Metal-free Synthesis of β-Nitrostyrenes via DDQ-Catalyzed Nitration

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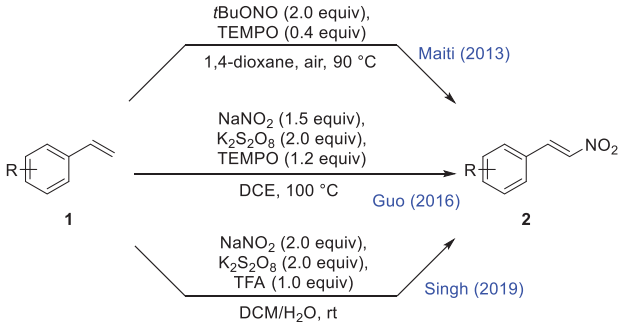
Nitrostyrenes are an important class of intermediates in synthetic organic chemistry, which are widely used for the synthesis of versatile building blocks in material or pharmaceutical chemistry.[1] For example, *p*-chloronitrostyrene derivative exhibited antitumor activity through inhibition of protein phosphatase.[1e] They are often used as versatile substrates for C—C bond forming reactions such as the Morita–Baylis–Hillman reaction, the Michael reaction, and cycloaddition reaction.[2] One of the classical synthetic methods for nitroalkenes is the Henry reaction followed by dehydration of the resultant β-nitro alcohols.[3] Alternatively, the direct incorporation of nitro group into readily available alkenes provides more convenient and efficient access to β-nitrostyrenes, which has been studied by many synthetic groups. In the early researches, these synthetic methods required metal nitrates or NO_x gases as a source of nitrating agents.[4,5] However, they have some drawbacks, such as the low selectivity to *E*- and *Z*-isomers, limited scope of substrates and harsh reaction conditions. Most recently, several research groups overcome such problems by using appropriate combination of nitrogen sources and mild oxidants under transition-metal free conditions (Scheme 1).[6–8] Maiti *et al*. developed the practical stereoselective nitration of styrenes with *tert*-butyl nitrite (TBN) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[6] Guo group also reported the nitration reactions of olefins with sodium nitrite, $K_2S_2O_8$ using TEMPO.[7] TEMPO served as an important reagent for hydrogen abstract in both reactions. Singh *et al*. published another simple stereoselective formation of nitrostyrenes using sodium nitrite and $K_2S_2O_8$ in the presence of trifluoroacetic acid as well.[8] All of these reactions granted an easy preparation of β-nitrostyrenes, but it is necessary to execute the reactions at high temperature or use stoichiometric amounts of oxidants or strong acid.

DDQ is an important oxidant for various reactions under mild and metal free condition.[9] Accordingly, we envisioned that DDQ, as an essential oxidant, could be involved in either a hydrogen atom transfer process or a single electron transfer process in the nitration reaction of styrenes with TBN as shown in Scheme 2. In this concept, TBN serves as a crucial nitrating agent,[10] of which homolytic cleavage by any hydrogen source might accelerate generation of NO radical at room temperature. Thus, the use of DDQ would be suitable for development of a mild reaction condition as well as our proposed nitration process.[11]

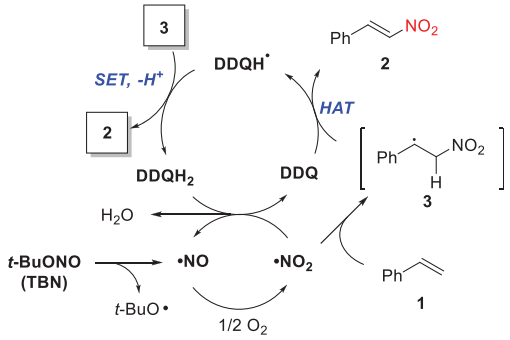
Herein, we report the synthesis of β-nitrostyrenes under mild aerobic condition using DDQ as a catalyst.

We initially investigated aerobic nitration of styrenes under various reaction conditions in the presence of DDQ as a catalyst. The results are demonstrated in Table 1. First, the reaction of styrene **1a** with TBN (2.0 equiv.) and DDQ (0.2 equiv.) in CH_3CN at room temperature afforded the corresponding (*E*)-β-nitrostyrene **2a** in 70% yield (entry 1). The stereochemistry of **2a** was determined by the analysis of proton NMR, in which the coupling constant of two olefinic protons was 13.7 Hz. When we increased the amount of DDQ up to 0.5 equivalent, the yield was improved to 90% and the reaction time was significantly reduced as well (entries 2–4). Additionally, we screened several solvent systems such as THF, CH_2Cl_2, *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and EtOH to study solvent effect on our nitration reaction. We observed relatively lower yields in most cases (entries 5–8) and no product was obtained when we performed the reaction in EtOH (entry 9). As control experiments, we found that the reaction in the absence of DDQ produced styrene **2a** only in 24% yield (entry 10) and the use of one equivalent TBN gave lower yield compared to that of the reaction under the optimized condition (entry 11). We also proved that the reaction did not proceed in the presence of radical scavenger (entry 12) and without air (entry 13). These overall results suggest that the nitration occurs through radical mechanism and TBN is not only a source of nitro radical, but also a crucial oxidant for conversion of $DDQH_2$ to DDQ during the catalytic process. On the other hand, we cannot rule out the mechanistic possibility of stoichiometric reaction with 0.5 equivalent of DDQ because DDQ should be involved twice in the catalytic cycle suggested in Scheme 2. Further mechanistic studies are currently underway in our laboratory.

Next, we examined the scope of our nitration process using a series of substituted styrenes possessing different electronic characters on phenyl ring (Scheme 3). In general, the nitration reactions of electron-rich styrenes such as methyl styrene and chloromethyl styrene produced the corresponding β-nitrostyrenes (**2b**, **2i**, and **2j**) in good

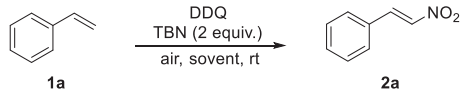


Scheme 1. Reported synthetic methods of β-nitrostyrenes via radical-mediated nitration.



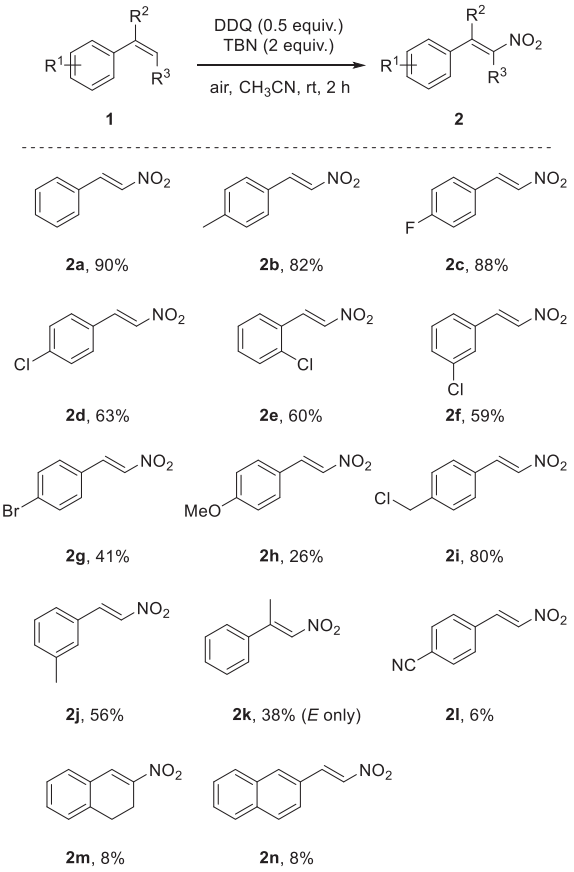
Scheme 2. Overview of DDQ-catalyzed nitration in this work.

Table 1. Optimization of stereoselective nitration reactions.



Entry	DDQ (equiv.)	Solvent	Time (h)	Yield[a] (%)
1	0.2	CH_3CN	6	70
2	0.3	CH_3CN	4	70
3	0.4	CH_3CN	4	80
4	0.5	CH_3CN	2	90
5	0.5	THF	18	73
6	0.5	CH_2Cl_2	18	34
7	0.5	DMF	18	34
8	0.5	DMSO	18	9
9	0.5	EtOH	18	-[b]
10	-[c]	CH_3CN	6	24
11[d]	0.5	CH_3CN	2	59
12[e]	0.5	CH_3CN	2	-[f]
13[g]	0.5	CH_3CN	2	-[f]

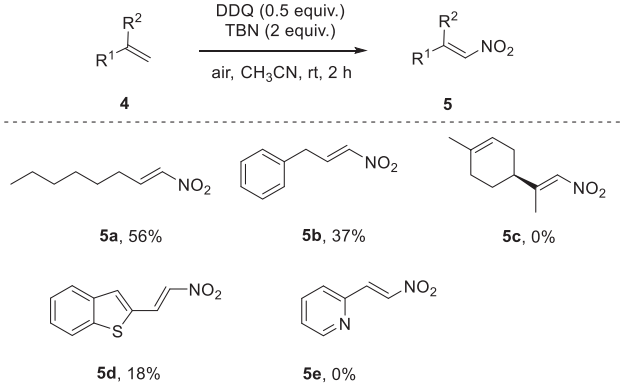
[a] Isolated yields.
[b] Only trace amount of product was observed.
[c] The reaction was performed without DDQ.
[d] The reaction was performed with one equivalent of TBN.
[e] The reaction was performed in the presence of butylated hydroxytoluene.
[f] No reaction.
[g] The reaction was performed without air.



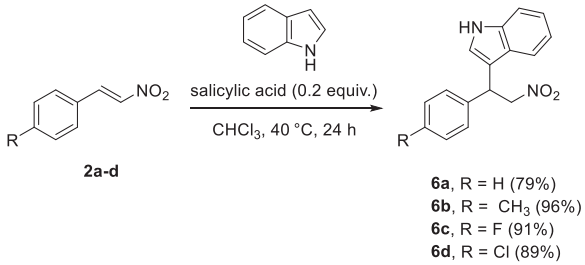
Scheme 3. Formation of various β-nitrostyrenes.

yields. However, the reaction of 4-methoxy styrene **1h** under the optimized condition proceeded to give compound **2h** in low yield, which resulted from decomposition of the product during the reaction. In case of halogen-substituted styrenes, we obtained β-nitrostyrenes derivatives **2c-g** in good to moderate yields regardless of a class of halogen and the substituent position. It is noteworthy that α-methylstyrene **1k** underwent the nitration reaction to afford only (*E*)-nitro olefin **2k** as a single stereoisomer although the yield is relatively moderate. On the other hand, when cyano styrene **1l**, dihydronaphthalene **1m**, and 2-vinylnaphthalene **1n** were used as substrates, we observed poor yields (less than 10%) of the desired products **2l-n**. This result indicated that the electron-poor aromatic ring system or the conformational restriction may not effectively stabilize the radical intermediate generated during the reaction process (see intermediate **3** in Scheme 1).

To extend our protocol to synthesize aliphatic or heteroaromatic nitroalkenes, we attempted the nitration reactions of several alkenes as shown in Scheme 4. The nitration of octene and allylbenzene under our standard condition produced the corresponding nitroalkenes **5a** and **5b** in 56% and 37%, respectively, whereas no desired nitroalkene (**5c**) was isolated from (*S*)-(−)-limonene. On the basis of this result, our nitration reaction would be appropriate only for



Scheme 4. Extension and limitation of substrate scope.



Scheme 5. Application of β-nitrostyrenes to conjugate addition of indole.

formation of simple aliphatic nitroalkenes. Additionally, when either 2-vinylbenzothiophene or 2-vinylpyridine containing heteroatoms such as sulfur and nitrogen liable to be oxidized was subjected to this aerobic nitration, only benzothiophene derivative **5d** was formed in low yield. Thus, the current reaction provides the synthetic method for a wide range of β-nitrostyrenes and terminal nitroalkenes, but it would be somewhat limited to electron-rich or halogenated styrenes and simple aliphatic olefins to obtain reasonable yields of desired products.

Finally, our efforts focused on the construction of synthetically useful building blocks using β-nitrostyrenes as a Michael acceptor (Scheme 5). According to the procedure reported in the literature,[12] the Michael addition of indole to the synthesized β-nitrostyrenes in the presence of salicylic acid as a catalyst provided 3-(2-nitro-1-phenylethyl) indoles **6a-d** in high yields without any difficulty. Therefore, this reaction could be combined with our nitration protocol to give an access to a large quantity of synthetically useful compounds having a nitro functional group.

In conclusion, we have developed a facile synthesis of (*E*)-β-nitrostyrenes by using TBN as a source of nitro group and DDQ as a key oxidant under aerobic condition.[13] This process highlighted that a wide range of β-nitrostyrenes could be synthesized under mild metal-free reaction conditions at room temperature starting from readily available styrenes. This method was extended to the synthesis of a few aliphatic and heteroaromatic nitroalkenes. The further application has been illustrated by the conjugate addition of indole to the synthesized β-nitrostyrenes. The study on a practical synthesis of biologically active β-nitrostyrenes using this strategy is currently in progress.

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Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

References

1. (a) R. Winkler, C. Hertweck, *Chembiochem* **2007**, *8*, 973. (b) K. Nepali, H. Y. Lee, J. P. Liou, *J. Med. Chem.* **2019**, *62*, 2851. (c) S. A. Bright, A. J. Byrne, E. Vandenberghe, P. V. Browne, A. M. Mcelligott, M. J. Meegan, D. C. Williams, *Oncol. Rep.* **2019**, *41*, 3127. (d) W. C. Chiu, Y. C. Lee, Y. H. Su, Y. Y. Wang, C. H. Tsai, Y. A. Hou, C. H. Wang, Y. F. Huang, C. J. Huang, S. H. Chou, P. W. Hsieh, S. F. Yuan, *PLoS One* **2016**, *11*, e0166453. e J. Park, D. Pei, *Biochemistry* **2004**, *43*, 15014. f S. Kaap, I. Quentin, D. Tamiru, M. Shaheen, K. Eger, H. J. Steinfelder, *Biochem. Pharmacol.* **2003**, *65*, 603.
2. (a) D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447. (b) D. K. Nair, S. M. Mobin, I. N. N. Namboothir, *Org. Lett.* **2012**, *14*, 4580. (c) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558. (d) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170. (e) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137. (f) D. A. Evans, S. Mito, D. Seidel, *J. Am. Chem. Soc.* **2007**, *129*, 11583. (g) L. Albrecht, G. Dickmeiss, F. C. Acosta, C. Rodríguez-Escrich, R. L. Davis, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 2543. (h) J.-Y. Son, G. U. Han, G. H. Ko, C. Maeng, S. Shin, P. H. Lee, *Bull. Kor. Chem. Soc.* **2019**, *40*, 696. (i) Y. Q. Zou, L. Q. Lu, L. Fu, N. J. Chang, J. Rong, J. R. Chen, W. J. Xiao, *Angew. Chem. Int. Ed.* **2011**, *50*, 7171.
3. (a) S. E. Milner, T. S. Moody, A. R. Maguire, *Eur. J. Org. Chem.* **2012**, *2012*, 3059. (b) S. Fioravanti, L. Pellacani, P. A. Tardella, M. C. Vergari, *Org. Lett.* **2008**, *10*, 1449.
4. (a) I. Jovel, S. Prateeptongkum, R. Jackstell, N. Vogl, C. Weckbecker, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2493. (b) H. Suzuki, T. Mori, *J. Org. Chem.* **1997**, *62*, 6498. (c) D. K. Bryant, B. C. Challis, J. Iley, *J. Chem. Soc., Chem. Commun.* **1989**, 1027. (d) S. Roy, J. P. Das, P. Sinha, *Org. Lett.* **2002**, *4*, 3055. (e) C. Zhou, T. Yang, Z. Yang, J. Li, J. Hua, J. Yi, *Synlett* **2017**, *28*, 1079.
5. (a) S. Maity, T. Naveen, U. Sharma, D. Maiti, *Synlett* **2014**, *25*, 603. (b) W.-W. Sy, A. W. By, *Tetrahedron Lett.* **1985**, *26*, 1193. (c) S. Maity, S. Manna, S. Rana, T. Naveen, A. Mallick, D. Maiti, *J. Am. Chem. Soc.* **2013**, *135*, 3355. (d) P. K. Kancharla, Y. S. Reddy, S. Dharuman, Y. D. Vankar, *J. Org. Chem.* **2011**, *76*, 5832. (e) R. S. Varma, K. P. Naicker, P. J. Liesen, *Tetrahedron Lett.* **1998**, *39*, 3977. (f) T. Taniguchi, T. Fujii, H. Ishibashi, *J. Org. Chem.* **2010**, *75*, 8126. (g) T. Naveen, S. Maity, U. Sharma, D. Maiti, *J. Org.*

Chem. **2013**, *78*, 5949. (h) E. Begari, C. Singh, U. Nookaraju, P. Kumar, *Synlett* **2014**, *25*, 1997.
6. S. Maity, T. Naveen, U. Sharma, D. Maiti, *Org. Lett.* **2013**, *15*, 3384.
7. A. Zhao, Q. Jiang, J. Jia, B. Xu, Y. Liu, M. Zhang, Q. Liu, W. Luo, C. Guo, *Tetrahedron Lett.* **2016**, *57*, 80.
8. S. Ambala, R. Singh, M. Singh, P. S. Cham, R. Gupta, G. Munagala, K. R. Yempalla, R. A. Vishwakarma, P. P. Singh, *RSC Adv.* **2019**, *9*, 30428.
9. For a recent review of DDQ-catalyzed reactions, see:A. E. Wendlandt, S. S. Stahl, *Angew. Chem. Int. Ed.* **2015**, *54*, 14638.
10. For recent reviews of TBN, see:(a)A. Dahiya, A. K. Sahoo, T. Alam, B. K. Patel, *Chem. Asian J* **2019**, *14*, 4454. b P. Li, X. Jia, *Synthesis* **2018**, *50*, 711. c S.-Z. Song, Y. Dong, G.-P. Ge, Q. Li, W.-T. Wei, *Synthesis* **2020**, *52*, 796.
11. For regeneration of DDQ from $DDQH_2$ by NO_2, see:Z. Shen, J. Dai, J. Xiong, X. He, W. Mo, B. Hu, N. Sun, X. Hua, *Adv. Synth. Catal.* **2011**, *353*, 3031.
12. K. Moriyama, T. Sugiue, Y. Saito, S. Katsuta, H. Togo, *Adv. Synth. Catal.* **2015**, *357*, 2143.
13. Representative procedure for the synthesis of **2a**: DDQ (109 mg, 0.48 mmol) was dissolved in 14 mL of dry CH_3CN in a reaction vessel and air was bubbled through the solution for 1 h. To this solution were added styrene **1a** (0.11 mL, 0.96 mmol) and TBN (0.23 mL, 1.92 mmol). The reaction was stirred for 2 h at room temperature. The solvent was removed under reduced pressure and the resulting crude material was purified by column chromatography on silica gel (hexane/ethyl acetate = 20:1) to give (*E*)-β-nitrostyrene **2a** (128 mg, 90%) as yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 13.7 Hz, 1H), 7.61 (d, J = 13.7 Hz, 1H), 7.57–7.46 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 137.3, 132.3, 130.2, 129.6, 129.3. GC-MS (EI): calcd for $C_8H_7NO_2$ $[M]^+$: 149.05, found 149.1. The spectral data of **2a** were identical to those reported in the reference 6.

