Tetrahedron Letters 55 (2014) 2243–2245

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# The direct C–H halogenations of indoles

Leilei Shi [a,b], Dongmei Zhang [c], Riyuan Lin [b], Chun Zhang [b], Xun Li [a,*], Ning Jiao [b,*]

[a] Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmaceutical Sciences, Shandong University, Ji'nan 250012, China
[b] State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Xue Yuan Rd. 38, Beijing 100191, China
[c] Shandong Institute for Food and Drug Control, Ji'nan 250101, China

ARTICLE INFO

*Article history:*
Received 20 December 2013
Revised 11 February 2014
Accepted 20 February 2014
Available online 28 February 2014

*Keywords:*
C–H funtionalization
Transition-metal free
Halogenation
Indoles

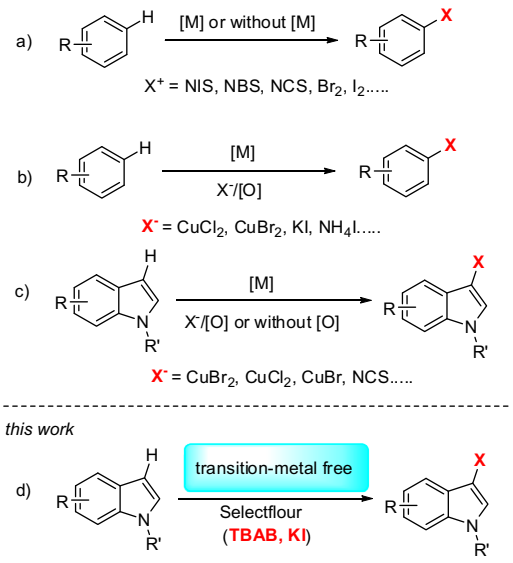
ABSTRACT

A novel and efficient transition metal-free C–H bond halogenation of indole derivatives has been developed. 3-Halogenated (3-Br, 3-I) indoles are highly regioselectively produced by this protocol. Simple and readily available halide salts (TBAB, KI) are employed as the halogen source. The transition metal-free and the mild conditions make this protocol very easy to handle and practical.



Organic halides are important building blocks for pharmaceuticals and fine chemicals.[1] The $sp^2$ C–X units are also significant structure fragments in many pharmaceuticals and natural products.[2] In order to prepare aryl halides, electrophilic halogenation of aromatic compounds through Friedel–Crafts reaction with electrophilic reagents such as NIS, NBS, NCS, $Br_2$ and $I_2$, as the halogen source has been realized several decades ago (a, Scheme 1).[3] Though this transformation exhibited good reactivity, it suffered some drawbacks in the functional group tolerance and regioselectivity. In recent decades, C–H functionalization has attracted considerable attentions.[4] More recently, transition-metal mediated oxidative C–H halogenation has been developed employing readily available halide salts as the halogen source (b, Scheme 1).[5] Despite the significance of these protocols with high atom economy and high efficiency, the relatively high price and considerable toxicity of transition metals may limit their further applications and improvements. Therefore, the development of a transition metal-free approach via C–H halogenation would be more meaningful and attractive.[6]

Due to the ubiquitous existence of indole skeleton in pharmaceuticals and bioactive natural products, indole skeleton based modification has attracted enormous interest of medicinal chemists.[7,8] 3-Halogenation of indoles has also been reported by using transition-metal salts catalysis.[9] Our group has been interested in designing and modifying indole derivatives (c, Scheme 1).[10] Herein, we describe an efficient transition-metal free approach for the synthesis of 3-halogenated (3-Br, 3-I) indoles using simple and readily available TBAB and KI as the halogen source, respectively, (d, Scheme 1). To the best of our knowledge, the direct halogenation of indoles under transition metal-free conditions with halide

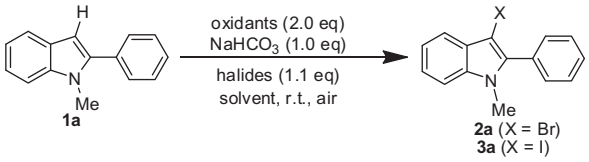



**Scheme 1.** Direct halogenation reactions.

* Corresponding authors. Tel./fax: +86 010 8280 5297.
*E-mail addresses:* tjulx2004@sdu.edu.cn (X. Li), jiaoning@bjmu.edu.cn (N. Jiao).

http://dx.doi.org/10.1016/j.tetlet.2014.02.071
0040-4039/

**Table 1**
Optimization of reaction conditions[a]




| Entry | Oxidants | Solvents | Halides | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Selectfluor | DCE | TBAB | **2a** | 85 |
| 2 | BQ | DCE | TBAB | **2a** | 0 |
| 3 | Air | DCE | TBAB | **2a** | 0 |
| 4 | $Ag_2CO_3$ | DCE | TBAB | **2a** | 0 |
| 5 | TBHP | DCE | TBAB | **2a** | 0 |
| 6 | Selectfluor | DCE | NaBr | **2a** | 71 |
| 7 | Selectfluor | DCE | KBr | **2a** | 67 |
| 8 | Selectfluor | DCE | NBS | **2a** | 74 |
| 9 | Selectfluor | Toluene | TBAB | **2a** | 96 |
| 10 | NFSI | Toluene | TBAB | **2a** | 75 |
| 11 | Selectfluor | DCM | TBAB | **2a** | 72 |
| 12 | Selectfluor | DMF | TBAB | **2a** | Trace |
| 13 | Selectfluor | DMSO | TBAB | **2a** | 0 |
| 14 | Selectfluor | THF | TBAB | **2a** | 77 |
| 15 | Selectfluor | Toluene | KI | **3a** | 96 |
| 16 | Selectfluor | Toluene | TBAI | **3a** | 76 |

[a] Unless otherwise noted, the reaction was carried out at room temperature using **1a** (0.2 mmol), oxidant (0.4 mmol), base (0.2 mmol), halides (0.22 mmol), solvents (2 mL) for 2 h under air atmosphere.
[b] Isolated yield. NFSI: N-Fluorodibenzenesulfonimide, Selectfluor: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane, TBAB: tetrabutylammonium bromide, TBAI: tetrabutylammonium iodide, NBS: 1-bromopyrrolidine-2,5-dione.

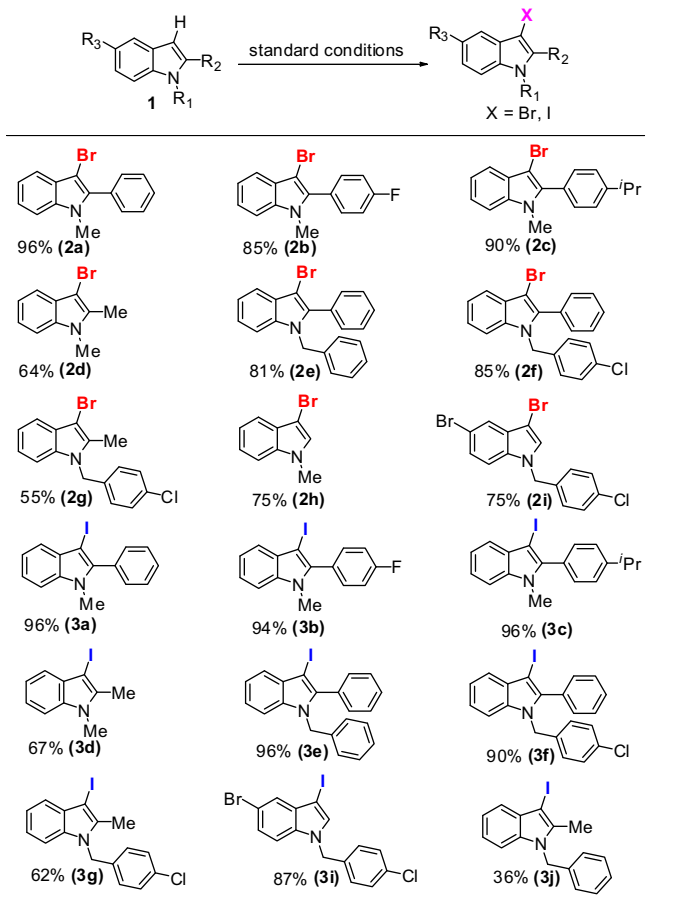
salts has rarely been realized.[11] The present approach achieves high regioselectivity with good substrate compatibility.

Initially, the halogenation of 1-methyl-2-phenyl-1*H*-indole **(1a)** with TBAB as a source of bromide ions was chosen as a model reaction. Interestingly, when Selectfluor[12] was used as an oxidant, the reaction in DCE in the presence of $NaHCO_3$ as a base produced the desired 3-halogenation product **2a** in 85% isolated yield at room temperature (Table 1, entry 1). Then, different oxidants were screened. However, no product was detected when Selectfluor was replaced by other oxidants such as BQ, dioxygen, $Ag_2CO_3$ and TBHP (Table 1, entries 2–5). These results indicate that Selectfluor was the most suitable oxidant for this halogenation transformation. Although the reactions with other bromide salts such as NaBr and KBr as the halogen source proceeded well, the reaction with TBAB showed the highest efficiency (Table 1, entries 7 and 8). Furthermore, when toluene was utilized as solvent, the product **2a** was obtained in 96% isolated yield (Table 1, entry 9). Similarly, NFSI was also suitable for our reaction giving the desired bromination product **2a** in moderate yields (Table 1, entry 10). Other solvents were not favourable for this bromination transformation, especially for those non-proton polar solvents (Table 1, entries 11–14). Moreover, various bases were screened. The results demonstrate that $NaHCO_3$ is most suitable for our reaction (see ESI). Based on the above screening results, the optimal conditions can be determined (Table 1, entry 9).

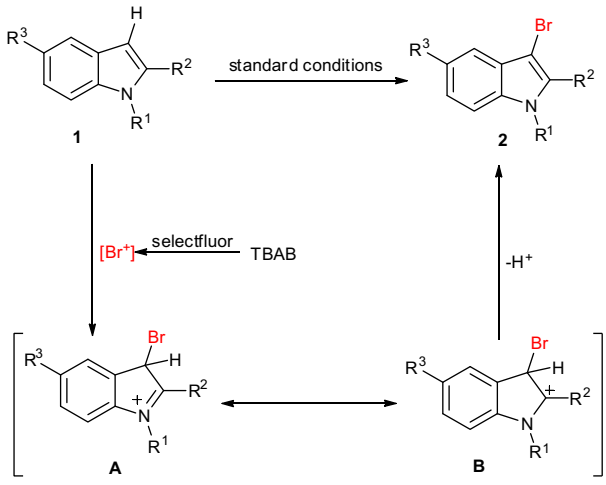
We next investigated whether iodination works under the optimized conditions. Gratifyingly, iodination of **1a** proceeded smoothly under the standard conditions with KI and TBAI as the iodinating reagents leading to the iodination product **3a** in 96% and 76% yields, respectively (Table 1, entries 15 and 16).

With the optimized conditions in hand, the substrate scope was studied as shown in Table 2. All substrates examined under optimized conditions afforded the corresponding products in moderate to excellent yields. The halogenation appears to be invariant to the electronic properties of the substrates as the reaction with both electron-efficient and electron-deficient substituents on the

**Table 2**
Halogenation of indoles with different halides[a,b]




[a] Standard reaction conditions: see (Table 1, entry 9) for bromination of indoles and (Table 1, entry 15) for iodination of indoles.
[b] Isolated yield.




**Scheme 2.** The proposed mechanism for this transformation.

2-phenyl group proceeded efficiently to give the halogenating products with moderate to excellent yields (Table 2, **2a**–**2c**, **3a**–**3c**). When the 2-phenyl was replaced by 2-methyl, both bromination and iodination completed smoothly to give the product with good isolated yields (Table 2, **2d**, **2g**, **3d**, **3j**, **3g**). When *N*-methyl was replaced by *N*-benzyl or 4-substituted benzyl, all of the substrates performed well to afford the desired products

with satisfactory isolated yields (Table 2, **2e**, **3e**, **2f**, **3f**). Substrates without any substituents on the 2-position of indole proceeded efficiently and halogenations occurred highly selectively at the 3-position of indoles with good isolated yields (Table 2, **2h**, **3i**). Halosubstituted indole also can be tolerated in this transformation (Table 2, **2i**, **3i**). Unfortunately, 2-phenyl-1*H*-indole did not work under the standard conditions, mainly because the unprotected indoles can be destructed by Selectfluor.

The proposed mechanism is illustrated in Scheme 2. As reported in literatures, some additional electrophilic reactions can be performed in the presence of Selectfluor.[13] The corresponding $Br^+$ and $I^+$ are generated in situ from TBAB and KI, respectively, upon oxidation with Selectfluor.[14] Then the bromide (iodine) cation is attacked by the electron-rich indoles highly regioselectively at C-3 position to form intermediate **A** or its resonance **B**. At last the proton was abstracted by the base ($NaHCO_3$) to give the product.

In summary, a novel and efficient protocol of transition metal-free C–H bond halogenation of indoles has been developed. 3-Halogenated (3-Br, 3-I) indoles are highly regioselectively produced by this protocol. Simple and readily available halide salts (TBAB, KI) are employed as the halogen source. The transition metal-free and the mild conditions make this protocol very easy to handle and practical. Further investigations on the reaction scope and the synthetic applications are ongoing in our group.

## Acknowledgments

Financial support from the National Science Foundation of China (Nos. 21325206, 21172006), National Young Top-notch Talent Support Program and the Ph.D. Programs Foundation of the Ministry of Education of China (No. 20120001110013) are greatly appreciated. We thank Yuepeng Yan in this group for reproducing the results of **2f** and **3d**.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.071.

## References and notes

1. (a)*Metal-Catalyzed Cross Coupling Reactions*; Meijere, A., Diederich, F., Eds., 2nd ed.; Wiley-VCH: Weinheim, 2004; (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-ACH: Weinheim, 2004; (c) Suzuki, A.; Brown, H. C. *Organic Synthesis via Boranes*; Aldrich: Milwaukee, WI, 2003; (d) Oestreich, M. *The Mizoroki-Heck Reaction*; Wiley: Weinheim, 2009; (e) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.
2. For some reviews see: (a) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049; (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534; (c) Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1439; (d) Negishi, E.; Anastasia, L. *Chem. Rev.* **1979**, *2003*, 103; (e) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365; (f) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434; (g) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
3. (a) Comins, D. L.; Killpack, M. O. *Tetrahedron Lett.* **1989**, *30*, 4337; (b) Duan, X.-H.; Mayr, H. *Org. Lett.* **2010**, *12*, 2238; (c) Roper, K. A.; Lange, H.; Polyzos, A.; Berry, M. B.; Baxendale, I. R.; Ley, S. V. *Beilstein J. Org. Chem.* **2011**, *7*, 1648; (d) Joseph, R.; Pallan, P.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* **1995**, *36*, 609; (e) Branytska, O. V.; Neumann, R. *J. Org. Chem.* **2003**, *68*, 9510.
4. For some reviews on C–H functionalization, see: (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651; (b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740; (c) Lu, H.; Zhang, X. P. *Chem. Soc. Rev.* **1899**, *2011*, 40; (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215; (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147; (f) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57; (g) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212; (h) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624; (i) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890; (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094; (k) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792; (l) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293.
5. (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300; (b) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416; (c) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5524; (d) Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14092; (e) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790; (f) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298; (g) Mo, F.; Yan, J. M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2028; (h) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4440.
6. For some examples of transition-metal free of C–H activation, see: (a) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044; (b) Zhang, H.; Shi, R.; Ding, A.; Lu, L.; Chen, B.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12524; (c) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737; (d) Shirakawa, E.; Itoh, K.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537; (e) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4674.
7. *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Saxton, J. E., Eds.; Wiley-Interscience: New York, 1983; Vol. 25, p 1994; (b) Sundberg, R. J. *Indoles*; Academic: New York, 1996; (c) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761; (d) Saracoglu, N. *Top. Heterocycl. Chem.* **2007**, *11*, 145.
8. For some reviews, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, 215; (b) Palmisano, G.; Penoni, A.; Sisti, M.; Tibiletti, F.; Tollarim, S.; Nicholas, K. M. *Curr. Org. Chem.* **2010**, *14*, 2409; (c) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449; (d) Zeng, M.; You, S.-L. *Synlett* **2010**, 1289; (e) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608; (f) Driver, T. G. *Angew. Chem., Int. Ed.* **2009**, *48*, 7974; (g) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673; (h) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357.
9. (a) Singh, P. P.; Thatikonda, T.; Kumar, K. A. A.; Sawant, S. D.; Sharma, A. K.; Sharma, P. R.; Singh, D.; Vishwakarma, R. A. *J. Org. Chem.* **2012**, *77*, 5823; (b) Yang, L.; Lu, Z.; Stahl, S. *Chem. Commun.* **2009**, 6460; (c) John, A.; Nicholas, K. M. *Organometallics* **2012**, *31*, 7914.
10. (a) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4752; (b) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895; (c) Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540; (d) Shi, Z.; Zhang, B.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *49*, 4036; (e) Shi, Z.; Cui, Y.; Jiao, N. *Org. Lett.* **2010**, *12*, 2908; (f) Xiang, S.-K.; Zhang, B.; Zhang, L.-H.; Cui, Y.; Jiao, N. *Chem. Commun.* **2011**, *47*, 8097; (g) Xiang, S.-K.; Wu, G.-L.; Zhang, B.; Cui, Y.; Jiao, N. *Tetrahedron Lett.* **2012**, *53*, 3802; (h) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374; (i) Lin, R.-Y.; Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2011**, *13*, 4498.
11. (a) Zolfigol, M. A.; Khazaei, A.; Kolvari, E.; Koukabi, N.; Soltani, H.; Behjunia, M. *Hel. Chim. Acta* **2010**, *93*, 587; (b) Khazaei, A.; Zolfigol, M. A.; Kolvari, E.; Koukabi, N.; Soltani, H.; Komaki, F. *Synthesis* **2009**, 3672.
12. (a) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1; (b) Singh, R.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31; (c) Shibata, N.; Ishimaru, T.; Nakamura, S.; Toru, T. *J. Fluorine Chem.* **2007**, *128*, 469; (d) Yin, F.; Wan, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401; (e) Li, Z.; Song, L.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 4640.
13. (a) Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron Lett.* **1997**, *38*, 6305; (b) Stavber, S.; Kralj, P.; Zupan, M. *Synlett* **2002**, 598; (c) Stavber, S.; Kralj, P.; Zupan, M. *Synthesis* **2002**, 1513; (d) Stavber, S.; Jereb, M.; Zupan, M. *Chem. Commun.* **2002**, 488; (e) Podgoršek, A.; Zupan, M.; Iskra, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8424; (f) Stavber, S. *Molecules* **2011**, *16*, 6432.
14. Selectfluor as an oxidant, see some examples: (a) Ye, C.; Shreeve, M. *J. Org. Chem.* **2004**, *69*, 8561; (b) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478; (c) Peng, Y.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 5062; (d) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3112; (e) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474.