with low conversion of **1b**, providing the quinoline products in low yield. Even in the presence of 1 to 5 equivalents of styrenes (such as 4-H, 4-Br and 4-MeO substituted styrenes), the intramolecular product was the exclusive product. However, to our great surprise, the ^{1}H NMR shows that the structure of the product is 2-phenylquinoline instead of 4-phenylquinoline, which means that the C–N bond of **1b** was broken during the process of the cyclization.

To maximize the yield of the desired product, an optimization of reaction conditions was performed, and the results are compiled in Table 1. From the solvent screen (entries 1–9), acetonitrile was the best solvent, and the quinoline product was isolated in 72% yield (entry 9). Evaluation of the reaction temperature shows that lower temperatures drastically decreased the yields (entries 10 and 11), and slightly lower yields could be obtained under elevated temperatures (entries 12 and 13). Screens of catalyst loading show that in the presence of 5 mol% $TBPA^{+\cdot}$, a 73% yield of the desired product was isolated with an elongated reaction time (entry 14). Under an argon atmosphere, only a trace of product was detected, so it is obvious that dioxygen is crucial to achieve full conversion of the starting material (entry 18). In the absence of $TBPA^{+\cdot}$, no reaction occurred, which implied that dioxygen could not oxidize the substrate and that the radical cation salt is vital to trigger the sp^3 C–H bond oxidation (entry 17). To further accelerate the cyclization, a catalytic amount of Lewis acid was added, but the reaction efficiency was decreased

Table 1. Optimization of the reaction conditions



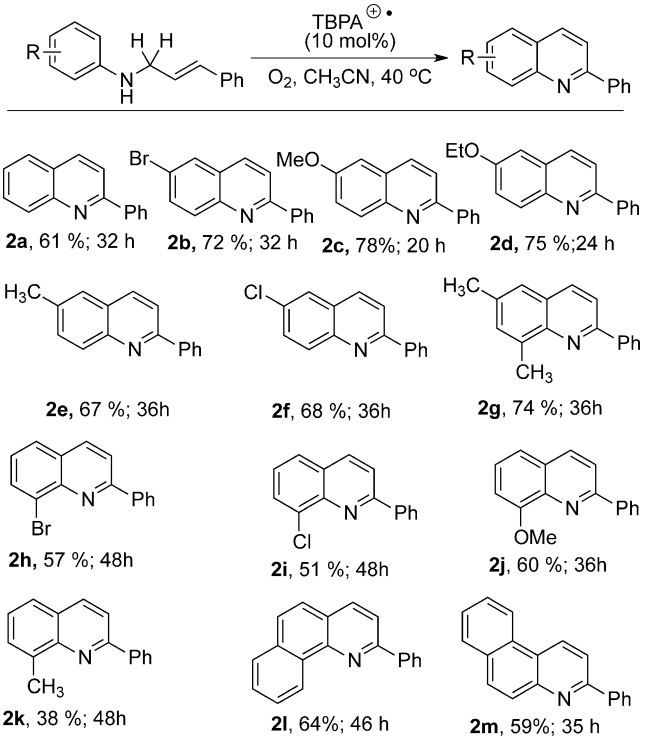
1b 2b

Entry	$TBPA^{+\cdot}$ (mol%)	Solvent	Temperature [°C]	Time [h]	Yield [%][a]
1	10	CH_3CN	40	72	33[b,d]
2	10	CH_2Cl_2	40	32	trace[b]
3	10	$CHCl_3$	40	32	trace[c]
4	10	CH_3CO_2Et	40	32	trace[c]
5	10	EtOH	40	32	trace[c]
6	10	$PhCH_3$	40	32	trace[c]
7	10	THF	40	18	35
8	10	DMF	40	18	45
9	10	CH_3CN	40	32	72
10	10	CH_3CN	10	48	trace
11	10	CH_3CN	20	32	39
12	10	CH_3CN	60	24	65
13	10	CH_3CN	80	20	63
14	5	CH_3CN	40	48	73
15	15	CH_3CN	40	24	45
16	20	CH_3CN	40	16	37
17	0	CH_3CN	40	48	0
18	10	CH_3CN	40	72	trace[c,e]
19	10	CH_3CN	40	32	55[f]

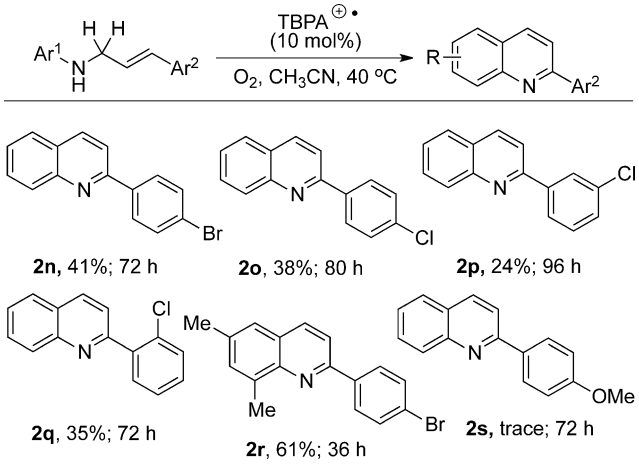
[a] Isolated yield.
[b] Under air atmosphere.
[c] Starting material was recovered.
[d] Conversion of the starting material is about 50%.
[e] Under argon.
[f] 10 mol% $InCl_3$ added.

(entry 19), which implied that the cyclization process was not the rate-determining step and the reaction efficiency could not be increased by a Lewis acid.

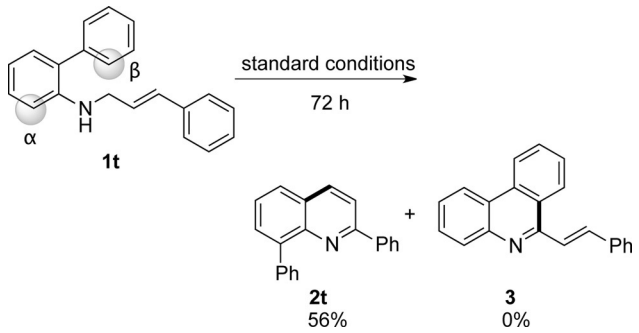
To determine the generality of this protocol, we turned our attention toward the construction of quinolines using the optimized conditions (Scheme 1). All tested *N*-cinnamylanilines exhibited good reactivity, affording the quinoline products in moderate to good yields. Electron-donating groups show higher reactivity towards intramolecular annulations, giving better yields of the desired quinoline products (**2c**, **2d**, **2e** and **2g**). Electron-withdrawing groups could also be tolerated. The reaction of *N*-cinnamyl-4-nitroaniline was also tested, but no reaction occurred (not shown in Scheme 1). The starting material remained unchanged and was recovered after reaction. This is due to the fact that the strong EWG makes the C–H bonds adjacent to nitrogen inactive and hard to be oxidized by $TBPA^{+\cdot}/O_2$. In accord with our previous results,[12] in the absence of a *para*-substituent to the aniline nitrogen, the quinolines were isolated in lower yields (**2h**–**2k**). This is due to the formation of a diarylmethane derivative which is more favored than quinolines.[14] *N*-Cinnamyl-α- and -β-naphthylamines also



Scheme 1. Reaction of *N*-cinnamylanilines. *Reaction conditions:* **1** (0.5 mmol), $TBPA^{+\cdot}$, MeCN (2 mL), 40 °C under O_2, isolated yields given.



Scheme 2. Reaction of substituted *N*-cinnamylanilines. *Reaction conditions:* **1** (0.5 mmol), $TBPA^{+\bullet}$ (10 mol%), MeCN (2 mL), 40 °C under O_2, isolated yields given.

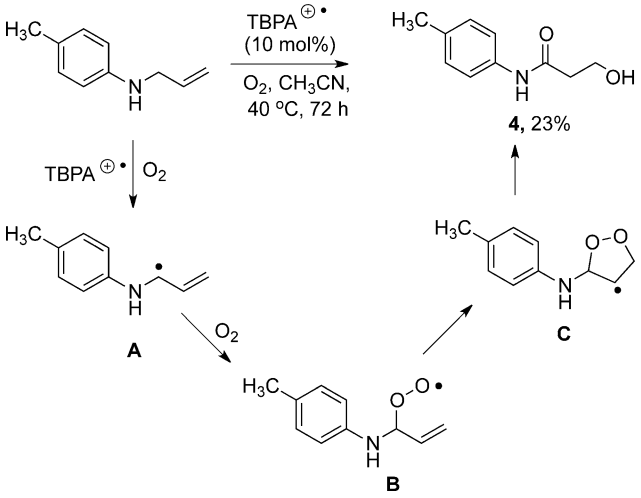


Scheme 3. Reaction of *N*-cinnamylbiphenyl-2-amine.

show good reactivity to provide the benzoquinolines in good yields (**2l** and **2m**).

To evaluate the effect of Ar^2, reactions of several substituted *N*-cinnamylanilines were performed under the standard reaction conditions (Scheme 2). Electron-withdrawing groups on Ar^2 decreased the yields dramatically (**2n**–**2q**), which suggested the existence of an electron-deficient intermediate. Increasing the electron density of nitrogen would be beneficial to oxidation of the sp^3 C–H bond, probably due to a stronger conjugative effect (see **2r** compared with **2n**).[15] We also installed a 4-methoxy group on the phenyl ring to test the reaction efficiency, but only a trace of the desired product **2s** was detected by TLC, together with decomposition of the starting material. The reason probably lies in the fact that the strong EDG group, MeO, made the substrate too electron-rich, and easy to be oxidized by $TBPA^{+\bullet}$ directly (single electron oxidation). So the C–H oxidation process (by $TBPA^{+\bullet}/O_2$) was suppressed.[16]

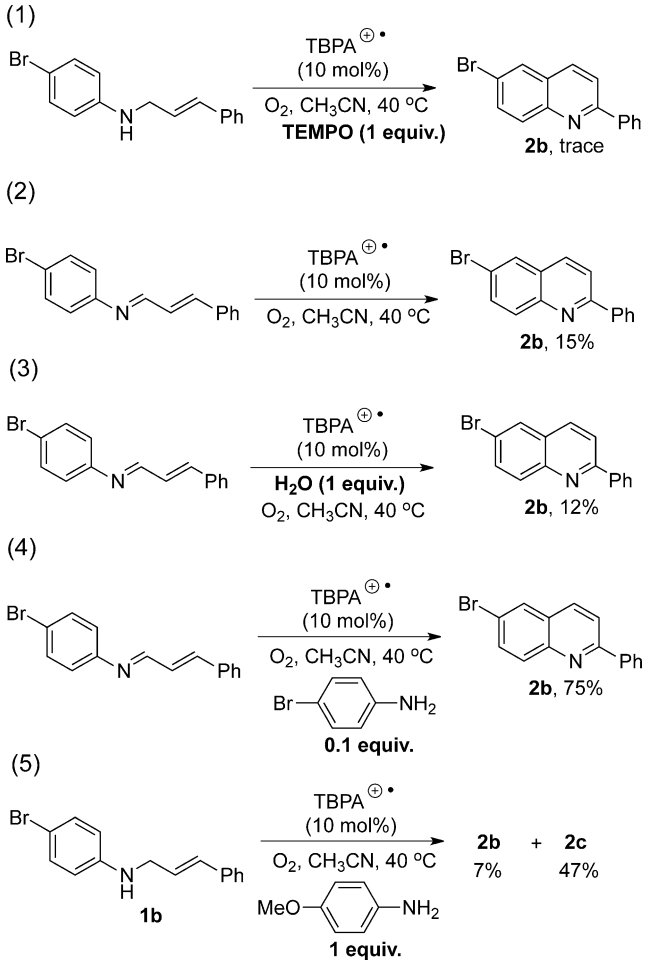
To test the other reaction possibility, *N*-cinnamylbiphenyl-2-amine **1t** was synthesized, in which two positions are active (Scheme 3). We questioned if cyclization on the β-position would be possible, providing a phenanthridine derivative. However, 2,8-diphenylquinoline **2t** was isolated exclusively in 56% yield, which was fully identified by single crystal X-ray structure analysis.



Scheme 4. Proposed mechanism for the oxidation of *N*-allyl-4-methylaniline.

We also tried the reaction of *N*-allyl-4-methylaniline, and a novel amide product **4** was isolated in 23% yield, together with some unidentified products. Although the exact mechanism to product **4** remains unknown, a plausible pathway was proposed (Scheme 4). *N*-Allyl-4-methylaniline was oxidized to radical intermediate **A**, which was trapped by dioxygen, providing a peroxide radical **B**. After 5-*endo*-*trig* cyclization,[17] an intermediate **C** was generated, which was further transformed to product **4**. This result implied that the phenyl group Ar^2 is crucial to stabilize the radical intermediate to achieve the cyclization.

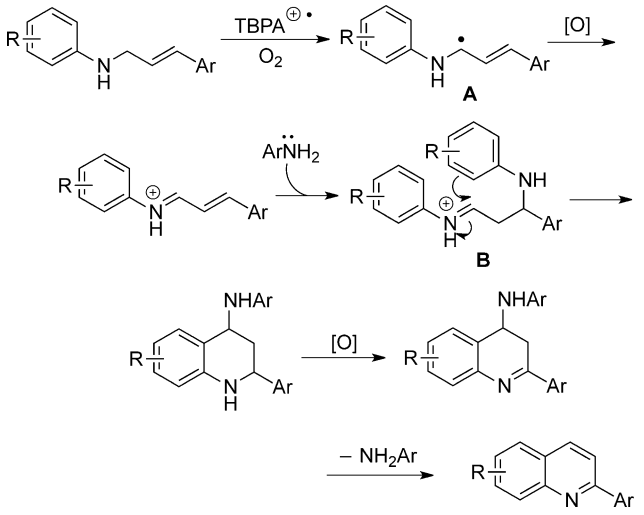
To probe the reaction mechanism, several control experiments were conducted (Scheme 5). In the presence of the radical inhibitor TEMPO (1 equivalent), the reaction was inhibited and only trace of the desired product was detected by ^1H NMR on the crude mixture [Scheme 5, Eq. (1)], which suggested that radical intermediates might be involved. The reaction of cinnamaldehyde imine was conducted under the standard conditions, and only 15% of the quinoline was isolated [Scheme 5, Eq. (2) compared with entry 9 in Table 1]. This result shows that Skraup reaction *via* a diazetidinium cation intermediate was not the dominant reaction pathway.[18] Addition of 1 eqivalent of water did not increase the yield of **2b** [Eq. (3)]. In the presence of 0.1 equivalent of 4-bromoaniline, the cyclization of the cinnamaldehyde imine occurred smoothly, yielding the desired product **2b** in 75% yield [Eq. (4)]. These results suggested that the existence of aniline is crucial to trigger the efficient transformation. The reaction of **1b** was con-



Scheme 5. Control experiments.

ducted in the presence of one equivalent of more nucleophilic 4-methoxylaniline and the corresponding quinoline products **2b** and **2c** were isolated in 7% and 47% yields, respectively. From these results we can see that the more nucleophilic aniline gave a higher yield, which supported that the C–N bond was broken during the reaction process. Furthermore, since aniline in high concentration could decompose the radical cation salt, the overall yield was lower.

Based on above results, a tentative mechanism to rationalize this radical cation salt-induced oxidation of sp^3 C–H bond is illustrated in Scheme 6. The sp^3 C–H bond adjacent to the anilino group was oxidized by $TBPA^{+\cdot}$ in the presence of O_2, yielding a radical intermediate **A**, which underwent further oxidation generating an iminium intermediate. Then a Michael-type addition occurred between cinnamaldehyde imine and aniline,[19] yielding an intermediate **B**. After an intramolecular Friedel–Crafts-type cyclization, a 4-anilinotetrahydroquinoline was formed, which was further oxidized to a dihydroquinoline intermediate. The desired quinoline product was obtained after



Scheme 6. Proposed mechanism for the cyclization of *N*-cinnamylanilines.

elimination of the aniline. The released aniline participates in the second reaction cycle.

In summary, we have developed an efficient synthesis of 2-arylquinoline using a radical cation salt-prompted sp^3 C–H aerobic oxidation. The study provides a new route for the direct formation of quinolines by using facile *N*-cinnamylanilines. Related studies including scope, mechanism and further applications are in progress in our laboratory.

Experimental Section

Typical Procedure

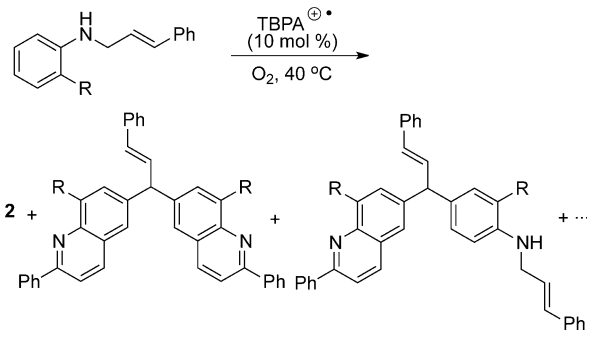
A solution of **1b** (0.5 mmol) in CH_3CN (2 mL) was mixed fully and flushed with O_2, then $TBPA^{+\cdot}$ (10 mol%) was added dropwise under an oxygen atmosphere. The reaction solution was stirred at under 40 °C. After completion as monitored by TLC (by UV visualization), the reaction was quenched by addition of saturated Na_2CO_3 solution in MeOH (10 mL). 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 products were separated by silica gel column chromatography eluted with petroleum ether/acetone (v/v 80:1) to afford the products.

Acknowledgements

The authors thank Natural Science Foundation of China (NSFC) (No. 21362030) for supporting our research.

References

[1] M. P. LaMontagne, P. Blumbergs, D. C. Smith, *J. Med. Chem.* **1989**, *32*, 1728.
[2] S. W. Elmore, M. J. Coghlan, D. D. Anderson, J. K. Pratt, B. E. Green, A. X. Wang, M. A. Stashko, C. W. Lin, C. M. Tyree, J. N. Miner, P. B. Jacobson, D. M. Wilcox, B. C. Lane, *J. Med. Chem.* **2001**, *44*, 4481.
[3] P. Narender, U. Srinivas, M. Ravinder, B. A. Rao, C. Ramesh, K. Harakishore, B. Gangadasu, U. S. N. Murthy, V. Rao, *J. Bioorg. Med. Chem.* **2006**, *14*, 4600.
[4] a) Y. Liu, Y. Feng, R. Wang, Y. Gao, L. Lai, *Bioorg Med. Chem. Lett.* **2001**, *11*, 1639; b) D. G. Batt, J. J. Petraitis, S. R. Sherk, R. A. Copeland, R. L. Dowling, T. L. Taylor, E. A. Jones, R. L. Magolda, B. D. Jaffee, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1745; c) C. Peifer, R. Urich, V. Schattel, M. Abadleh, M. Röttig, O. Kohlbacher, S. Laufer, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1431; d) D. Mabire, S. Coupa, C. Adelinet, A. Poncelet, Y. Simonnet, M. Venet, R. Wouters, A. S. J. Lesage, L. V. Beijsterveldt, F. Bischoff, *J. Med. Chem.* **2005**, *48*, 2134.
[5] a) A. C. W. Curran, *J. Chem. Soc. Perkin Trans. 1* **1976**, 975; b) F. Misani, M. T. Bogert, *J. Org. Chem.* **1945**, *10*, 347; c) B. K. Chan, M. A. Ciufolini, *J. Org. Chem.* **2007**, *72*, 8489.
[6] a) N. Sakai, D. Aoki, T. Hamajima, T. Konakahara, *Tetrahedron Lett.* **2006**, *47*, 1261; b) Y. C. Wu, L. Liu, H. J. Li, D. Wang, Y. J. Chen, *J. Org. Chem.* **2006**, *71*, 6592; c) S. E. Denmark, S. Venkatraman, *J. Org. Chem.* **2006**, *71*, 1668; d) J. J. Eisch, T. Dluzniewski, *J. Org. Chem.* **1989**, *54*, 1269.
[7] a) S. V. Ryabukhin, V. S. Naumchik, A. S. Plaskon, O. O. Grygorenko, A. A. Tolmachev, *J. Org. Chem.* **2011**, *76*, 5774; b) W. Luo, Q. Mu, W. Qiu, T. Liu, F. Yang, X. Liu, J. Tang, *Tetrahedron* **2011**, *67*, 7090; c) S. Atechian, N. Nock, R. D. Norcross, H. Ratni, A. W. Thomas, J. Verron, R. Masciadri, *Tetrahedron* **2007**, *63*, 2811; d) J. Wu, H. G. Xia, K. Gao, *Org. Biomol. Chem.* **2006**, *4*, 126; e) A. Arcadi, M. Chiarini, S. D. Giuseppe, F. Marinelli, *Synlett* **2003**, 203; f) S. S. Palimkar, S. A. Siddiqui, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *J. Org. Chem.* **2003**, *68*, 9371; g) C. S. Cho, B. T. Kim, H. J. Choi, T. J. Kim, S. C. Shim, *Tetrahedron* **2003**, *59*, 7997; h) B. Jiang, Y. G. Si, *J. Org. Chem.* **2002**, *67*, 9449.
[8] a) X. Li, Z. Mao, Y. Wang, W. Chen, X. Lin, *Tetrahedron* **2011**, *67*, 3858; b) H. Huang, H. Jiang, K. Chen, H. Liu, *J. Org. Chem.* **2009**, *74*, 5476; c) N. T. Patil, V. S. Raut, *J. Org. Chem.* **2010**, *75*, 6961.
[9] For review of Povarov reaction, see: a) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721. For recent progress, see: b) P. Ribelles, V. Sridharan, M. Villacampa, M. T. Ramos, J. C. Menéndez, *Org. Biomol. Chem.* **2013**, *11*, 569; c) K. K. H. Chandrashekarappa, K. M. Mahadevan, K. B. Manjappa, *Tetrahedron Lett.* **2013**, *54*, 1368.
[10] a) Z. Wang, S. Li, B. Yu, H. Wu, Y. Wang, X. Sun, *J. Org. Chem.* **2012**, *77*, 8615; b) B. Gabriele, R. Mancuso, G. Salerno, G. Ruffolo, P. Plastina, *J. Org. Chem.* **2007**, *72*, 6873; c) J. Zhao, C. Peng, L. Liu, Y. Wang, Q. Zhu, *J. Org. Chem.* **2010**, *75*, 7502; d) M. Suginome, T. Fukuda, Y. Ito, *Org. Lett.* **1999**, *1*, 1977; e) R. Halim, P. J. Scammells, B. L. Flynn, *Org. Lett.* **2008**, *10*, 1967; f) M. Rehan, G. Hazra, P. Ghorai, *Org. Lett.* **2015**, *17*, 1668; g) Q. Gao, S. Liu, X. Wu, A. Wu, P. Zhao, X. Yan, H. Yin, C. Xi, *Org. Lett.* **2014**, *16*, 1120; h) K. Wu, Z. Huang, C. Liu, H. Zhang, A. Lei, *Chem. Commun.* **2015**, *51*, 2286; i) L. Zhang, L. Zheng, B. Guo, R. Hua, *J. Org. Chem.* **2014**, *79*, 11541.
[11] J. A. Terrett, M. D. Clift, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 6858.
[12] a) X. D. Jia, F. F. Peng, C. Qing, C. D. Huo, X. C. Wang, *Org. Lett.* **2012**, *14*, 4030; b) X. D. Jia, Y. X. Wang, F. F. Peng, C. D. Huo, L. L. Yu, X. C. Wang, *J. Org. Chem.* **2013**, *78*, 9450; c) Y. X. Wang, F. F. Peng, J. Liu, C. D. Huo, X. C. Wang, X. D. Jia, *J. Org. Chem.*; **2015**, *80*, 609; d) X. D. Jia, Y. X. Wang, F. F. Peng, C. D. Huo, L. L. Yu, J. Liu, X. C. Wang, *Adv. Synth. Catal.* **2014**, *356*, 1210; e) J. Liu, F. Liu, Y. Z. Zhu, X. G. Ma, X. D. Jia, *Org. Lett.* **2015**, *17*, 1409.
[13] a) X. D. Jia, C. Qing, C. D. Huo, F. F. Peng, X. C. Wang, *Tetrahedron Lett.* **2012**, *53*, 7140; b) X. D. Jia, F. F. Peng, C. Qing, C. D. Huo, Y. X. Wang, X. C. Wang, *Tetrahedron Lett.* **2013**, *54*, 4950; c) X. D. Jia, L. L. Yu, C. D. Huo, Y. X. Wang, J. Liu, X. C. Wang, *Tetrahedron Lett.* **2014**, *55*, 264.
[14] In the absence of a *para* group, the reaction became complicated and diarylmethanes could be detected by crude ^{1}H NMR. Similar results were also reported by Mancheño. For details, see: a) H. Richter, O. G. Mancheño, *Org. Lett.* **2011**, *13*, 6066; b) R. Rohlmann, T. Stopka, H. Richter, O. G. Mancheño, *J. Org. Chem.* **2013**, *78*, 6050.



[15] According to a reviewer's suggestion, the difference of the yields might also be attributed to the existence of *para*-substitution on the aniline ring, which blocked the formation of diarylmethane compounds.
[16] The decomposition of the *N*-cinnamylaniline (**1s**) was found, and the free aniline was not obtained, for in the presence of TBPA$^{+\bullet}$ the aniline was oxidized. The corresponding aldehyde was isolated in 56% yield. This result could also explained why in some cases low yields are obtained, probably due to the stronger decomposition of the iminium ion intermediate to form the corresponding anilines and aldehydes.
[17] For radical *5-endo-trig* cyclization, see: a) C. Chatgilialoglu, C. Ferreri, M. Guerra, V. Timokhin, G. Froudakis, T. Gimisis, *J. Am. Chem. Soc.* **2002**, *124*, 10765; b) O. Tamura, H. Matsukida, A. Toyao, Y. Takeda, H.

Ishibashi, *J. Org. Chem.* **2002**, *67*, 5537; c) H. Fuwa, M. Sasaki, *J. Org. Chem.* **2009**, *74*, 212; d) Y. Nonami, J. Baran, J. Sosnicki, H. Mayr, A. Masuyama, M. Nojima, *J. Org. Chem.* **1999**, *64*, 4060; e) K. C. Majumdar, S. Alam, *Org. Lett.* **2006**, *8*, 4059; f) H. Fuwa, M. Sasaki, *Org. Lett.* **2007**, *9*, 3347; g) S. Bommezijn, C. G. Martin, A. R. Kennedy, D. Lizos, J. A. Murphy, *Org. Lett.* **2001**, *3*, 3405.

[18] L. Kürti, B. Czakó *Strategic Applications of Named Reactions in Organic Synthesis,* Elsevier Academic Press, **2005**, p 414.

[19] The original aniline might come from decomposition of the corresponding iminium intermediate.

