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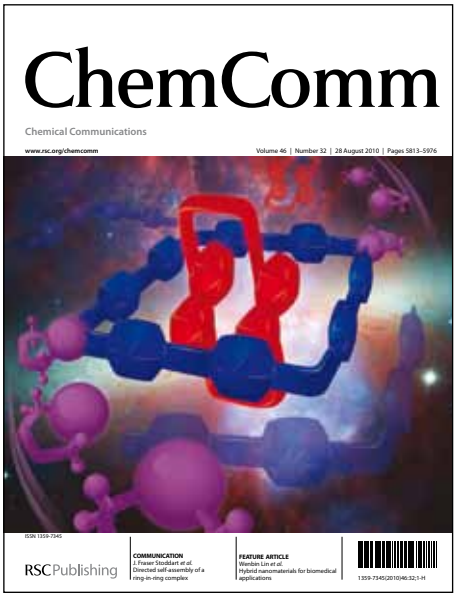

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ARTICLE TYPE

Metal-Free Nitro-Carbocyclization of Activated Alkenes: Direct Approach to Oxindoles by Cascade C-N and C-C Bond Formation**

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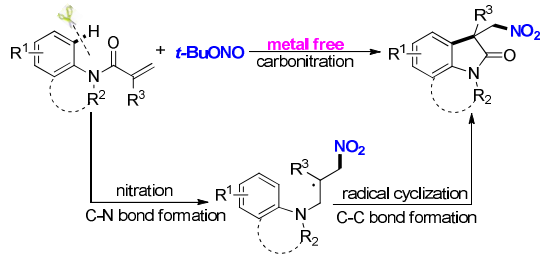
A novel and direct metal-free nitro-carbocyclization of activated alkenes leading to valuable nitro-containing oxindoles via cascade C-N and C-C bond formation has been developed. The mechanistic study indicates that the initial NO and NO_2 radical addition and the following C-H functionalization processes are involved in this transformation.

As an importantclass of biological organic compounds, nitrogen-containing moleculeshave been widely used as functional materials, synthetic intermediates, and pharmaceuticals.[1] Nitro compounds are also important and useful precursors for the corresponding functional molecules such as amines and ketones. Therefore, many nitration methodologies for the synthesis of aromatic and aliphatic nitro compounds have been developed.[2,3] As one of the most attractive topics in organic chemistry, the activation of inert C-H bonds has drawed interests of chemists in the past decades.[4] Moreover, recently the transition metal – free C–H functionalization reactions has arrtacted more attentions due to the economical and environmental viewpoints.[5] Under this concept, some examples of sp^2 C-H activition *via* radical pathway for the synthesis of oxindoles which are a large class of natural products withunique biological activity and represent one of the privileged scaffolds for library design and drug discovery,[6,7] have been significantly disclosed.[8,9]Although some elegant works on NO_2 radical trapped by alkenes have been achieved,[10] the metal free direct tandem nitration and C-H functionalization still remains challenge.

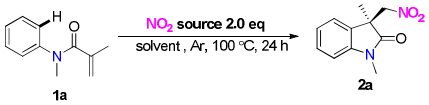


Scheme 1. The metal-free C-H nitrification of activated alkenes

Herein, we report a novel and direct metal-free nitro-carbocyclization of activated alkenes leading to oxindoles via cascade C-N and C-C bond formation (Scheme 1). The significance of the present chemistry is threefold: 1) To our best of knowledge, the addition of the NO_2 radical to alkenes followed by a C-H functionalization for the synthesis of oxindoles has not been reported till this work and are in high demand. 2) The metal free and mild conditions make it a convenient way to prepare nitrogen-containing compounds. 3) The mechanistic study indicates that the initial NO and NO_2 radical addition and the following C-H functionalization processes are involved in this transformation.

N-methyl-*N*-arylacrylamide **1a** was initially investigated as the model substrate for the direct carbonitration of activated alkenes. Gratifyingly, the desired 1,3-dimethyl-3-(nitromethyl)indolin-2-one **2a** was isolated in 31% yield by using 2.0 eq $Fe(NO_3)_3 \cdot 9H_2O$ as NO_2 source in MeCN (Table 1, entry 1). Encouraged by this result, we further optimized the reaction conditions by changing the NO_2 source. When *t*-BuONO was employed as the nitrogen source, the desired oxindole was obtained in 44% yield (Table 1, entry 5). Although few solvents did not promote the efficiency of the desired transformation (Table 1, entries 6 - 11), DMF was found to be superior with 68% yield for **2a** (Table 1, entries 12). To our delight, when the loading of *t*-BuONO was increaced to 2.5 eq with two portions addition, the yield of **2a** was improved to 74% yield (Table 1, entry 14).

Table 1. Optimization for the direct carbonitration of activated alkenes[a]



Entry	NO_2 source	solvent	yield of **2a** (%)
1	$Fe(NO_3)_3$ $9H_2O$	MeCN	31
2	$AgNO_3$	MeCN	12
3	$NaNO_2$	MeCN	0
4	$AgNO_2$	MeCN	38
5	*t*-BuONO	MeCN	44
6	*t*-BuONO	THF	trace
7	*t*-BuONO	$CHCl_3$	trace
8	*t*-BuONO	DMF	68
9[c]	***t*-BuONO**	**DMF**	**74**
10	*t*-BuONO	DMSO	36
11	*t*-BuONO	toluene	31
12	*t*-BuONO	HOAc	22

[a] Reaction conditions: **1a** (0.2 mmol) and *t*-BuONO(0.4 mmol) in dry DMF (2 mL) with stirring at 100℃ for 24 h. Isolated yield[b] 10% TEMPO was used. [c]2.5 eq of *t*-BuONO was used and was added into two portions.

To explore the scope of this carbonitration of alkenes, various *N*-arylacrylamides were subjected to the optimized reaction conditions to prepare. 3-substituted oxindoles(Table 2) which are a large class of natural products with unique biological activity a wide range of natural products,

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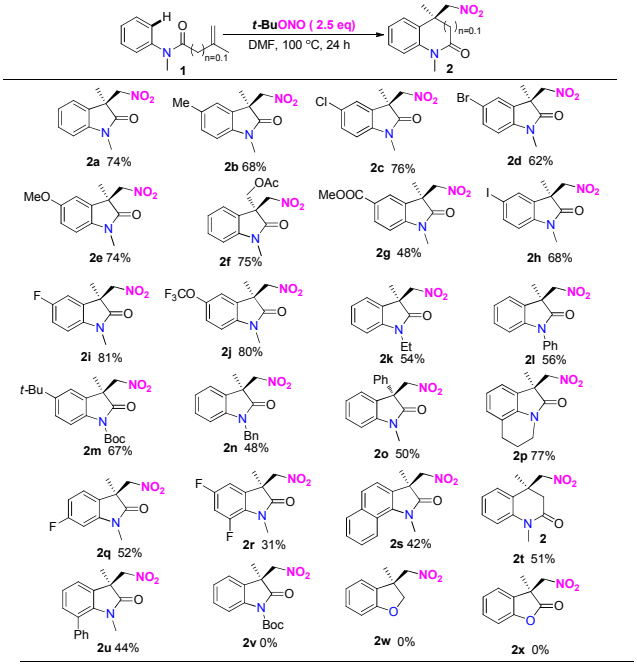
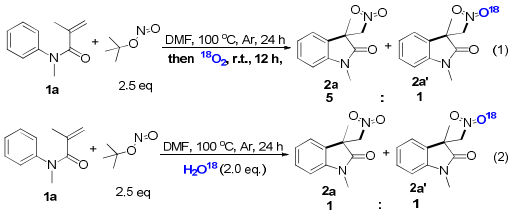
pharmaceuticals, and agrochemicals and represent one of the privileged scaffolds for drug discovery and library design.[11] In general, very smooth nitro-carbocyclization progress occurred for *N*-arylacrylamides having substituents at *para* and *meta* aswell as *ortho* positions in the aniline. Substrates bearing an electron-donating groups (e.g., Me, ^{t}Bu, OMe) or a strong electron-withdrawing group (e.g., CF_3 and CO_2Me) at the aryl ring are tolerant in this transformation. It is noteworthy that the halo-substituted (F, Cl, Br, I) *N*-methyl-*N*-phenylmethacrylamides worked well to afford the corresponding halo-substituted oxindoles in good yields(**2c**, **2d**, **2h**, **2i**). To our delight, cyclization of the tetrahydroquinoline derivative furnished the tricyclic oxindole **2p** in 77% yield. Moreover, the unactivated alkenes can also undergo carbonitration smoothly, generating corresponding products in moderate yields (**2t**). Polysubstituted derivatives provided carbonitration oxindoles in good yields (Table 2, **2r**). Unfortunately, when change the frameworks of the substrates by replacing the heteroatoms from N to O, no desired product was obvserved (Table 2, **2v**, **2x**).

Table 2 Metal-free C-H nitrification of activated alkenes. [a]



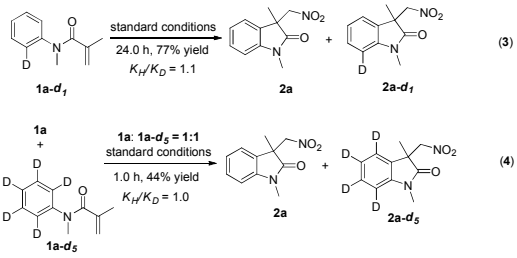
[a]Reaction conditions: 1 (0.2 mmol) and t-BuONO (0.5 mmol) in DMF (2 mL) at 100 °C under Ar for 24 h. Isolated yields are reported.

In the reported nitration reactions of alkenes with *t*-BuONO, it is well known to proceed by a radical process.[12,13] When the reaction was trapped by TEMPO, the carbonitration process was suppressed and only trace amount product obtained (Eq. S1, see SI). Besides, the corresponding oxime, which could be converted to nitro compound by some oxidants,[15] failed to give nitro compound under O_2 or the standard conditions (see SI), which may exclude oxime as an intermediate involved in this transformation. Furthermore, to interpret why oxidation product **2a** could be obtained under Ar in high yield, some ^{18}O labeled experiments were tested. After ensured the reaction finished in 24 h under standard reaction conditions, $^{18}O_2$ was filled in reaction system and went on reaction for 12 h at room temperature. The ratio of ^{16}O product and ^{18}O product is 5:1 (Eq. 12, see SI), which indicated that one pass way for the process may the addition of generated NO radical from *t*-BuONO is followed by O_2 oxidation in the subsequent processing. Besides, when 2.0 eq $H_2{}^{18}O$ was added under the standard reaction conditions, The ratio of ^{16}O product and ^{18}O product turned to be 1:1 (Eq. 2, see SI), which suggested that maybe H_2O promoted the generated of NO_2 radical, and NO_2 radical is prior to add to alkenes rather than NO radical. In contrast, when **2a** was heated under $^{18}O_2$ or in $H_2{}^{18}O$, the ^{18}O labeled product was hardly observed (see SI). These control experiments may exclude the possible exchange after the product generation.



Scheme 2

To look insight the catalytic procedure, the intramolecular and intermolecular kinetic isotope effect (KIE) experiments were carried out with the deuteriumlabeled substrates [D1]-**1a** and [D5]-**1a** (Eq. 3-4). Two secondary kinetic isotope effects were observed (the intramolecular K_H/K_D=1.1, and intermolecular K_H/K_D=1.0).



On the basis of these preliminary results, two possible mechanisms are proposed (Scheme 2). Initially, generation of NO from tert-butyl nitrite and its conversion to the NO_2 radical under aerobic conditions has strong literature precedent.[14] Morever, trace amount O_2 and H_2O could also promote this transformation(a, Scheme 2).[3d,14c] Then the NO_2 radical addition to the activated alkenes **1a** generates radical intermediate **A**, followed by intramolecular carbocyclization affording radical intermediate **B**, which is oxidized by NO_2 to generate **2a** *via* a SET process. Alternatively, another process with the NO radical addition could not be excluded (b, Scheme 2). The generated NO radical from tert-butyl nitrite directly attacks **1a** to give radical intermediate **D**, which undergoes intramolecular carbocyclization to generate radical **E**. Further single electron oxidation of **E** by NO_2 radical affording NO substituted oxindole **F** which is very active and easily oxidized by air to afford the desire product **2a** in the subsequent purification processing.[16]

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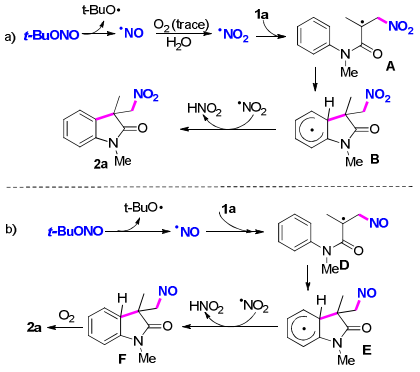

Scheme 2 Proposed mechanisms

In conclusion, we have developed a highly efficient protocol for the preparation of various biologically interesting nitro oxindoles by metal free nitro-carbocyclization of activated alkenes *via* cascade C-N and C-C bond formation. The mechanistic study indicates that both of the NO and NO_2 radical addition are involved in this transformation. NO_2 radical addition is prior than NO radical addition to the activated alkene. Further studies on the clarification of the reaction mechanism and application of this transformation are undergoing.

Acknowledgment

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (a) A. G. M. Barrett and G. G. Graboski, *Chem. Rev.* 1986, **86**, 751; (b) N.Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH: New York, 2001.

2 (a) K. Schofield, *Aromatic Nitration*, Cambridge University Press, Cambridge, 1980; (b) G. A. Olah, R. Malhotra and S. C. Narang, *Nitration: Methods and Mechanisms*, VCH, Weinheim, 1989.

3 (a) P. J. Campos, B. Garcia and M. A. Rodriguez, *Tetrahedron Lett.* 2000, **41**, 979; (b) Y. Nishiwaki, S. Sakaguchi and Y. Ishii, *J. Org. Chem.* 2002, **67**, 5663; (c) K. Jayakanthan, K. P. Madhusudanan and Y. D. Vankar, *Tetrahedron.* 2004, **60**, 397; (d) I. Jovel, S. Prateeptongkum, R Jackstell, N. Vogl, C. Weckbecker and M. Beller, *Adv.Synth. Catal.* 2008, **350**, 2493, and references cited therein.

4 For some reviews on C-H functionalization, see: (a) G. Song, F.Wang and Li, X. *Chem. Soc. Rev.* 2012, **41**, 3651; (b) J.Wencel-Delord, T. Dro□ge, F. Liu and Glorius, F. *Chem. Soc. Rev.* 2011, **40**, 4740; (c) H. Lu and X. P. Zhang, *Chem. Soc. Rev.* 2011, **40**, 1899; (d) C. S.Yeung and V. M.Dong, *Chem. Rev.* 2011, **111**, 1215; (e) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew.Chem., Int. Ed.*, 2009, **48**, 5094; (f) T.W. Lyons and M. S. Sanford, *Chem.Rev.*, 2010, **110**, 1147; (g) M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704; (h) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315.

5 For some recent examples of transition metal-free C–H functionalization, see: (a) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem.* 2010, **2**, 1044; (b)M. Ochiai, K. Miyamoto, T. Kaneaki, S. Hayashi and W. Nakanishi, *Science,* 2011, **332**, 448; (c)E. Shirakawa and T. Hayashi, *ChemLett.*, 2012, **41**, 130; (d) J. A. Souto, D. Zian and K. Mun˜iz, *J. Am. Chem. Soc.*, 2012, **134**, 7242.

6 For some reviews on oxindoles, see: (a) J. E. M. N. Klein and R. J. K. Taylor*, Eur. J. Org. Chem.* 2011, 6821; (b) A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.* 2010, 4527; (c) B. M. Trost and M. K. Brennan, *Synthesis.* 2009, 3003.

7 For some reported synthesis of oxindoles from aniline derivatives in recent two years, see: (a) C. Tsukano, M. Okuno and Y. Takemoto, *Angew. Chem. Int. Ed.* 2012, **51**, 2763; (b) C. Dey and E. P. Kundig, *Chem. Commun.* 2012, **48**, 3064; (c) T. Wu, X. Mu and G. Liu, *Angew. Chem. Int. Ed.* 2011, **50**, 12578; (d) L. Liu, N. Ishida, S. Ashida, M. Murakami, *Org. Lett.* 2011, **13**, 1666; (e) C. Dey, D. Katayev, K. E. O. Ylijoki and E. P. Kundig, *Chem. Commun.* 2012, 10957; (f) A. Beyer, J. Buendia and C. Bolm, *Org. Lett.* 2012, **14**, 3948; (g) D. C. Fabry, M. Stodulski, S. Hoerner, and T. Gulder, *Chem. Eur. J.* 2012, **18**, 10834.

8 For some transition metal-mediated radical synthesis of oxindoles from aniline derivatives, see: (a) W.-T. Wei, M.-B. Zhou, J.-H. Fan, W. Liu, R.-J. Song, Y. Liu, M. Hu, P. Xie and J.-H. Li, *Angew. Chem. Int. Ed.* 2013, **52**, 3638; (b) Y.- M. Li, M. Sun, H.-L.Wang, Q.-P. Tian and S.-D. Yang, *Angew. Chem. Int. Ed.*2013, **52**, 3972.

9 For some metal-free radical synthesis of oxindoles from aniline derivatives, see: (a) M.-B. Zhou, R.-J. Song, X.-H. Ouyang, Y. Liu, W.-T. Wei, G.-B. Deng and J.-H. Li, *Chem. Sci.* 2013, **4**, 2690; (b) K. Matcha, R. Narayan and A. P. Antonchick, *Angew. Chem. Int. Ed.* 2013, **52**, 7985; (c) Y. Meng, L.-N.Guo, H. Wang and X.-H. Duan, *Chem. Commun.*2013, 7540; (d) X.-Q. Li, X.-S. Xu, P.-Z. Hu, X.-Q. Xiao and C. Zhou, *J. Org.Chem*. 2013, **78**, 7343;

10 For examples of addition of nitrogen dioxide to alkenes, see: (a)T. E.Stevens and W. D. Emmons, *J. Am.Chem. Soc.*1958, **80**, 338; (b) H. Suzuki and T. Mori, *J. Org.Chem*.1997, **62**, 6498; (c) L. Grossi, P. C. Montevecchi and S. Strazzari, *Eur. J. Org. Chem.* 2001, 741; (d) M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian. *Tetrahedron.* 2010*,* **66**, 9077; (e) S. Goldstein,; J. Lind and G. Merenhi, *Chem. Rev.* 2005, **105**, 2457.

11 For some recent reviews, see: (a) B. Trost and M. K.Brennan, *Synthesis.* 2009, 3003; (b) A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.* 2010, 4527; (c) F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.* 2010, **352**,1381.

12 (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; (c) S. Ranganathan and S. K. Kar, *J. Org. Chem.*1970, **35**, 3962.

13 For examples of autoxidation of nitrogen monoxide, see: (a) S. Goldstein and G. Czapski, *J. Am. Chem. Soc.*1995, **117**, 12078; (b) L. Grossi and S. Strazzari, *J. Org. Chem.*1999, **64**, 8076.

14 (a) Y. Liu, *Synlett*. 2011, **2011**, 1184; (b) D. Koley, O. C. Colon and S. N. Savinov, *Org. Lett.* 2009, **11**, 4172; (c) T. Taniguchi, A. Yajima and H. Ishibashi, *Adv. Synth. Catal.* 2011, **353**, 2643; (d) B. Kilpatrick, M. Heller and S. Arns, *Chem. Commun.* 2013, **49**, 514; (e) T. Taniguchi, Y. Sugiura, T. Hatta, A. Yajima and H. Ishibashi, *Chem. Commun.*2013,**49**, 2198.

15 (a) C. Francesca, G. Andrea, S. Gianluca and G. Andrea, *Synlett.* 2004, **9**, 155; (b) B. Roberto, M. Enrico and P. Marino, *Tetrahedron Lett*. 1992, **33**, 4835.

16 A. Paola, C. Patricia, G. Lucedio, M. Milvia, S. Pierluigi, D. Elisabetta and R. Corrado, *Eur. J. Org. Chem.* 2008, **19**, 3279.

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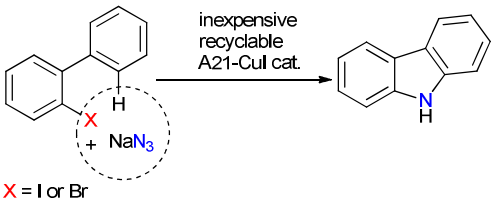
Metal-Free Nitro-Carbocyclization of Activated Alkenes: Direct Approach to Oxindoles by Cascade C-N and C-C Bond Formation



A direct nitro-carbocyclization of activated alkenes leading to nitro-containing oxindoles via cascade C-N and C-C bond formation has been developed.