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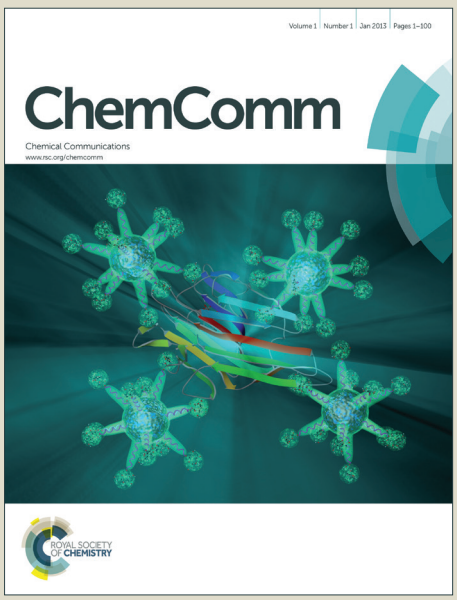

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Metal-Free Nitrative Cyclization of *N*-Aryl Imines with *tert*-Butyl Nitrite: Dehydrogenative Access to 3-Nitroindoles

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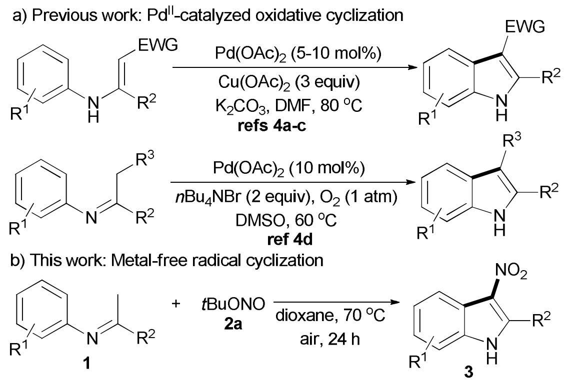
Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
First published on the web Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

We here describe a new metal-free route to the synthesis of 3-nitroindoles by the nitrative cyclization of *N*-aryl imines with *tert*-butyl nitrite. The radical transformation allows the assembly of the indole framework through oxidative cleavage of multi C-H bonds, nitration, cyclization and isomerization cascade.

Indoles are an important motif that found in a wide range of natural products, pharmaceuticals and organic dyes.[1] Owing to their remarkable biological and medicinal activities, much attention has been attracted on the discovery of efficient methods for the indole framework construction.[2-6] Among the elegant methods for indole synthesis, recent cyclization approaches involving the C-H oxidative functionalization process are particularly fascinating due to their efficiency, highly atom-economy and sustainablity.[3-6] For example, many groups have developed efficient Rh-, Ru- or Pd-catalyzed annulation of aryl C(sp^2)-H bonds with 2π components to assemble indoles.[3] However, the majority of these approaches are restricted to the requirement of noble transition metal catalysts and limited substrate scope. In 2008, Glorius and co-workers reported a new route to indoles by the Pd^{II}-catalyzed oxidative cyclization of N-aryl enamines through intramolecular dual C-H activation (Scheme 1a).[4a-c] Recently, Yoshikai and co-workers have described a new strategy for the synthesis of indoles by Pd-catalyzed oxidative cyclization of *N*-aryl imines (Scheme 1a).[4d] Although these Pd^{II}-catalyzed oxidative cyclization approaches possess operationally simple, high atom-economy and broad substrate scope, they are limited to the requirement of expensive Pd catalysts and additives. Thus, developing a new metal-free oxidative C-H functionalization alternative to the synthesis of indoles would be desirable and essential.[5] Herein, we report a novel metal-free nitrative cyclization of *N*-aryl imines with *tert*-butyl nitrite[7] for the assembly of 3-nitroindoles[6] (Scheme 1b); this transformation achieves oxidative cleavage of multi C-H bonds, nitration, cyclization and isomerization sequence, and represents a new shortcut for building 3-substituted indole skelectons with high functional group compatibility and excellent selectivity control.

The reaction condition optimization for the nitrative cyclization reaction was carried out by using 2-methyl-*N*-(1-phenylethylidene)aniline (**1a**) as the model substrate (Table 1). In the presence of 2 equiv *t*BuONO, substrate **1a** was converted into the desired 7-methyl-3-nitro-2-phenyl-1*H*-indole (**3a**) in 60% yield together with some by-products, (*E*)-2-methyl-*N*-(2-nitro-1-phenylvinyl)aniline (**4a**) and 5-methyl-



Scheme 1 Dehydrogenative Cyclization Routes to Indoles.

3-phenylquinoxaline 1-oxide (**5a**) (entry 1). Further screening revealed that the amount of *t*BuONO had a fundamental influence on the reaction (entries 2 and 3). The presence of 1.5 equiv *t*BuONO gave products **3a** and **4a** in 38% and 40% yield, respectively (entry 2). However, both products **3a** and **5a** were obtained in low yields from the reaction of substrate **1a** with 3 equiv *t*BuONO (entry 3). the reason is because substrate **1a** is readily decomposed in the presence of excess *t*BuONO. Among the reaction temperature (entries 4 ad 5) and solvents (entries 6 ad 7)examined, the reaction at 70 °C in 1,4-dioxane gave the best results (entry 1 vs. entries 4-7). Subsequently, three other NO_2 resources, including *i*BuONO (**2b**), *n*AmONO (**2c**) and $AgNO_2$ (**2d**), were tested (entries 8-10). The use of *i*BuONO (**2b**) or *n*AmONO (**2c**) shifted the chemoselectivity toward **4a** as the major product with a trace amount of **3a** and **5a** (entries 8 and 9). However, $AgNO_2$ (**2d**) showed lower reactivity and lower selectivity (entry 10). In the previous report of Jiao group, nBu$_4$NBr was employed to improve the nitrogen incorporation into substrate **1a**. Interestingly, nBu$_4$NBr could improve the reaction with substrate **1a**, but it shifted the chemoselectivity toward product **5a** in 60% yield, not the desired indole **3a** (entry 11). It should be noted that in argon the chemoselectivity of the reaction is not desirable, and a mixture of three products **3a**, **4a** and **5a** was observed in low yields (entry 12). The results suggest that air plays an important role in the reaction.

As shown in Table 2, the substrate scope of this nitrative cyclization reaction was investigated with a variety of *N*-aryl imines **1** under the optimal reaction conditions. Initially, our study focused on the substitution effect of the N-aryl moiety of substrate **1** in the presence of *t*BuONO (**2a**) (Products **3b-j**).

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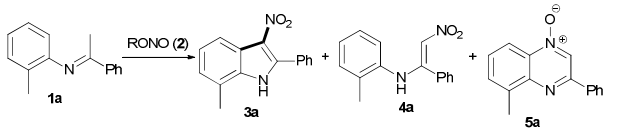
Table 1 Screening of the Optimal Conditions[a]



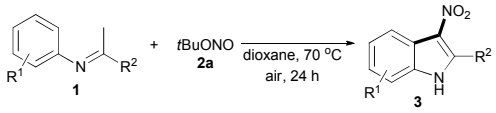
Entry	RONO (equiv)	Solvent	T (°C)	Isolated yield (%) 3a	4a	5a
1	*t*BuONO **2a** (2)	1,4-dioxane	70	60	<5	<5
2	*t*BuONO **2a** (1.5)	1,4-dioxane	70	38	40	trace
3	*t*BuONO **2a** (3)	1,4-dioxane	70	15	trace	20
4	*t*BuONO **2a** (2)	1,4-dioxane	60	55	trace	trace
5[c]	*t*BuONO **2a** (2)	1,4-dioxane	80	50	trace	trace
6	*t*BuONO **2a** (2)	*c*-hexane	70	trace	trace	trace
7	*t*BuONO **2a** (2)	toluene	70	20	17	0
8	*i*BuONO **2b** (2)	1,4-dioxane	70	trace	55	trace
9	*n*AmONO **2c** (2)	1,4-dioxane	70	<5	56	<5
10	$AgNO_2$ **2d** (2)	1,4-dioxane	70	15	16	trace
11[b]	*t*BuONO **2a** (2)	1,4-dioxane	70	trace	trace	61
12[c]	*t*BuONO **2a** (2)	1,4-dioxane	70	10	8	25

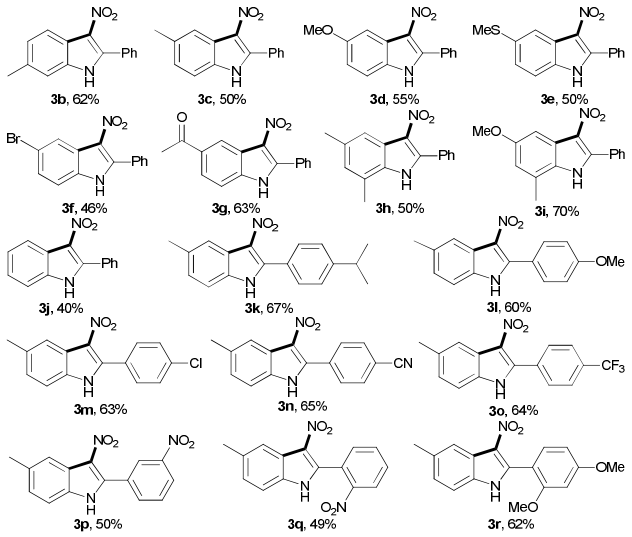
[a] Reaction conditions: **1a** (0.2 mmol), RONO **2**, and solvent (4 mL, 0.05% w/w of water in dioxane) in air for 24 h. Some other by-products from decomposition of substrate **1a**, particularly cleavage of the C=N bond, were observed. [b] nBu_4NOBr (5 mol%) was added. [c] In argon.

The results indicated that a range of substituents, including Me, MeO, MeS, Br and COMe, were well-tolerated. For example, *m*-Me-substituted substrate **1b** regioselectively formed 6-methyl-3-nitro-2-phenyl-1*H*-indole **3b** in 62% yield. Substrates **1c-e** with an electron-donating group, Me, MeO or MeS, also showed high reactivity, giving **3c-e** in moderate yields. Gratifyingly, substrate **1g** with an electron-withdrawing COMe group was successfully converted into **3g** in 63% yield. Substrates **1h** and **1i** with two substituents at the 2 and 4 positions were also viable for constructing **3h** and **3i** in good yields. Subsequently, the substitution effect of the ethylimine moiety was evaluated (Indoles **3k-r**). A variety of aryl groups, either electron-rich groups (iPrC$_6$H$_4$ and MeOC$_6$H$_4$) or electron-deficient aryl groups (ClC$_6$H$_4$, CNC$_6$H$_4$, CF$_3$C$_6$H$_4$ and NO$_2$C$_6$H$_4$), at the 1 position of the ethylimine moiety perfectly worked with *t*BuONO leading to **3k-r** in moderate yields, but an aliphatic group (Me) has no reactivity for the reaction. For instance, substrate **1k** with a iPrC$_6$H$_4$ group delivered **3k** in 67% yield. Using substrates **1l** and **1r** having a MeOC$_6$H$_4$ group or two MeOC$_6$H$_4$ groups to react with *t*BuONO afforded the desired indoles **3l** and **3r** in high yields. It is noteworthy that a halo group, such as Br and Cl, on the aromatic ring is amendable to the optimal conditions, thereby providing an opportunity for additional modifications at the halogenated position (**3f** and **3m**). Although substrates **1p** and **1q** with a *m*-NO$_2$C$_6$H$_4$ group or a *o*-NO$_2$C$_6$H$_4$ group have lower reactivity, moderate yields were still achieved (**3p** and **3q**). However, *N*-(1-phenylpropylidene)aniline (**1s**) was not asuitable susbtrate.

Gratifyingly, this nitrative cyclization reaction could be applicable to 2-(1-(3,4-dimethoxyphenyl)ethylidene)-1-methyl-1-phenylhydrazine (**1t**) (Eq 1 in Scheme 2). In the presence of *t*BuONO (**2a**), substrate **1t** assembled 4,6-dinitro-

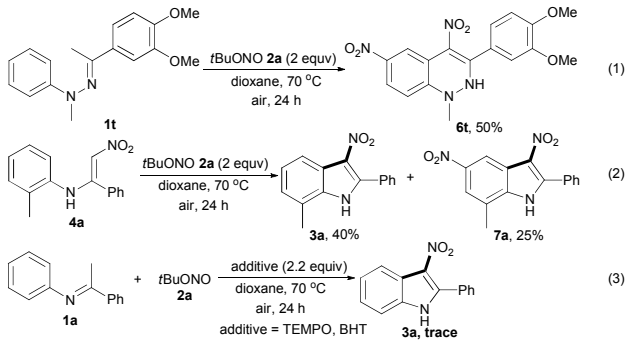
Table 2 Nitrative Cyclization of *N*-aryl imines (**1**) with *t*BuONO (**2a**)[a]





[a] Reaction conditions: **1** (0.2 mmol), **2a** (2 equiv), and 1,4-dioxane (4 mL) in air for 24 h.

1,2-dihydrocinnoline **6t**, a six-membered-ring, in 50% yield. Notably, by-product **4a** could be converted into product **3a** in 40% yield along with another over-nitration product **7a** in 25% yield (Eq 2). The results imply that by-product **4a** is an intermediate among the nitrative cyclization process. Additionally, two radical inhibitors, TEMPO and BHT, were added to the reaction of substrate **1a** with tBuONO (**2a**), which resulted in no detectable **3a** (Eq 3). The results suggest that the current reaction may include a radical process.



Scheme 2 Other Substrates and Control Experiments.

The possible mechanism outlined in Scheme 3 was proposed for the nitrative cyclization reaction.[7,8] Initially, *t*BuONO is easily split into *t*BuO· radical and ·NO radical under heating.[7,8] Reaction of ·NO radical with H_2O occurs to form HNO_2, which is rapidly decomposed into NO_2, NO and H_2O. The process is supported by the ^{18}O-labeled experiment using $H_2{}^{18}O$ (Figure S1 in the Supplementary Information). In the presence of NO_2, NO and air, substrate **1a** is converted into intermediate **A**, followed by hydrogen-abstraction of

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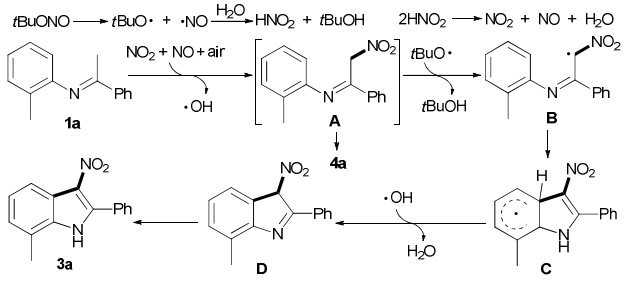
intermediate **A** by *t*BuO· radical forms radical intermediate **B**. Cyclization of intermediate **B** takes place to produce radical intermediate **C**. Finally, dehydrogenation and isomerization of intermediate **C** gives product **3a**.



Scheme 3 Possible Mechanism.

In summary, we have developed the first nitrative cyclization of *N*-aryl imines with *tert*-butyl nitrite under metal-free conditions for the synthesis of 3-nitroindoles. This method is realized through oxidative dehydrogenation, nitration, cyclization and isomerization sequence, and provides a operationally simple and atom-economical access to indoles with high functional group compatibility and excellent selectivity control.

This research was supported by the Hunan Provincial Natural Science Foundation of China (No. 13JJ2018), Natural Science Foundation of China (No. 21172060), and Specialized Research Fund for the Doctoral Program of Higher Education (No. 20120161110041). G.-B. Deng also thanks the Presidential Scholarship for Doctoral Students.

Notes and references

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1 For selected reviews and papers: *(a)* R. J. Sundberg, *Indoles*, Academic, New York, 1996; *(b)* A. Rahman, *Indole Alkaloids*, Harwood Academic Publisher, Amsterdam, 1998; *(c)* W. Hu, Z. Guo, F. Chu, A. Bai, X. Yi, G. Cheng and J. Li, *Bioorg. Med. Chem.* 2003, **11**, 1153; *(d)* T. Eicher and S. Hauptmann, *The Chemistry of Heterocycles*, Wiley-VCH, Weinheim, 2003; *(e)* M. Somei and F. Yamada, *Nat. Prod. Rep.* 2005, **22**, 73; *(f)* G. W. Gribble, *Heterocyclic Scaffolds II: Reactions and Applications of Indoles*, Springer, Berlin, 2010; *(g)* A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.* 2010, **110**, 4489; *(h)* M. Baumann, I. R. Baxendale, S. V. Ley and N. Nikbin, *Beilstein J. Org. Chem.*, 2011, **7**, 442; *(i)* N. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. Kim, A. Verma and E. Choi, *Molecules,* 2013, **18**, 6620; *(j)* B. P. Smart, R. C. Oslund, L. A. Walsh and M. H. Gelb, *J. Med. Chem.,* 2006, **49**, 2858; *(k)* S. Petit, Y. Duroc, V. Larue, C. Giglione, C. Léon, C. Soulama, A. Denis, F. Dardel, T. Meinnel and I. Artaud, *ChemMedChem,* 2009, **4**, 261; *(l)* R. M. Phillips, H. R. Hendriks and G. J. Peters, *Br. J. Pharmacol.,* 2013, **168**, 11; *(m)* A. Asberg and H. Holdaas, *Expert Rev. Cardiovasc. Ther.,* 2004, **2**, 641; *(n)* J. T. Zacharia, T. Tanaka and M. Hayashi, *J. Org. Chem.,* 2010, **75**, 7514.

2 *(a)* E. Fischer and F. Jourdan, *Ber. Dtsch. Chem. Ges.,* 1883, **16**, 2241; *(b)* B. Robinson, *Chem. Rev.,* 1963, **63**, 373; *(c)* G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1,* 2000, 1045; *(d)* G. R. Humphrey and J. T. Kuethe, *Chem. Rev.,* 2006, **106**, 2875; *(e)* M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.,* 2009, **48**, 9608; *(f)* D. F. Taber and P. K. Tirunahari, *Tetrahedron,* 2011, **67**, 7195; *(g)* S. A. Patil, R. Patil and D. D. Miller, *Curr. Med. Chem.,* 2011, **18**, 615; *(h)* M. Shiri, *Chem. Rev.,* 2012, **112**, 3508; *(i)* M. Inman and C. J. Moody, *Chem. Sci.,* 2013, **4**, 29.

3 For representative papers: *(a)* D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess and K. Fagnou, *J. Am. Chem. Soc.,* 2008, **130**, 16474; *(b)* K. Tsuchikama, Y.-K. Hashimoto, K. Endo and T. Shibata, *Adv. Synth. Catal.,* 2009, **351**, 2850; *(c)* Z.-Z. Shi, C. Zhang, S. Li, D.-L. Pan, S.-T. Ding, Y.-X. Cui, N. Jiao, *Angew. Chem. Int. Ed.,* 2009, **48**, 4572; *(d)* J. Chen, G. Song, C.-L. Pan and X. Li, *Org. Lett.,* 2010, **12**, 5426; *(e)* D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, *J. Am. Chem. Soc.,* 2010, **132**, 18326; *(f)* M. P. Huestis, L. Chan, D. R. Stuart and K. Fagnou, *Angew. Chem. Int. Ed.,* 2011, **50**, 1338; *(g)* J. Chen, Q. Pang, Y. Sun and X. Li, *J. Org. Chem.,* 2011, **76**, 3523; *(h)* L. Ackermann and A. V. Lygin, *Org. Lett.,* 2012, **14**, 764; *(i)* T. Nanjo, C. Tsukano and Y. Takemoto, *Org. Lett.,* 2012, **14**, 4270; *(j)* S. Maity and N. Zheng, *Angew. Chem., Int. Ed.,* 2012, **51**, 9562; *(k)* T. W. Liwosz and S. R. Chemler, *Chem. Eur. J.,* 2013, **19**, 12771; *(l)* W. Song and L. Ackermann, *Chem. Commun.,* 2013, 6638; *(m)* A. Cajaraville, S. S. López, J. A. Varela and C. Saá, *Org. Lett.,* 2013, **15**, 4576; *(n)* C. Wang, H. Sun, Y. Fang and Y. Huang, *Angew. Chem. Int. Ed.,* 2013, **52**, 5795; *(o)* C. Wang and Y. Huang, *Org. Lett.,* 2013, **15**, 5294; *(p)* B. Liu, C. Song, C. Sun, S. Zhou and J. Zhu, *J. Am. Chem. Soc.,* 2013, **135**, 16625; *(q)* D. Zhao, Z. Shi and F. Glorius, *Angew. Chem. Int. Ed.,* 2013, **52**, 12426; *(r)* Y. H. Jang and S. W. Youn, *Org. Lett.,* 2014, **16**, 3720; *(s)* T. Matsuda and Y. Tomaru, *Tetrahedron Lett.,* 2014, **55**, 3302; *(t)* X.-D. Xia, J. Xuan, Q. Wang, L.-Q. Lu, J.-R. Chen and W.-J. Xiao. *Adv. Synth. Catal.*. 2014. **356**. 2807: *(u)* G. Zhang, H. Yu, G. Qin and H. Huang, *Chem. Commun.,* 2014, **50**, 4331.

4 *(a)* S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge and F. Glorius, *Angew. Chem. Int. Ed.,* 2008, **47**, 7230; *(b)* J. J. Neumann, S. Rakshit, T. Dröge, S. Würtz and F. Glorius, *Chem. Eur. J.,* 2011, **17**, 7298; *(c)* X.-L. Lian, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.,* 2014, **16**, 3360; *(d)* Y.Wei, I. Deb and N. Yoshikai, *J. Am. Chem. Soc.,* 2012, **134**, 9098; for a review: *(e)* Z. Shi, F. Glorius, *Angew. Chem. Int. Ed.,* 2012, **51**, 9220; For other papers using Cu or Fe catalysts: *(f)* R. Bernini, G. Fabrizi, A. Sferrazza and S. Cacchi, *Angew. Chem. Int. Ed.,* 2009, **48**, 8078; *(g)* Z.-H. Guan, Z.-Y. Yan, Z.-H. Ren, X.-Y. Liua, Y.-M. Liang, *Chem. Commun.,* 2010, **46**, 2823.

5 For representative papers on the synthesis of indoles using the metal-free oxidative strategy: *(a)* W. Yu, Y. Du and K. Zhao, *Org. Lett.,* 2009, **11**, 2417; *(b)* L. Fra, A. Millán, J. A. Souto and K. Muñiz, *Angew. Chem. Int. Ed.,* 2014, **53**, 7349.

6 For selected papers on the 3-nitroindole synthesis and applications: *(a)* E. Shaw and D. W. Woolley, *J. Am. Chem. Soc.,* 1953, **75**, 1977; *(b)* W. E. Noland and K. R. Rush, *J. Org. Chem.,* 1966, **31**, 70; *(c)* W. E. Noland, L. R. Smith, and K. R. Rush, *J. Org. Chem.,* 1965, **30**, 3457; *(d)* B. J. Stokes, S. Liu and T. G. Driver, *J. Am. Chem. Soc.,* 2011, **133**, 4702; *(e)* J. Tang and H. Wang, *Int. J. Antimicrob. Agents,* 2008, **31**, 497; *(f)* W. Al-Zereini, I. Schuhmann, H. Laatsch, E. Helmke and H. Anke, *J. Antibiot.,* 2007, **60**, 301; *(g)* G. W. Gribble, E. T. Pelkey, F. L. Switzer, *Synlett,* 1998, 1061; *(h)* Gribble, G. W.; Pelkey, E. T.; Simon, W. M.; Trujillo, H. A. *Tetrahedron,* 2000, **56**, 10133; *(i)* S. Roy, T. L. S. Kishbaugh, J. P. Jasinski and G. W. Gribble, *Tetrahedron Lett.,* 2007, **48**, 1313; *(j)* E. T. Pelkey, L. Chang and G. W. Gribble, *Chem. Commun.,* 1996, 1909; *(k)* S. Lee, S. Diab, P. Queval, M. Sebban, I. Chataigner and S. R. Piettre, *Chem. Eur. J.,* 2013, **19**, 7181; *(l)* I. Chataigner and S. R. Piettre, *Org. Lett.,* 2007, **9**, 4159; *(m)* H. Gérard and I. Chataigner, *J. Org. Chem.,* 2013, **78**, 9233; *(n)* A. Awata and T. Arai, *Angew. Chem. Int. Ed.,* 2014, **53**, 10462.

7 For selected reviews and papers on the use of *t*BuONO in synthesis: *(a)* D. Fang, Q.-r. Shi, K. Gong, Z.-l. Lu and C.-x. Lü, *Chin. J. Energ. Mater.,* 2008, **16**, 103; *(b)* J. Song and Z. Zhou, *Sci. Tech. Rev.,* 2013, **31**, 69; *(c)* D. Koley, O. C. Colón and S. N. Savinov, *Org. Lett.,* 2009, **11**, 4172; *(d)* T. Taniguchi, A. Yajima and H. Ishibashi, *Adv. Synth. Catal.,* 2011, **353**, 2643; *(e)* B. Kilpatrick, M. Hellera and S. Arns, *Chem. Commun.,* 2013, **49**, 514; *(f)* S. Manna, S. Jana, T. Saboo, A. Maji and D. Maiti, *Chem. Commun.,* 2013, **49**, 5286; *(g)* S. Maity, T. Naveen, U. Sharma and D. Maiti, *Org. Lett.,* 2013, **15**, 3384; *(h)* T. Shen, Y. Yuan and N. Jiao, *Chem. Commun.,* 2014, **50**, 554; *(i)* Y. Liu, J.-L. Zhang, R.-J. Song, P.-C. Qian and J.-H. Li, *Angew. Chem. Int. Ed.,* 2014, **53**, 9017; For a paper on the reaction between N-aryl imines and *t*BuONO to synthesize quinoxaline *N*-oxides: *(j)* F. Chen, X. Huang, X. Li, T. Shen, M. Zou and N. Jiao, *Angew. Chem. Int. Ed.,* 2014, **53**, 10495.

8 *(a)* M. P. Doyle, J. W. Terpstra, R. A. Pickering and D. M. LePoire, *J. Org. Chem.,* 1983, **48**, 3379; *(b)* J.-Y. Park and Y.-N. Lee, *J. Phy. Chem.,* 1988, **92**, 6294.