Organic & Biomolecular Chemistry

Accepted Manuscript

Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 1 | Number 1 | Jan 2013 | Pages 1–100

ROYAL SOCIETY OF CHEMISTRY

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Copper (II) - Promoted Direct Conversion of Methyl Arenes into Aromatic Oximes

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Abstract

A simple and efficient catalytic system for direct conversion of methyl arenes into aromatic oximes has been developed, with $Cu(OAc)_2$ as catalyst, NHPI (*N*-Hydroxyphthalimide) as additive, TBN (*tert*-butyl nitrite) as both the nitrogen source and the oxidant. This process proceeds under mild conditions, tolerates a wide range of substrates, affording the targeted aromatic oximes in 63-86% yields.

Introduction

Oximes are an important class of nitrogenous compounds, which can be used as intermediates, have found wide application in the synthesis of medicine, fine chemicals, and biologically active compounds,[1-5] and the oxime group is a prevalent functional group in organic synthesis and can be easily used for functional group transformations, such as the formation of amines, nitrile oxides,[6-7] nitriles and amides.[8] Great effort has been made in the development of efficient procedures to construct these important compounds. The classic method to prepare oximes is mainly based on the reaction of a carbonyl compound with hydroxylamine hydrochloride in the presence of a stoichiometric amount of base.[9-10] Despite this methodology is also applied industrially on a large scale for the production of various oximes, some drawbacks have also been restricted its further application, such as stoichiometric or excess amounts of hydroxylamine salt cost relative to the respective substrates, equal equivalent of base should be used relative to the hydroxylamine salt, large amounts of by-products are generated during the oximation reactions, and the poor yields of the oximes because the resulting oximes can undergo either dehydration to nitriles or acid-catalyzed Beckmann rearrangement to amides.

In our previous work, we developed some novel methods for aerobic oxidative synthesis of oximes from primary amines under several oxidative systems, including TEMPO/ acetaldoxime/ InCl₃, acetaldoxime/ THICA or acetaldoxime/ 3-methyl-4-oxa-5-azahomoadamantane.[11-13]

Recently, the catalytic activation of unreactive C - H bond has experienced significant progress, and the method, especially those based on sp³ C - H bonds activation, has attracted much attention for the straightforward construction of C - C[14] and C - hetero bonds (C - O,[15] C - N,[16] C - F,[17] C - S[18]) in synthetic methodologies for the production of pharmaceuticals and natural products, molecular materials and polymers. Compared with traditional strategies, the methodologies for direct conversion of aryl methylene C - H bonds into C - C and C-hetero bonds have been developed that exhibit synthetic efficiency and atom economy. In addition, oximation via aryl methylene C - H bonds activation is an efficient way to prepare C - N bond compounds. The aryl methylene C - H bond activation of toluenes is particularly important since it can produce industrially important chemicals. Despite these advances, however, the introduction of toluene derivatives to construct oximes via C - H bonds activation has been little explored.[19] Although, Lynn and his co-worker tried to produce benzaldoxime from toluene by reacting with nitrosyl chloride long time ago, drawbacks were apparent, such as low yield, harsh reaction conditions

(nitrosyl chloride was a unstable gas at room temperature), benzaldoxime which could be partly converted to benzaldehyde, benzoic acid and benzanilide catalyzed by the by-product hydrogen chloride.[20] In the recent, Wang and co-workers reported a palladium-catalyzed direct conversion of methyl arenes into aromatic nitriles.[21] In 2014, Yang and co-workers disclosed a Brønsted acid catalyzed benzylic C - H bond functionalization of azaarenes: the nucleophilic addition to *tert*-butylnitrite (TBN) yields azaarene-2-oximes in high yields.[22] Encouraged by these previous work, herein, we report a copper-promoted direct conversion of methyl arenes into aromatic oximes with NHPI (*N* - hydroxyphthalimide) as the additive, *tert*-butyl nitrite (TBN) as both the nitrogen source and the oxidant. The reaction proceeds under mild conditions, affording moderate to excellent yields of aromatic oximes (Scheme 1).
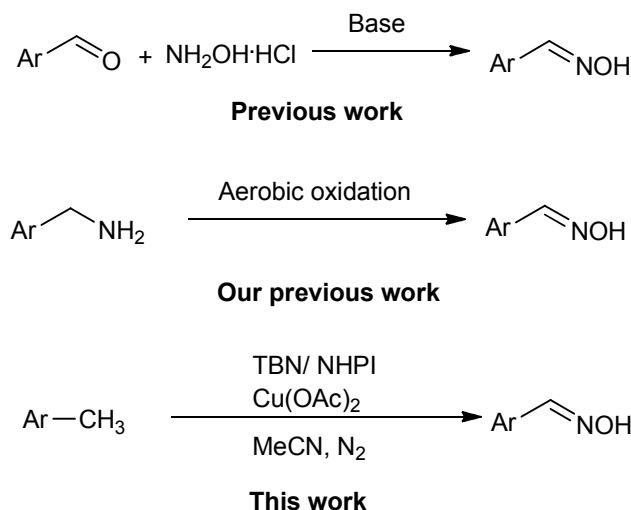

Scheme 1. Various methods for the synthesis of oximes.

Results and Discussion

As a representative example, the direct ammoxidation of *para*-methylanisole was selected to optimize the reaction conditions (Table 1). Interestingly, when we chose 3 equivalent tert-butylnitrite (TBN) as the nitrogen source and the oxidant, 10 mol% Cu(OAc)$_2$ as the catalyst and 30 mol% *N* - hydroxyphthalimide (NHPI) as additive in acetonitrile at 80 $^{\circ}$C under N$_2$ atmosphere for 24 h, the reaction provided *p*-methoxybenzaldoxime in 85% yield and *p*-methoxybezaldehyde in 5% yield after 24 h (Table 1, entry 1). Control experiments showed that the reaction proceeded in low yield without Cu(OAc)$_2$, and almost no product could detected in absence NHPI (entries 2 - 3). Other metal catalysts, including CuBr, Co(OAc)$_2$ and InCl$_3$, have also been examined but only afforded a very low yield (47%, CuBr) or poor yields (< 15%, the major product is *p*-methoxybezaldehyde when Co(OAc)$_2$ or InCl$_3$ was used) (entries 4 - 6). Some other nitrogen oxides catalysts, such as THICA (N′, N″, N‴, -trihydroxyisocyanuric acid), TEMPO (2, 2, 6, 6-tetramethylpiperidine-1-oxyl), A (3-methyl-4-oxa-5-azahomoadamantane), and NHS (*N* - hydroxysuccinimide) were also examined, the result revealed that trace amount of *p*-methoxybenzaldoxime could be detected and the major product were *p*-methoxybezaldehyde, among which NHPI was the only suitable nitrogen oxides catalysts (entries 7 - 10). Subsequently, the amounts of the Cu(OAc)$_2$, TBN and NHPI were screened. And the result showed that 10 mol%

Cu(OAc)$_2$, 3 equivalent TBN and 30 mol% NHPI were optimum amount (entries 11 - 14). Screening of different solvents revealed that the solvent played an important role in this reaction. Notably, MeCN was the only effective solvent, a trace amount of *p*-methoxybenzaldoxime could be obtained in EtOH or DMF, besides, the reaction in dioxane produced the desired product in only 16% yield (entries 15 - 17). Reducing reaction temperature from 80 °C to room temperature led to great decrease in the yields (entries 18 - 20).

Table 1. Optimization of the reaction conditions.[a]
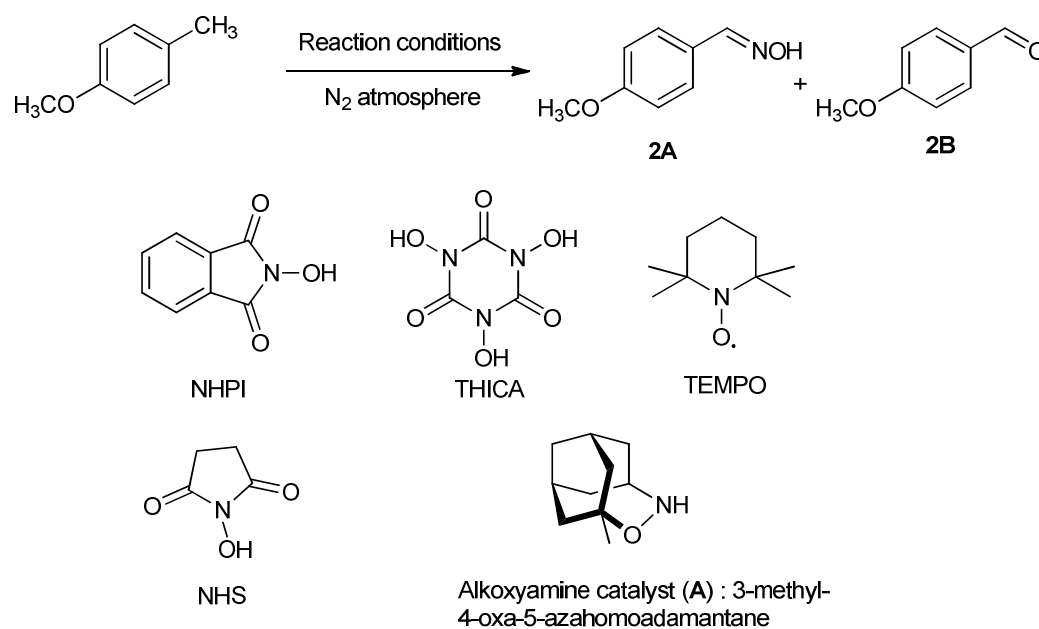
Entry	Catalyst (mol %)	TBN (equiv)	Additive (mol %)	Solvent	T (°C)	Yield [%][b] (2A/2B)
1	Cu(OAc)$_2$ (10)	3	NHPI (30)	MeCN	80	85/5
2	-	3	NHPI (30)	MeCN	80	35/43
3	Cu(OAc)$_2$ (10)	3	-	MeCN	80	trace
4	Co(OAc)$_2$ (10)	3	NHPI (30)	MeCN	80	8/70
5	CuBr (10)	3	NHPI (30)	MeCN	80	47/39
6	InCl$_3$ (10)	3	NHPI (30)	MeCN	80	12/67
7	Cu(OAc)$_2$ (10)	3	THICA (30)	MeCN	80	0/75
8	Cu(OAc)$_2$ (10)	3	TEMPO (30)	MeCN	80	0/86
9	Cu(OAc)$_2$ (10)	3	A (30)	MeCN	80	0/83
10	Cu(OAc)$_2$ (10)	3	NHS (30)	MeCN	80	0/78
11	Cu(OAc)$_2$ (5)	3	NHPI (30)	MeCN	80	77/10
12	Cu(OAc)$_2$ (10)	2	NHPI (30)	MeCN	80	73/9
13	Cu(OAc)$_2$ (10)	3	NHPI (20)	MeCN	80	75/6
14	Cu(OAc)$_2$ (10)	3	NHPI (40)	MeCN	80	84/6
15	Cu(OAc)$_2$ (10)	3	NHPI (30)	Dioxane	80	16/5
16	Cu(OAc)$_2$ (10)	3	NHPI (30)	EtOH	80	trace

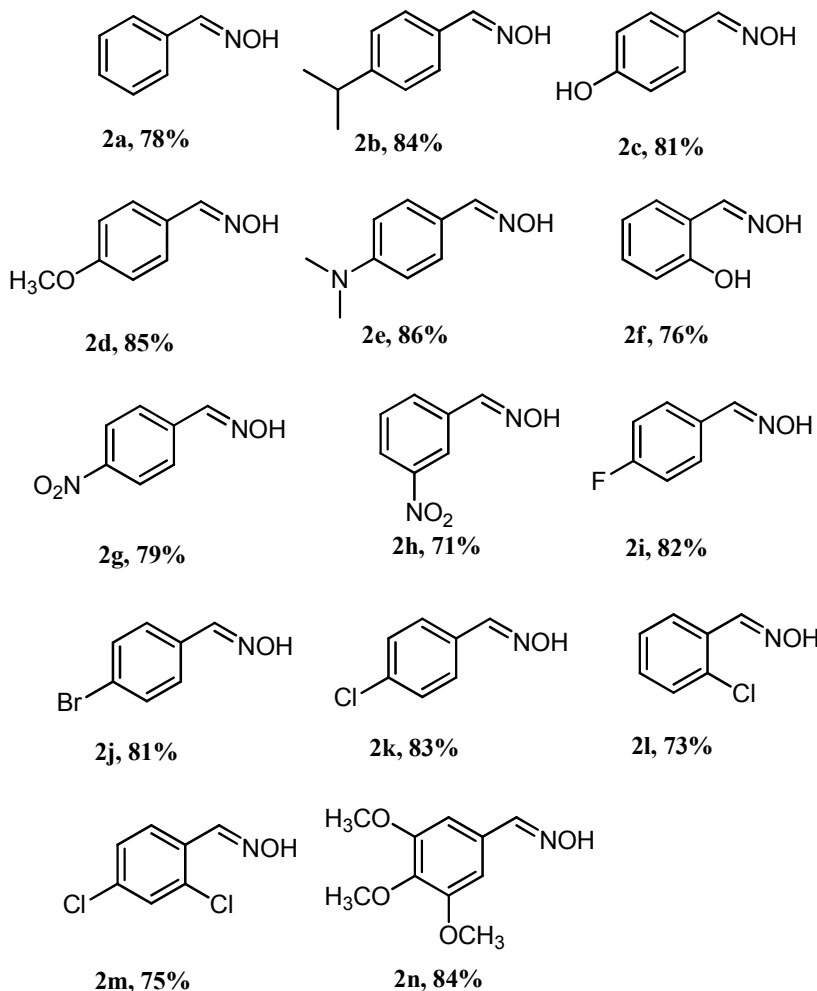| 17 | Cu(OAc)$_2$ (10) | 3 | NHPI (30) | DMF | 80 | trace |
18	Cu(OAc)$_2$ (10)	3	NHPI (30)	MeCN	60	74/5
19	Cu(OAc)$_2$ (10)	3	NHPI (30)	MeCN	40	45/5
20	Cu(OAc)$_2$ (10)	3	NHPI (30)	MeCN	RT	trace

[a] Reaction conditions: 1 mmol *para*-methylanisole, TBN, catalyst, additive were dissolved in 5 mL solvent. and the mixture stirred for 24 h under N$_2$ atmosphere at different temperatures.

[b] The isolated yield.

Having established the optimal reaction conditions, various methyl arenes were then investigated to extend the scope of the present catalytic system under the optimized conditions. In case of toluenes with electron-donating or electron-withdrawing groups, good yields in range 71 - 86% could be achieved (Table 2). Electron-donating substituents, such as CH(CH$_3$)$_2$, OH, OCH$_3$, and N(CH$_3$)$_2$ on the benzene ring of the toluenes did not affect the reaction, affording the corresponding aromatic oximes in 76 - 86% yields (entries b - f). When the toluenes bear the same substituent, the oxime yield for the *ortho* substituted compound is lower than that for *para* substitution (entries c, f). Substrates substituted with electron-withdrawing groups, such as NO$_2$, also worked well and afforded the desired products in high yields, and the yield at the *para* position is higher than that for *meta* substrate (entries g, h). Additionally, the reaction conditions were also compatible with halo-substituted toluenes, such as F, Cl, Br (entries i - m). Substrates with two or three substituents on benzene ring, could also be successfully converted into the corresponding oximes in good yields in this catalytic system (entries m - n).

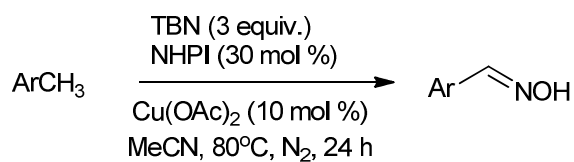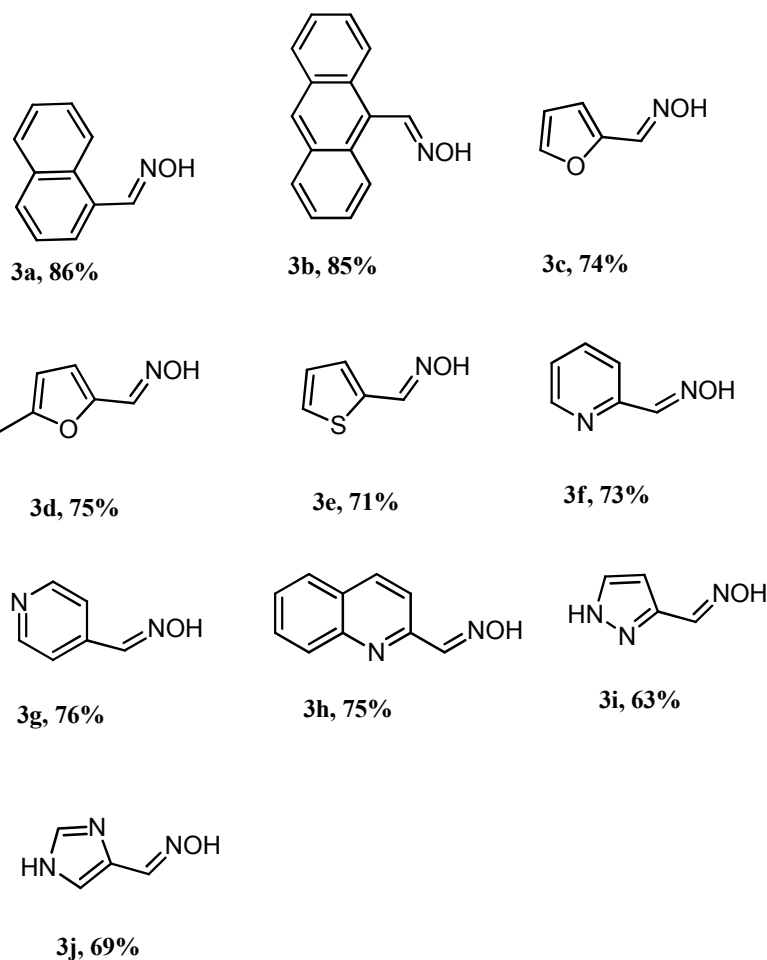Table 2. Direct conversion of methyl arenes into aromatic oximes.[a]

2a, 78%   **2b, 84%**   **2c, 81%**

2d, 85%   **2e, 86%**   **2f, 76%**

2g, 79%   **2h, 71%**   **2i, 82%**

2j, 81%   **2k, 83%**   **2l, 73%**

2m, 75%   **2n, 84%**
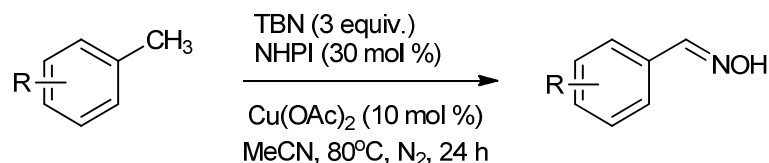
[a] Reaction conditions: 1 mmol metyl arene, 3 mmol TBN, 0.1 mmol Cu(OAc)$_2$, 0.1 mmol NHPI were dissolved in 5 mL MeCN at 80°C under N$_2$ atmosphere for 24 h.

[b] The isolated yield.

Encouraged by these results, various polycyclic aromatic hydrocarbons and heteroaromatic compounds were then subjected to this catalytic system to extend the substrate scope. As shown in Table 3, fortunately, the results showed that polycyclic aromatic hydrocarbons showed high reactivity to give the corresponding oximes in good yields, respectively, 1-naphtylaldehyde oxime in a yield of 86% and 9-anthracenealdehyde oxime in 85% yield (entries a, b). Besides, the activity of heteroaromatic compounds seemed a slightly lower than substituted toluene compounds, affording the corresponding oximes in 63-76% yields (entries c - j).

Table 3. The conversion of polycyclic aromatic hydrocarbons and heteroaromatic compounds to oximes.[a]

$$ArCH_3 \xrightarrow[\substack{Cu(OAc)_2 \ (10 \ mol \ \%) \\ MeCN, \ 80^oC, \ N_2, \ 24 \ h}]{\substack{TBN \ (3 \ equiv.) \\ NHPI \ (30 \ mol \ \%)}} Ar \diagdown NOH$$

3a, 86%   **3b, 85%**   **3c, 74%**

3d, 75%   **3e, 71%**   **3f, 73%**

3g, 76%   **3h, 75%**   **3i, 63%**

3j, 69%

[a] Reaction conditions: 1 mmol polycyclic aromatic hydrocarbon or heteroaromatic compound, 3 mmol TBN, 0.1 mmol $Cu(OAc)_2$, 0.1 mmol NHPI were dissolved in 5 mL MeCN at 80 ^{o}C under N_2 atmosphere for 24 h.

[b] The isolated yield.

To demonstrate the scope and efficiency of the present method, this catalytic system was then extended for the synthesis of ketone oximes from the substrates such as diphenyl methane, 9-alkyl fluorene and ethyl benzene. Unfortunately, lower amounts of ketone oximes could be detected after these substrates were conducted respectively in this catalytic system for 24 h under the optimized conditions (Diphenylketone oxime 28%; Acetophenone oxime 35%; 9-Fluorenone oxime 10%).
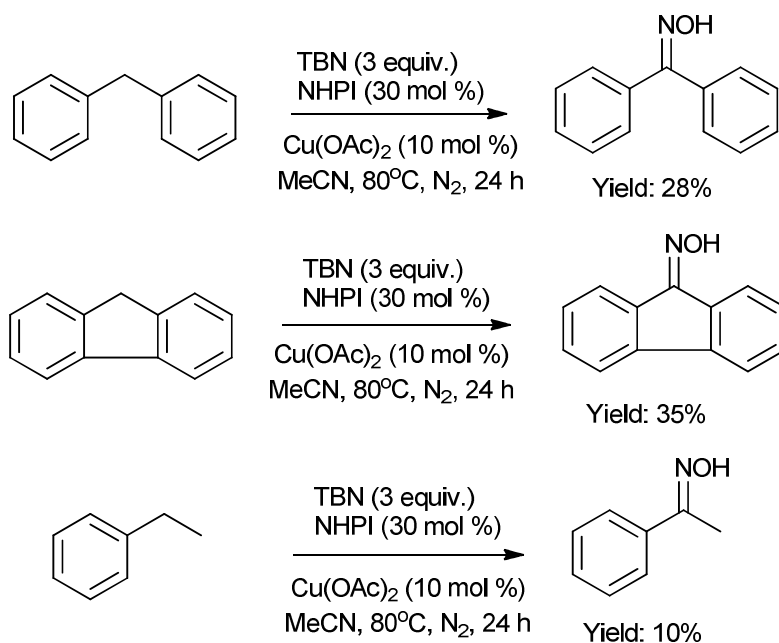
Scheme 2. The conversion for the synthesis of ketone oximes.

Based on these results and literatures about the conversion of methyl arenes or allyl arenes into the corresponding nitriles[21, 23] reported by Wang and co-workers, a proposed reaction pathway for the formation of oximes is shown in Scheme 3. The first step of the reaction was to involve the corresponding N - oxy radical PINO (phthalimide N - oxyl), which was formed by the Cu(OAc)$_2$ oxidized NHPI (N - hydroxyphthalimide). And then, this N - oxy radical abstracted a hydrogen atom from the methyl arene **1** to recover the NHPI and the methyl arene convers into benzylic radical **2** at the same time. Simultaneously, PhCH$_2$ radical **2** reacted with tBuONO (TBN) to form PhCH$_2$NO **3** intermediate and tBuO radical. Finally, the PhCH$_2$NO converted into the product oxime **4**, which involvement in the thermodynamically favored tautomerization. The generated tBuO radical underwent abstraction of hydrogen atom from NHPI to form PINO, and the regenerated PINO to complete the catalytic cycle.
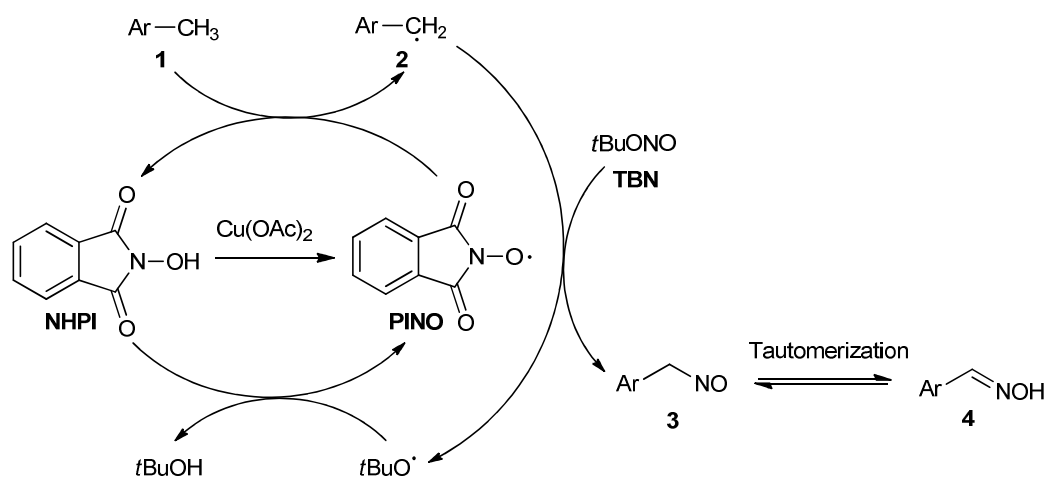
Scheme 3. The possible reaction mechanism.

Conclusion

In conclusion, we have developed a novel and efficient catalytic system consisting of $Cu(OAc)_2$, TBN and NHPI for the conversion of methyl arenes into aromatic oximes. This reaction uses TBN as both the nitrogen source and the oxidant, proceeds under mild conditions, tolerates a wide range of substrates, affording moderate to excellent yields of aromatic oximes.

Experimental Section

All starting materials were purchased from commercial sources and used without further treatment. All known compounds were identified by appropriate technique and compared with previously reported data. NMR (500 MHz) was recorded on a Bruker 500 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on an Agilent technologies 6110 quadrupole MS equipped with electrospray ionization (ESI) probe operating in positive/negative ion mode. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Yields refer to the isolated yields of the products after purification by silica-gel column chromatography (300 mesh). All the analytical data and Spectrum are available in the supporting information.

General procedure for the synthesis of oximes from methyl arenes

A mixture of 1 mmol methyl arenes, 3 mmol TBN, 30 mol% NHPI, 10 mol% $Cu(OAc)_2$, 5ml MeCN, were placed into a three-necked flask. The reaction mixture was stirred at $80^{\circ}C$ under N_2 atmosphere for 24 hours and the reaction progress was monitored by TLC. After cooling to room temperature, the solution was directly evaporated to dryness and the residue was purified by column chromatography on silica gel (ethyl acetate/ n-hexane=1:8) to give the corresponding oximes.

Reference

[1] G. M. Robertoson , in *Comprehensive Functional Group Transformation*, ed. A. R. Katritzky, O. Meth-Cohn and C.W. Rees, Elsevier, Oxford, 1995, vol. 3, pp. 425.

[2] (a) H. Iwamura, *J. Med. Chem.* **1980**, 23, 308-312; (b) Y. Takahashi, Y. Miyashita, Y. Tanaka, H. Abe, S. Sasaki, *J. Med. Chem.* **1982**, 25, 1245-1248.

[3] P. A. Eyer, F. Worek, In *Chemical Warfare Agents Toxicology and Treatment*; T. C. Marrs, R. L. Maynard, F. R. Sidell, Eds.; Wiley, 2007; pp 305-329.

[4] a) A. Atria, M. Michael, *Pharmazie* **1982**, 37, 551-553; b) A. Nakayama, H. Iwamura, A. Niwa, Y. Nakagawa, T. Fujita, *J. Agric. Food Chem.* **1985**, 33, 1034-1041; c) J. P. Ley, H. J. Bertram, *Eur. J. Lipid Sci. Technol.* **2002**, 104, 319-323; d) M. Kato, S. Nishino, M. Ohno, S. Fukuyama, Y. Kita, Y. Hirasawa, Y. Nakanishi, H. Takasugi, K. Sakane, *Bioorg. Med. Chem. Lett.* **1996**, 6 , 33-38.

[5] R. W. Hartmann, M. Hector, S. Haidar, P. B. Ehmer, W. Reichert, J. Jose, *J. Med. Chem.* **2000**, 43, 4266-4277.

[6] B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh, M. A. Ciufolini, *Org. Lett.* **2009**, 11, 1539-1542.

[7] N. A. Owston, A. J. Parker, J. M. J. Williams, *Org. Lett.* **2007**, 9, 3599-3601.

[8] a) T. Shono, Y. Matsumura, K. Tsubata, T. Kamada and K. Kishi, *J. Org. Chem.*, **1989**, 54,

2249-2251; b) S. H. Yang and S. Chang, *Org. Lett.*, **2001**, 3, 4209-4211; c) K. Yamaguchi, H. Fujiwara, Y. Ogasawara, M . Kotani and N. Mizuno, *Angew. Chem., Int. Ed.*, **2007**, 46, 3922-3925; d) N. A. Owston, A. J. Parker and J. M. J. Williams, *Org. Lett.*, **2007**, 9, 3599-3601; e) H. Fujiwara, Y. Ogasawara, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed.*, **2007**, 46, 5202-5205.

[9] A. Pohjakallio, P. M. Pihko, *Chem. Eur. J.* **2009**, 15, 3960-3964.

[10] C. L. Allen, S. Davulcu, J. M. J. Williams, *Org. Lett.* **2010**, 12, 5096-5099.

[11] J. Yu, X. Cao, M. Lu, *Tetrahedron Lett.* 2014, 55, 5751–5755.

[12] J. Yu, M. Lu, *Synlett* **2014**, 25, 1873-1878.

[13] J. Yu, J. Yon, M. Lu, *Adv. Synth. Catal.* **2015**, 357, 1175 – 1180.

[14] a) B. Schweitzer-Chaput, A. Sud, A. Pinter, S. Dehn, P. Schulze, M. Klussmann, *Angew. Chem. Int. Ed.* **2013**, 52, 13228; b) Y. N. Wu, P. Y. Choy, F. Mao, F. Y. Kwong, *Chem. Commun.* **2013**, 49, 689; c) M.-B. Zhou, C.-Y. Wang, R.-J. Song, Y. Liu, W.-T. Wei, J.-H. Li, *Chem. Commun.* **2013**, 49, 10817; d) S.-L. Zhou, L.-N. Guo, S. Wang, X.-H. Duan, *Chem. Commun.* **2014**, 50, 3589; e) H. Yang, H. Yan, P. Sun, Y. Zhu, L. Lu, D. Liu, G. Rong, J. Mao, *Green Chem.* **2013**, 15, 976; f) F. Xiong, C. Qian, D. Lin, W. Zeng, X. Lu, *Org. Lett.* **2013**, 15, 5444.

[15] a) J. Feng, S. Liang, S.-Y. Chen, J. Zhang, S.-S. Fu, X.-Q. Yu, *Adv. Synth. Catal.* **2012**, 354, 1287; b) G. Majji, S. Guin, A. Gogoi, S. K.Rout, B. K. Patel, *Chem.Commun.* **2013**, 49, 3031; c) S. K. Rout, S. Guin, W. Ali, A. Gogoi, B. K. Patel, *Org. Lett.* **2014**, 16, 3086; d) H. Liu, G. Shi, S. Pan, Y. Jiang, Y. Zhang, *Org. Lett.* **2013**, 15, 4098; e) S. K. Rout, S. Guin, K. K. Ghara, A. Banerjee, B. K. Patel, *Org. Lett.* **2012**, 14, 3982; f) S. K. Rout, S. Guin, A. Banerjee, N. Khatun, A. Gogoi, B. K. Patel, *Org. Lett.* **2013**, 15, 4106.

[16] a) R. Vanjari, T. Guntreddi, K. N. Singh, *Org. Lett.* **2013**, 15, 4908; b) D. L. Priebbenow, C. Bolm, *Org. Lett.* **2014**, 16, 1650; c) N. Wang, R. Li, L. Li, S. Xu, H. Song, B. Wang, *J. Org. Chem.* **2014**, 79, 5379; d) Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem. Int. Ed.* **2013**, 52, 1739; e) Q. Xue, J. Xie, H. Li, Y. Cheng, C. Zhu, *Chem. Commun.* **2013**, 49, 3700; f) W. Xiao, J. Wei, C.-Y. Zhou, C.-M. Che, *Chem. Commun.* **2013**, 49, 4619; g) J. Ramon Suarez, J. Luis Chiara, *Chem. Commun.* **2013**, 49, 9194; h) X. Zhang, M. Wang, P. Li, L. Wang, *Chem. Commun.* **2014**, 50, 8006.

[17] a) W. Liu, J. T. Groves, *Angew. Chem. Int. Ed.* **2013**, 52, 6024; b) J.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, 135, 17494; c) K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, 128, 7134.

[18] a) C. Chen, X.-H. Xu, B. Yang, F.-L. Qing, *Org. Lett.* **2014**, 16, 3372; b) B. Du, B. Jin, P. Sun, *Org. Lett.* **2014**, 16, 3032.

[19] a) T. Xiong, Y. Li, X. Bi, Y. Lv, Q. Zhang, *Angew. Chem. Int. Ed.* **2011**, 50, 7140; b) L. Gu, C. Jin, J. Guo, L. Zhang, W. Wang, *Chem. Commun.* **2013**, 49, 10968; c) T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett.* **2012**, 14, 4270.

[20] E. V. Lynn, H. L. ARKLE, *J. Am. Chem. Soc.* **1923**, 45, 1045.

[21] Z. Shu, Y. Ye, Y. Deng, Y. Zhang and J. Wang, *Angew. Chem. Int. Ed.* **2013**, 52, 10573.

[22] X. Gao, F. Zhang, G. Deng, and L. Yang, *Org. Lett.* **2014**, 16, 3664.

[23] Z. Shu, Y. Zhou, Y. Zhang and J. Wang, *Org. Chem. Front.* **2014**, 1, 1123.