SHORT COMMUNICATION

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201500780

Selectfluor–Bu_4NI-Mediated C(sp^3)–H Oxidation in Aqueous Media: Synthesis of Δ^2-Isoxazolines from Oximes

Di Shi,[a] Hai-Tao Qin,[a] Chen Zhu,*[b] and Feng Liu*[a]

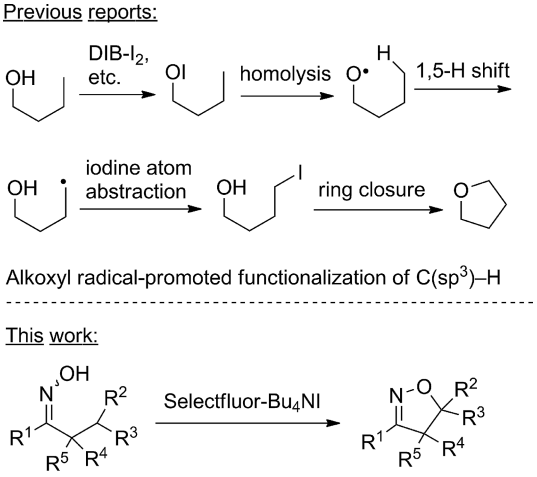
Keywords: Radical reactions / C–H activation / Oxidation / Hydrogen transfer / Oximes

The direct functionalization of an aliphatic C–H bond within a complex molecule through a free-radical pathway is a valuable tool in synthetic chemistry. Herein, we developed an efficient transition-metal-free approach to generate Δ^2-isoxazolines from oximes by radical-mediated C(sp^3)–H oxidation. Investigation of the mechanism suggested that in the presence of Selectfluor and Bu_4NI, the homolysis of the in situ formed O–I bond generated an iminoxyl radical that facilitated subsequent 1,5-H transfer and C(sp^3)–H oxidation.

Introduction

Direct functionalization of alkyl C(sp^3)–H bonds is one of the most atom- and step-economical pathways to generate complex molecules from simple precursors.[1] However, it remains a challenge in terms of reactivity, owing to the inert nature of the C–H bond and the site selectivity in the molecules containing multiple C–H bonds.[1] To achieve good regioselectivities of aliphatic C–H activation in complex molecules, strategies combining transition-metal catalysis and chelating groups have been extensively investigated in recent years.[2] Alternatively, free-radical-promoted functionalization of C(sp^3)–H bonds by intramolecular hydrogen-atom abstraction, in particular 1,5-hydrogen-atom transfer (1,5-HAT),[3] provides a powerful tool in synthetic chemistry.[4]

Oximes are versatile precursors for the synthesis of heterocycles, including isoxazole structural motifs. Single-electron oxidation of oximes readily generates iminoxyl radicals, which can be captured by C=C bonds to initiate olefin difunctionalization.[5] We hypothesized that if these iminoxyl radicals could enable intramolecular 1,5-HAT, an efficient approach for direct C(sp^3)–H oxidation leading to the corresponding isoxazoline products might be realized. As part of our ongoing project aimed at the synthesis of diverse isoxazolines,[6] we herein disclose a novel synthesis of Δ^2-isoxazolines from oximes by use of Selectfluor[7] and Bu_4NI in aqueous media under transition-metal-free conditions through iminoxyl radical-promoted functionalization of C(sp^3)–H bonds (Scheme 1).



Scheme 1. Iminoxyl radical promoted C(sp^3)–H functionalization; DIB = (diacetoxyiodo)benzene.

Δ^2-Isoxazolines are not only versatile intermediates in organic synthesis,[8] but they show remarkable biological activity against many human disease related targets.[9] The conventional method for the synthesis of Δ^2-isoxazolines involves intermolecular cycloaddition of nitrile oxides with alkenes.[10,11] However, it is difficult to obtain satisfactory regioselectivities in the synthesis of polysubstituted derivatives.[11] Very recently, Chiba reported oxime-involved cyclization by 1,5-HAT[12] to synthesize Δ^2-isoxazolines by using 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) as the iminoxyl radical initiator. Compared to that method,[12] the current methodology demonstrates significant advantages:

[a] Jiangsu Key Laboratory of Translational Research and Therapy for Neuro-Psycho-Diseases and Department of Medicinal Chemistry, College of Pharmaceutical Sciences, Soochow University,
199 Ren-Ai Road, Suzhou, Jiangsu 215123, P. R. China
E-mail: fliu2@suda.edu.cn
http://pharm.suda.edu.cn/team/shizijieli/394.html
[b] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University,
199 Ren-Ai Road, Suzhou, Jiangsu 215123, P. R. China
E-mail: chzhu@suda.edu.cn
http://chemistry.suda.edu.cn/index.aspx?lanmuid=69&sublanmuid=604&id=353

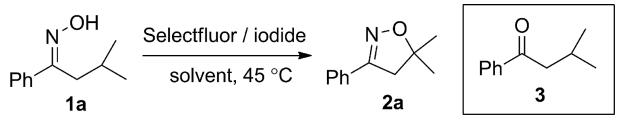
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500780.

(1) milder reaction conditions, (2) extended substrate scope, and (3) good chemoselectivity (Scheme 1).

Results and Discussion

At the outset, we conducted the reaction by using Selectfluor (2.0 equiv.) and Bu_4NI (20 mol-%) in CH_3CN or DMF at 45 °C. Unfortunately, model substrate **1a** completely decomposed into ketone **3** (Table 1, entries 1 and 2). Considering that both Selectfluor and Bu_4NI are water soluble, biphasic solvent systems were then evaluated. Desired Δ^2-isoxazoline **2a** was obtained in 20% yield by using a 1,2-dichloroethane (DCE)/H_2O co-solvent system, though 40% of **1a** was recovered (Table 1, entry 3). Increasing the amount of Bu_4NI accelerated the reaction and improved the yield of isolated product **2a** (Table 1, entries 4 and 5). A further increase in the amount of Selectfluor to 3.0 equivalents led to a higher yield of **2a** (Table 1, entry 6). The employment of other iodides or co-solvent systems was not beneficial to the outcome (Table 1, entries 7–10). Changing the ratio of DCE/H_2O also did not help (Table 1, entry 11). Notably, elevating the reaction temperature significantly improved the reaction yield, and ketone **3** was identified as the principal byproduct (Table 1, entries 12 and 13).

Table 1. Optimization of reaction conditions.[a]



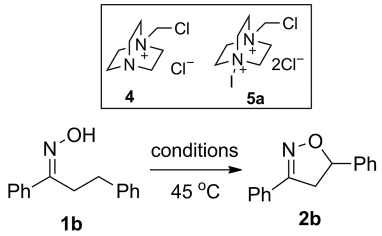
Entry	Solvent	Iodide	t[b] [h]	Yield [%][c]
1[d]	CH_3CN	Bu_4NI (20 mol-%)	2	0
2[d]	DMF	Bu_4NI (20 mol-%)	2	<5
3[d]	DCE/H_2O (1:1)	Bu_4NI (20 mol-%)	5	20 (40)[e]
4[d]	DCE/H_2O (1:1)	Bu_4NI (1 equiv.)	5	33
5[d]	DCE/H_2O (1:1)	Bu_4NI (2 equiv.)	5	44
6	DCE/H_2O (1:1)	Bu_4NI (2 equiv.)	2	54
7	DCE/H_2O (1:1)	NaI (2 equiv.)	5	37
8	DCE/H_2O (1:1)	LiI (2 equiv.)	4	32
9	EtOAc/H_2O (1:1)	Bu_4NI (2 equiv.)	4	35
10	PhCl/H_2O (1:1)	Bu_4NI (2 equiv.)	2	33
11	DCE/H_2O (2:1)	Bu_4NI (2 equiv.)	2	47
12[f]	DCE/H_2O (1:1)	Bu_4NI (2 equiv.)	2	65
13[g]	DCE/H_2O (1:1)	Bu_4NI (2 equiv.)	2	73

[a] Unless noted otherwise, reactions were performed by using **1a** (1.0 equiv.) and Selectfluor (3.0 equiv.) at 45 °C. [b] Based on entire conversion. [c] Yield of isolated **2a**. [d] Selectfluor: 2.0 equiv. [e] Substrate **1a** (40%) recovered. [f] 60 °C. [g] 80 °C.

With the optimized reaction conditions in hand, we turned to define the substrate scope and the limitations of the reaction (Figure 1). The reaction proceeded regardless of the electronic properties of the R^1 substituent on the aryl ring, and Δ^2-isoxazolines **2b**–**i** were produced in good yields at 45 °C. The reaction of polysubstituted oximes **1j**–**n** also took place smoothly, albeit with reaction times that were sometimes prolonged or with a reaction temperature that was elevated (80 °C). In the case of **1l**, *trans* Δ^2-isoxazoline **2l** was generated with unique stereoselectivity owing to the thermodynamic stability of the product. The reactions of 3,3-diaryl oximes **1o** and **1p** gave desired products **2o** and **2p**, respectively, in a higher yield at 80 °C. The oxidation of non-benzylic C(sp^3)–H bonds succeeded as well, and products **2a** and **2q**–**s** were obtained in moderate to excellent yields.

To gain mechanistic insight into this transformation, several cyclization conditions were examined by using **1b**. The reaction was first performed under the conditions that were well established to form alkoxyl radicals[4c,13] and amidyl radicals[14] with in situ generated AcOI (Table 2, entries 1 and 2). The yield of **2b** turned out to be low as a result of the concurrence of an undesired hydrolysis reaction. Upon using a combination of DIB, I_2, and 1,4-diazabicyclo[2.2.2]-octane (DABCO) salt **4**, the transformation of **1b** into **2b** was greatly improved (Table 2, entry 3). We speculated that a complex of iodinated DABCO salt might be generated as the virtual reactive species in the reaction. To test this hypothesis, we treated **1b** with bench-stable iodinating reagent **5a**,[15] which was readily prepared from **4** with an excess amount of iodine chloride (ICl) (Table 2, entries 4 and 5). Both reactions gave desired product **2b** in good yield (71 and 79%).

Table 2. Investigations on other iodine(I) systems.



Entry	Conditions	Yield (%)
1	AgOAc (2.5 equiv.) / I_2 (2.5 equiv.) DCE, 4 h	28%
2	DIB (2.5 equiv.) / I_2 (2.5 equiv.) DCE, 6 h	< 5%
3	DIB (1.5 equiv.) / I_2 (1.5 equiv.) **4** (3 equiv.), DCE, 1 h	83%
4	**5a** (3 equiv.), DCE, 24 h	71%
5	**5a** (3 equiv.), DCE/H_2O, 4 h	79%

On the basis of the above results, a postulated mechanism is depicted in Scheme 2. The reaction of oxime **1** and **5b** provides hypoiodite intermediate **A**, in which the O–I bond is prone to homolyzing to iminoxyl radical **B**.[4e] Subsequent 1,5-HAT generates C-centered radical intermediate **C**, which is intercepted by an iodine atom to give β-iodo oxime **D** or oxidized to form carbon cation **D′**. The following nucleophilic substitution or addition eventually affords Δ^2-isoxazoline **2**. Although the α,β-unsaturated oxime was proposed to be the key intermediate in TEMPO-mediated reactions,[12] the reaction of α,β-unsaturated oxime **6** led to isoxazole **7** rather than Δ^2-isoxazoline **2b** under the current reaction conditions [Scheme 3, Equation (1)].[16] This result suggested that the formation of **2** from **D** or **D′** should go

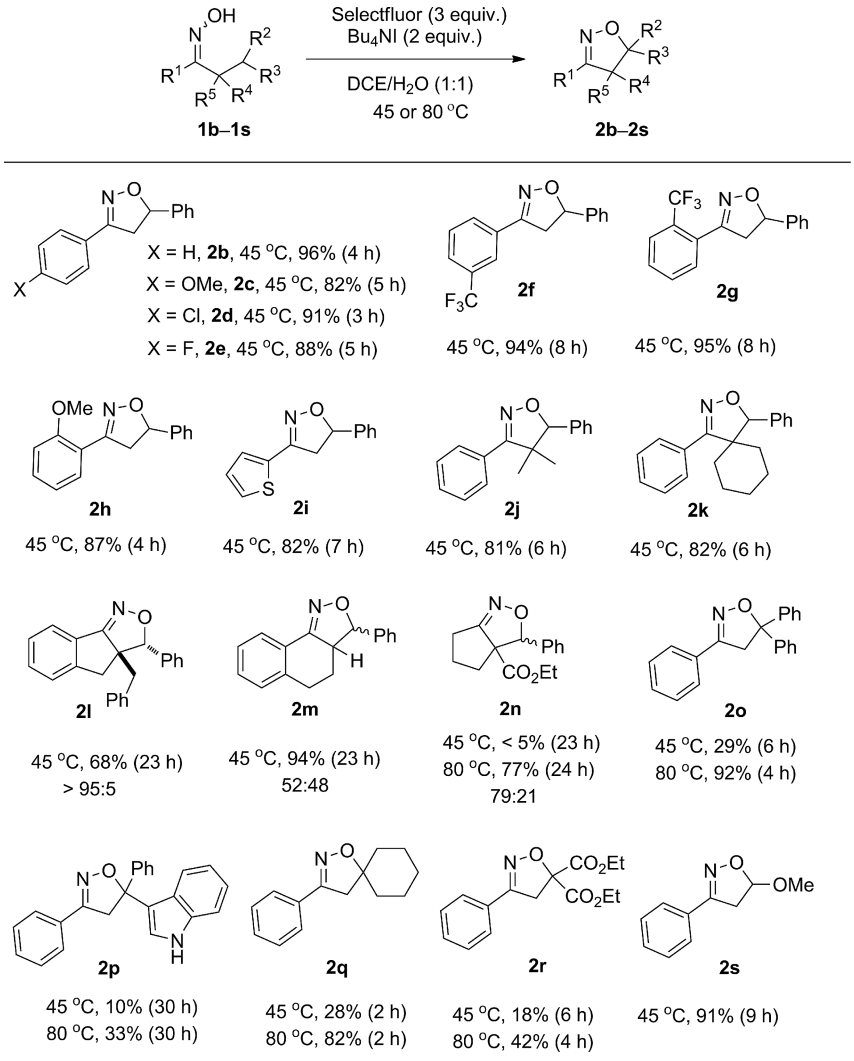
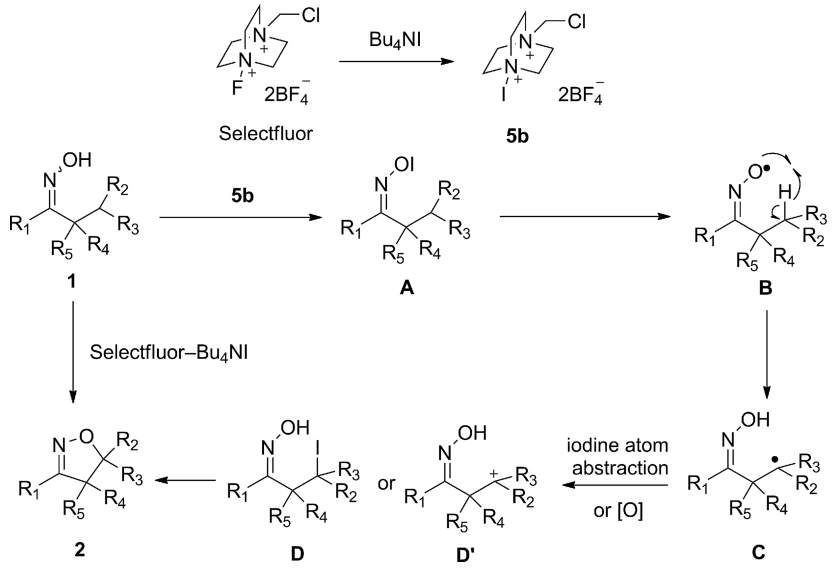
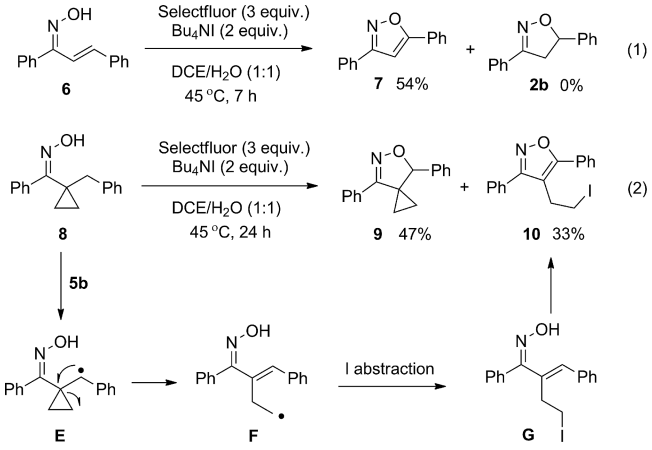


Figure 1. Substrate scope.



Scheme 2. Proposed mechanism.

through direct intramolecular nucleophilic substitution or addition. To gain more mechanistic evidence, oxime **8** with a cyclopropyl moiety was subjected to the optimized condition. The reaction gave not only expected Δ^2-isoxazoline **9** but also isoxazole **10** by radical-mediated ring opening of cyclopropane [Scheme 3, Equation (2)]. These experimental results might support our hypothesis that the isoxazoline product is not generated through Michael addition of the α,β-unsaturated oxime. Remarkably, whereas the reaction of α-quaternary oximes gave no desired C–H oxygenation products with TEMPO,[12] the reaction under the current conditions readily afforded corresponding Δ^2-isoxazolines such as **2j**–**l** and **2n** (Figure 1).



Scheme 3. Further evidence for the proposed mechanism.

We then examined the regioselectivity of the reaction (Scheme 4). The reaction of **1t** (*Z*/*E* = 40:60) under the optimized conditions afforded the Δ^2-isoxazoline **2t** in 84% yield with excellent site selectivity [Scheme 4, Equation (3)]. We also conducted the competitive reactions 1,5-HAT versus 1,6-HAT [Scheme 4, Equation (4)] and 1,5-HAT versus 1,4-HAT [Scheme 4, Equation (5)]. Although 1,4-HAT and 1,6-HAT have been documented,[17,18] only 1,5-HAT products **2u** and **2v** were found.

Conclusions

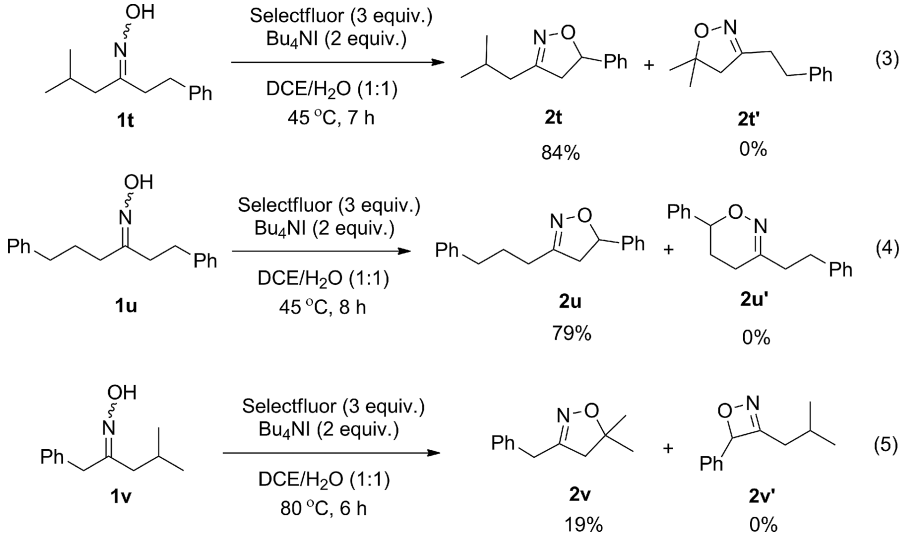
In conclusion, we described the Selectfluor–Bu_4NI-mediated synthesis of Δ^2-isoxazolines from oximes through remote C(sp^3)–H oxidation in aqueous media under metal-free conditions. A variety of isoxazolines were furnished in good yields. Preliminary mechanistic investigations suggested that a novel 1,4-diazabicyclo[2.2.2]octane–iodine complex might be involved in the reaction. From a mechanistic point of view, this method provides a new route to generate iminoxyl radicals.

Experimental Section

General Procedure: A mixture of oxime **1** (0.12 mmol, 1 equiv.), Selectfluor (0.36 mmol, 3 equiv.), and Bu_4NI (0.24 mmol, 2 equiv.) in 1,2-dichloroethane (2 mL) and water (2 mL) was stirred at 45 °C (or 80 °C). The reaction was monitored by TLC until the oxime was completely consumed. The cooled mixture was extracted with dichloromethane (3 × 5 mL). The combined organic phase was dried with anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel; hexane/ethyl acetate, 40:1 v:v) to give isoxazoline **2**.

Acknowledgments

F. L. and C. Z. are grateful for financial support from the National Natural Science Foundation of China (NSFC) (grant numbers 21302134 and 21402134, respectively), the Natural Science Foundation of Jiangsu (grant numbers BK20130338 and BK20140306, respectively), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).



Scheme 4. Regioselectivity of C(sp^3)–H oxidation.

[1] For recent selected reviews on C–H functionalization, see: a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; b) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.

[2] For recent selected examples, see: a) G. He, S.-Y. Zhang, W. A. Nack, Q. Li, G. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 11124; *Angew. Chem.* **2013**, *125*, 11330; b) Z. Ren, F. Mo, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 16991; c) G. He, G. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; *Angew. Chem.* **2011**, *123*, 5298; d) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965.

[3] a) A. E. Dorigo, K. N. Houk, *J. Am. Chem. Soc.* **1987**, *109*, 2195; b) A. E. Dorigo, M. A. McCarrick, R. J. Loncharich, K. N. Houk, *J. Am. Chem. Soc.* **1990**, *112*, 7508.

[4] For examples of 1,5-H radical transfer used, in: organic Synthesis see: a) M. Lachia, F. Denes, F. Beaufils, P. Renaud, *Org. Lett.* **2005**, *7*, 4103; b) B. Frey, A. P. Wells, D. H. Rogers, L. N. Mander, *J. Am. Chem. Soc.* **1998**, *120*, 1914; c) L. A. Paquette, L. Q. Sun, D. Friedrich, P. B. Savage, *J. Am. Chem. Soc.* **1997**, *119*, 8438; d) P. M. Burden, H. T. A. Cheung, T. H. Ai, T. R. Watson, *J. Chem. Soc. Perkin Trans. 1* **1983**, 2669; e) G. Majetich, *Tetrahedron* **1995**, *51*, 7095 and references cited therein.

[5] a) B. Han, X.-L. Yang, R. Fang, W. Yu, C. Wang, X.-Y. Duan, S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 8816; *Angew. Chem.* **2012**, *124*, 8946; b) X.-X. Peng, Y.-J. Deng, X.-L. Yang, L. Zhang, W. Yu, B. Han, *Org. Lett.* **2014**, *16*, 4650; c) X.-L. Yang, F. Chen, N.-N. Zhou, W. Yu, B. Han, *Org. Lett.* **2014**, *16*, 6476.

[6] a) K.-Y. Dong, H.-T. Qin, X.-X. Bao, F. Liu, C. Zhu, *Org. Lett.* **2014**, *16*, 5266; b) K.-Y. Dong, H.-T. Qin, F. Liu, C. Zhu, *Eur. J. Org. Chem.* **2015**, 1419.

[7] a) P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C.-H. Wong, *Angew. Chem. Int. Ed.* **2005**, *44*, 192; *Angew. Chem.* **2005**, *117*, 196; b) R. P. Singh, J. M. Shreeve, *Acc. Chem. Res.* **2004**, *37*, 31.

[8] For synthetic applications, see: a) D. Kim, J. Lee, P. J. Shim, J. I. Lim, H. Jo, S. Kim, *J. Org. Chem.* **2002**, *67*, 764; b) M. Kambe, E. Arai, M. Suzuki, H. Tokuyama, T. Fukuyama, *Org. Lett.* **2001**, *3*, 2575; c) D. P. Curran, T. A. Heffner, *J. Org. Chem.* **1990**, *55*, 4585; d) A. P. Kozikowski, *Acc. Chem. Res.* **1984**, *17*, 410.

[9] For biological evaluation of Δ^2-isoxazolines, see: a) G. C. Rodrigues, D. F. Feijó, M. T. Bozza, P. Pan, D. Vullo, S. Parkkila, C. T. Supuran, C. Capasso, A. P. Aguiar, A. B. Vermelho, *J. Med. Chem.* **2014**, *57*, 298; b) S. Castellano, D. Kuck, M. Viviano, J. Yoo, F. López-Vallejo, P. Conti, L. Tamborini, A. Pinto, J. L. Medina-Franco, G. J. Sbardella, *J. Med. Chem.* **2011**, *54*, 7663; c) D. J. Parks, W. H. Parsons, R. W. Colburn, S. K. Meegalla, S. K. Ballentine, C. R. Illig, N. Qin, Y. Liu, T. L. Hutchinson, M. L. Lubin, D. J. Stone Jr., J. F. Baker, C. R. Schneider, J. Ma, B. P. Damiano, C. M. Flores, M. R. Player, *J. Med. Chem.* **2011**, *54*, 233; d) Y.-G. Suh, N.-J. Kim, B.-W. Koo, K.-O. Lee, S.-H. Moon, D.-H. Shin, J.-W. Jung, S.-M. Paek, D.-J. Chang, F. Li, H.-J. Kang, T. V. T. Le, Y. N. Chae, C. Y. Shin, M.-K. Kim, J. I. Lim, J.-S. Ryu, H.-J. Park, *J. Med. Chem.* **2008**, *51*, 6318.

[10] a) A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev, V. V. Zhdankin, *Org. Lett.* **2013**, *15*, 4010; b) H. Yao, J. Ren, R. Tong, *Chem. Commun.* **2013**, *49*, 193; c) N. Chatterjee, P. Pandit, S. Halder, A. Patra, D. K. Maiti, *J. Org. Chem.* **2008**, *73*, 7775; d) H. Feuer (Ed.), *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis* Wiley, Hoboken, NJ, **2007**; e) M. P. Yeh, C. Jou, W. Yeh, D. Chiu, N. R. K. Reddy, *Tetrahedron* **2005**, *61*, 493.

[11] K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863.

[12] a) X. Zhu, Y.-F. Wang, W. Ren, F.-L. Zhang, S. Chiba, *Org. Lett.* **2013**, *15*, 3214.

[13] a) H. Kim, C. Ziani-Cherif, J. Oh, J. K. Cha, *J. Org. Chem.* **1995**, *60*, 792; b) J. Lee, J. Oh, S.-J. Jin, J.-R. Choi, J. L. Atwood, J. K. Cha, *J. Org. Chem.* **1994**, *59*, 6955.

[14] a) S. Zhuang, K. Liu, C. Li, *J. Org. Chem.* **2011**, *76*, 8100; b) X. Yuan, K. Liu, C. Li, *J. Org. Chem.* **2008**, *73*, 6166; c) Hu, M. Shen, Q. Chen, C. Li, *Org. Lett.* **2006**, *8*, 2647.

[15] For brominating/iodinating reagent analogues of **5a**, see: a) W. Xie, G. Jiang, H. Liu, J. Hu, X. Pan, H. Zhang, X. Wan, Y. Lai, D. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 12924; *Angew. Chem.* **2013**, *125*, 13162; b) Y.-M. Wang, J. Wu, C. Hoong, V. Rauniyar, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 12928.

[16] The cyclization of **6** by using the Selectfluor–Bu_4NI system could proceed in either an ionic or a radical 5-*endo* manner, followed by HI elimination to afford **7**.

[17] For 1,4-HAT, see: M. Gulea, J. M. Lopez-Romero, L. Fensterbank, M. Malacria, *Org. Lett.* **2000**, *2*, 2591.

[18] For 1,6-HAT, see: D. Denenmark, T. Winkler, A. Waldner, A. De Mesmaeker, *Tetrahedron Lett.* **1992**, *33*, 3613.

Received: June 12, 2015
Published Online: July 15, 2015

