RSC Advances

This article can be cited before page numbers have been issued, to do this please use: K. sun, Y. Lv, Z. zhu, Y. jiang, Q. Jiejie, H. Wu, Z. Zhang, Z. Guisheng and X. wang, *RSC Adv.*, 2015, DOI: 10.1039/C5RA07065A.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A Convenient Access to β-Iodo Sulfone by Iodine-Mediated Iodosulfonylation of Alkenes

Kai Sun,*[a] Yunhe Lv,[a] Zhonghong Zhu,[a] Yongqing Jiang,[a] Jiejie Qi,[a] Hankui Wu,[a] Zhiguo Zhang,[b] Guisheng Zhang[b] and Xin Wang*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

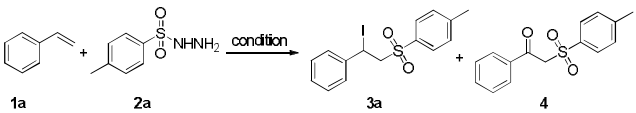
A novel iodine-mediated intermolecular iodosulfonylation reaction of alkenes for daul C–S and C–I bonds formation is described. A series of alkenes could be selectively converted into the corresponding β-iodo sulfones, which are versatile building blocks in organic synthesis and medicinal chemistry. Molecular iodine acted in this reaction as iodine source.

Difunctionalization of alkenes is a class of significant synthetic transformations that allow for the buildup of molecular complexity in a single procedure.[1] Recent, transition-metal-catalyzed difunctionalization of alkenes provide a powerful strategy for the synthesis of two new vicinal chemical bonds simultaneously, and diamination,[2] aminooxygenation,[3] dioxygenation,[4] cyanotrifluoromethylation,[5] fluoroamination,[6] phosphonofluorination,[7] and oxysulfonylation[8] have been elegantly demonstrated. Despite of the overall efficiency and versatility of these transformations, significant limitations such as costly and toxic metal catalyst that led to the emergence of a metal-free approach for difunctionalization of alkenes. Difunctionalization of unsaturated bonds via a radical pathway is an attractive alternative compared to transition-metal-catalyzed difunctionalization of alkenes.[9] Molecular-iodine catalyst, in combination with TBHP as environmentally benign and inexpensive co-oxidant, has been increasingly explored in place of rare or toxic heavy metal oxidants in recent years.[10] Simple iodine has broad transformation ability of functional groups and can be used widely in organic synthesis.[11] The advantages of iodine are operational simplicity, low cost, and less toxicity. However, research towards the development of iodine-catalyzed/mediated methods for the direct functionalization of C–H bonds is still in its infancy, and further explore this fascinating area is highly desirable in synthetic chemistry.[12]

Sulfonyl group is of great importance in medical chemistry, photovoltaic materials, nonlinearoptics, and synthetic chemistry.[13] Therefore, it is valuable to develop new strategies to introduce sulfonyl groups to the designated molecular frameworks. Difunctionalization of alkenes to incorporate the sulfone group is also an attractive target to pursue. Recently, Lei and co-workers reported an elegant aerobic oxysulfonylation of alkenes using sulfinic acids as sulfonyl group.[8a] The similar work was achieved by Itoh group using sodium sulfinates as sulfonyl group promoted by molecular iodine.[8b] We noticed that β-iodo sulfone was eliminated as a possible intermediate in Itoh's work. β-iodo sulfone is a versatile building blocks in organic synthesis and medicinal chemistry, as well as valuable intermediates since the chemical structure can be further elaborated in the construction of a series of useful active molecules. However, conevnient and direct synthetic method for β-iodo sulfone is rare.[14,9b] Sulfonyl hydrazides have been widely used as reductants and as well as a source of sulfonylation and arylation,[15] And concerning our continuing interest in radical oxidative cross-coupling reactions,[16] we now disclose an iodine-mediated intermolecular iodosulfonylation reaction of alkenes by using sulfonylhydrazides as sulfonyl source.[17]

We started our investigations with styrene **1a** and 4-methylbenzenesulfonohydrazide **2a** as model substrates. Several parameters, such as iodine sources, solvents and temperature

Table 1: Screening of Reaction Conditions[a]



1a 2a 3a 4

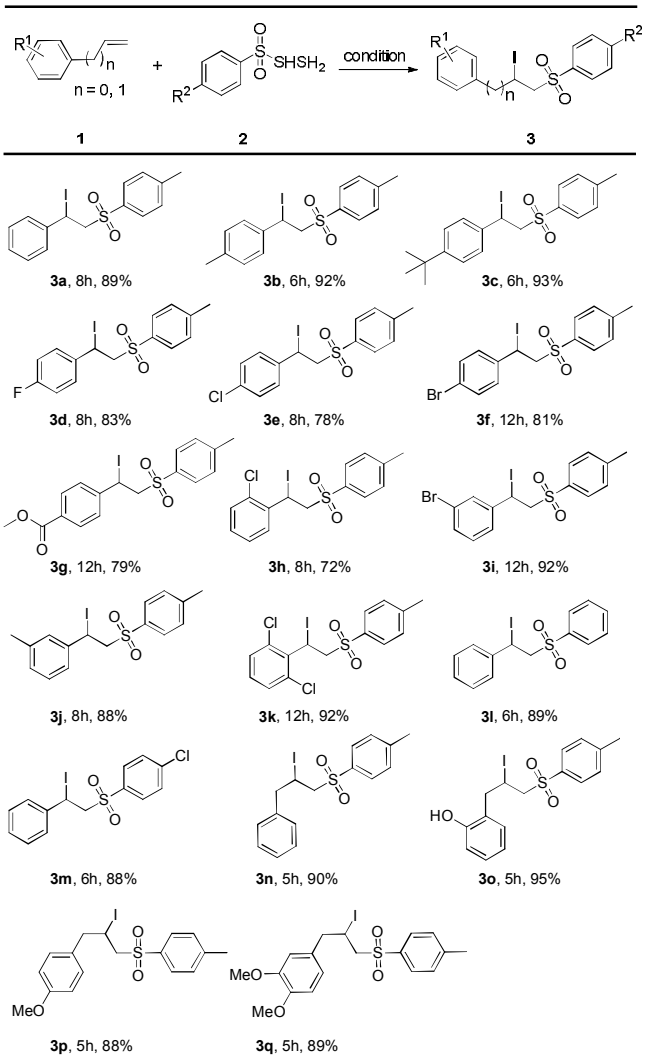
entry	Iodine source	oxidant	solvent	yield of **3a** / **4** (%) [b]
1	I_2	TBHP	EtOAc	0/79 [c]
2	I_2	TBHP	EtOAc	23/57[d]
3	I_2	TBHP	EtOAc	52/0
4	NaI	TBHP	EtOAc	0/0
5	KI	TBHP	EtOAc	0/0
6	nBu$_4$NI	TBHP	EtOAc	0/0
7	I_2	TBHP	MeCN	20/0
8	I_2	TBHP	DCE	0/0
9	I_2	TBHP	EtOH	89/0
10	I_2	TBHP	THF	79/0
11	I_2	TBHP	H_2O	0/0
12	I_2		EtOH	42/0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), iodine source (0.25 mmol) and TBHP (1.0 mmol) at 0-20 °C for 8 h. [b] Yield of isolated product. [c] Reaction performed at 80 °C. [d] Reaction performed at 40 °C.

View Article Online
DOI: 10.1039/C5RA07065A

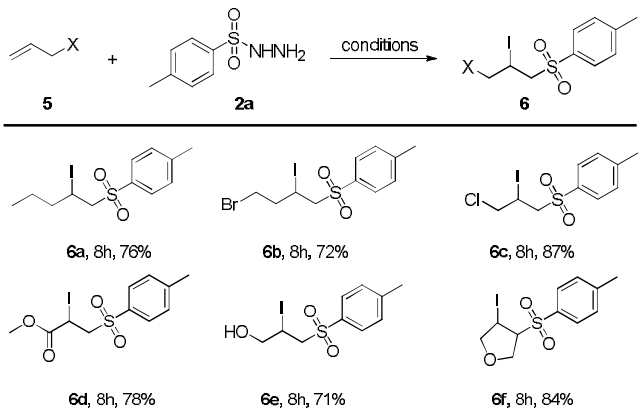
were all conducted to investigate the impact of the reaction outcome, the results are listed in Table **1**. Initially, the reaction of **1a** with **2a** was performed in EtOAc at 80 °C utilizing molecular iodine and TBHP (70% in water) combinations, but we can not detect the iodosulfonylation product **3a**. The unexpected oxysulfonylation product **4** was obtained in 79% yield (Table 1, entry 1). To our delight, the reaction could gave a low yield of **3a** when we decreased the temperature to 40 °C, although **4** was still the main product (Table 1, entry 2). The yield of **3a** could be increased to 52% when the reaction was performed at room temperature, and any of **4** can not be detected (Table 1, entry 3). Other iodine sources, such as NaI, KI and nBu$_4$NI were tested, but all of them completely do not work (Table 1, entries 4–6). A variety of solvents were subsequently tested (Table 1, entries 7–11). EtOH was clearly the best choice for this catalytic system and the yield of **3a** was improved to 89% (Table 1, entry 9). Meanwhile, THF was also good choice for this procedure and gave the desired **3a** in 79% yield (Table 1, entry 10). Further screening revealed that the yield of **3a** was decreased severely when TBHP was absent (Table 1, entries 12). Obviously, TBHP plays a pivotal role in the catalytic cycle, although the exact reason need to be revealed.

Table 2: Scope of Styrene and Propylene. [a, b]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), molecular-iodine source (0.25 mmol) and TBHP (1.0 mmol) at 0-20 °C for 5-12 h. [b] Yield of isolated product.

Table 3: Scope of Chain and Cyclic Alkenes. [a, b]



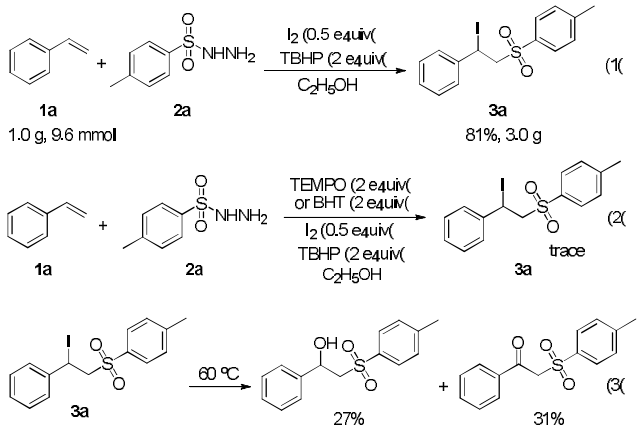
[a] Reaction conditions: **5** (0.5 mmol), **2a** (0.55 mmol), molecular-iodine source (0.25 mmol) and TBHP (1.0 mmol) at 0-20 °C for 8 h. [b] Yield of isolated product.

Using the optimized conditions, we next explored the scope and generality of the process. As shown in Table 2, Various substitutents on the benzene ring of styrene were well tolerated such as electron-withdrawing groups (F, Cl, Br and CO_2Me) and -donating groups (Me and t-buyl). Some of these functional groups are useful for further synthetic diversification. Substitution groups on aromatic ring at different positions, such as 2-Cl, 3-Br, 4-F, 4-Cl and 4-Br did not show obvious yield disparity during this iodine-mediated procedure, thus affording the corresponding iodosulfonylation products in good-to-high yields (72−92%). Notably, the reaction of sterically bulky 1,6-dichloro-2-vinylbenzene **1k** also reacted smoothly, affording the corresponding β-iodo sulfone **3k** in 92% yield. Other than 4-methylbenzenesulfonohydrazide, benzenesulfonohydrazide and 4-chlorobenzenesulfonohydrazide were suitable sulfonyl source and provided the desired products **3l** and **3m** in high yields (89% and 88%). In addition, the reactivity of several allylbenzene derivatives (**1n**, **1o**, **1p** and **1q**) were investigated, and the corresponding products **3n**, **3o**, **3p** and **3q** were obtained in good yields (88−95%).

Iodosulfonylation of alkenes is an important chemical process because the corresponding products are useful for further transformation. Encouraged by these results, we further investigated the scope of other easily accessible chain and cyclic olefins. As shown in Table 3, pent-1-ene **5a** was effective substrate and gave the desired product **6a** in 76% yield. Notably, substrates bearing sensitive substituents, such as 4-bromobut-1-ene **5b**, 3-chloroprop-1-ene **5c**, methyl acrylate **5d** and prop-2-en-1-ol **5e**, can still provide the desired products in moderate to good yields (71−87%). 2,5-dihydrofuran **5f** was also subjected to the process, thus affording the corresponding **6f** in 84% yield. Finally, this reaction can be scaled up to gram level, which suggests that it can be potentially applied in chemical industry (eqn 1).

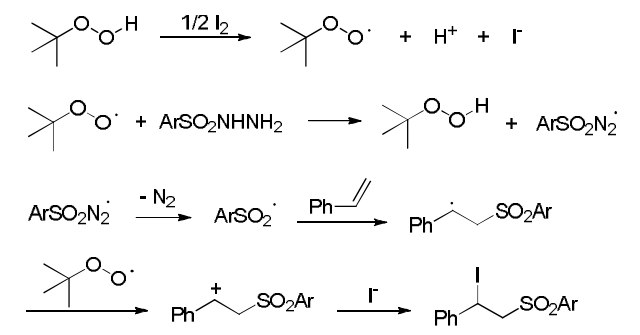
Having established the scope of the method, a preliminary study on the reaction mechanism was performed. 2,2,6,6-

View Article Online
DOI: 10.1039/C5RA07065A



tetramethyl-1-piperidinyloxy (TEMPO) and 2,4-di-tertbutyl-4-methylphenol (BHT), which were well-known radical scavengers, were introduced into the reaction mixture, respectively. The reaction progress was severely suppressed and only trace desired product **3a** can be detected even after longer times (eqn 2). When the reaction was carried out in the dark, the system is chaotic and no main product was obtained. β-iodo sulfone **3a**, which was eliminated as a possible intermediate in Itoh's work, can convert to the β-hydroxy sulfone and β-oxo-sulfone in 27% and 31% yields at 60 °C in our system, respectively (eqn 3). At present, we assume a radical iodosulfonylation mechanism, although nucleophilic attack on an iodonium intermcdiate can not be excluded (scheme 1).

Scheme 1: Proposed reaction mechanism.



In conclusion, we reported an iodosulfonylation reaction between alkenes and sulfonyl hydrazides using molecular iodine as iodine source and sulfonyl hydrazides as sulfonyl source. This reaction also provides an important method for preparing β-iodo sulfones, which are versatile building blocks and valuable intermediates in organic synthesis and medicinal chemistry. The features of mild condition, wide substrate scope and easily scaled up operation make this reaction attractive in industrial production. Further mechanistic studies are underway and will be demonstrated in due course.

Notes and references

[a]*Prof. K Sun,* Y Lv, Z Zhu, Y Jiang, J Qi, H Wu, and Prof. X Wang*
College of Chemistry and Chemical Engineering
Anyang Normal University Anyang, Henan 455000, P. R. China
E-mail: sunk468@nenu.edu.cn; wangx933@nenu.edu.cn

[b]*Prof. Z Guo, and Prof. G Zhang*
College of Chemistry and Chemical Engineering
Henan normal university Xinxiang, Henan 453007, P. R. China

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

1 For selected reviews, see: (a) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (b) K. H. Jensen and M. S. Sigman *Org. Biomol. Chem*., 2008, **6**, 4083; (c) R. I. McDonald, G. Liu and S. S. Stahl, *Chem. Rev.*, 2011, **111**, 2981; (d) C. Francesca and A. Goti, *Nat. Chem*. 2009, **1**, 269.

2 (a) J. Streuff, C. H. Hovelmann, M. Nieger and K. Muniz, *J. Am. Chem. Soc*., 2005, **127**, 14586; (b) K. Muniz, *J. Am. Chem. Soc*., 2007, **129**, 14542; (c) K. Muniz, C. H. Hovelmann and J. Streuff, *J. Am. Chem. Soc*., 2008, **130**, 763; (d) P. A. Sibbald, C. F. Rosewall, R. D. Swartz and F. E. Michael, *J. Am. Chem. Soc*., 2009, **131**, 15945; (e) P. A. Sibbald and F. E. Michael, *Org. Lett*., 2009, **11**, 1147; (f) A. Iglesias, E. G. Pérez and K. Muniz, *Angew. Chem*., *Int. Ed*., 2010, **49**, 8109; (g) B. Zhao, H. Du, S. Cui and Y. Shi, *J. Am. Chem. Soc*., 2010, **132**, 3523; (h) B. Zhao, X. Peng, S. Cui and Y. Shi, *J. Am. Chem. Soc*., 2010, **132**, 11009; (i) R. G. Cornwall, B. Zhao and Y. Shi, *Org. Lett*., 2011, **13**, 434; (j) B. Zhao, X. Peng, Y. Zhu, T. A. Ramirez, R. G. Cornwall and Y. Shi, *J. Am. Chem. Soc*., 2011, **133**, 20890; (k) M. C. Paderes, L. Belding, B. Fanovic, T. Dudding, J. B. Keister and S. R. Chemler, *Chem. Eur. J*., 2012, **18**, 1711; (l) P. Chávez, J. Kirsch, J. Streuff and K. Muniz, *J. Org. Chem*., 2012, **77**, 1922.

3 (a) E. J. Alexanian, C. Lee and E. J. Sorensen, *J. Am. Chem. Soc*., 2005, **127**, 7690; (b) G. Liu and S. S. Stahl, *J. Am. Chem. Soc*., 2006, **128**, 7179; (c) L. V. Desai and M. S. Sanford, *Angew. Chem*., *Int. Ed*., 2007, **46**, 5737; (d) K. Muniz, A. Iglesias and Y. Fang, *Chem. Commun*., 2009, 5591; (e) M. C. Paderes and S. R. Chemler, *Org. Lett*., 2009, **11**, 1915; (f) H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang and Q. Zhu, *Angew. Chem*., *Int. Ed*., 2011, **50**, 5678; (g) R. Zhu and S. L. Buchwald, *Angew. Chem*., *Int. Ed*., 2012, **51**, 1926; (h) S. D. Karyakarte, T. P. Smith and S. R. Chemler, *J. Org. Chem*., 2012, **77**, 7755.

4 (a) Y. Li, D. Song and V. M. Dong, *J. Am. Chem. Soc*., 2008, **130**, 2962; (b) A. Wang, H. Jiang and H. Chen, *J. Am. Chem. Soc*., 2009, **131**, 3846; (c) W. Wang, F. Wang and M. Shi, *Organometallics*, 2010, **29**, 928.

5 (a) H.-W. Zhang, W.-Y. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu and Q. Zhang, *Angew. Chem*., *Int. Ed*., 2013, **52**, 2529; (b) Z.-D. Pan, S. M. Pound, N. R. Rondla and C. J. Douglas, *Angew. Chem*., *Int. Ed*., 2014, **53**, 20; (c) H.-F. Jiang, H.-L. Gao, B.-F. Liu and W.-Q. Wu, *Chem. Commun*., 2014, **50**, 15348.

6 (a) T. Wu, G. Yin and G. Liu, *J. Am. Chem. Soc*., 2009, **131**, 16354; (b) S. Qiu, T. Xu, J. Zhou, Y. Guo and G. Liu, *J. Am. Chem. Soc*., 2010, **132**, 2856; (c) C. Appayee and S. E. Brenner-Moyer, *Org. Lett*., 2010, **12**, 3356; (d) H.-T. Huang, T. C. Lacy, B. Blachut, G. X. Ortiz and Q.Wang, *Org. Lett*., 2013, **15** , 1818; (e) W. Kong, P. Feige, T. Haro and C. Nevado, *Angew. Chem*., *Int. Ed*., 2013, **52**, 2469; (f) Z.-D. Li, L.-Y. Song and C.-Z. Li, *J. Am. Chem. Soc*., 2013, **135**, 4640; (g) H.-W. Zhang, Y.-C. Song, J.-B. Zhao, J.-P. Zhang and Q. Zhang, *Angew. Chem*., *Int. Ed*., 2014, **126**, 1.

7 (a) W. Liu and J. T. Groves, *Angew. Chem*., *Int. Ed*., 2013, **52**, 6024; (b) C.-W. Zhang, Z.-D. Li, L. Zhu, L.-M. Yu, Z.-T. Wang and C.-Z. Li, *J. Am. Chem. Soc*., 2013, **135**, 14082.

8 (a) Q. Lu, J. Zhang, F. Wei, Y. Qi, H. Wang, Z. Liu and A. Lei, *Angew. Chem*., *Int. Ed*., 2013, **52**, 7156; (b) A. Kariya, T. Yamaguchi, T. Nobuta, N. Tada, T. Miura and A. Itoh, *RSC Adv*., 2014, **4**, 13191.

9 (a) M. P. Sibi, N. A. Porter, *Acc. Chem. Res*., 1999, **32**, 163; (b) A. P. Schaffner, K. Sarkunam, P. Renaud, *Helv. Chim. Acta*., 2006, **89**, 2450; (b) C. E. Hoyle, A. B. Lowe, C. N. Bowman, *Chem. Soc. Rev*., 2010, **39**, 1355; (c) G. Povie, A.-T. Tran, D. Bonnaffee, J. Habegger, Z. Hu, C. L. Narvor, P. Renaud, *Angew. Chem*., I*nt. Ed.*, 2014, **53**, 3894; (d) *RSC Adv*., 2015, **5**, 37013; (e) *Tetrahedron Letters*, 2015, **56**, 1808 and references therein.

10 (a) M. Kirihara, Y. Asai, S. Ogawa, T. Noguchi, A. Hatano and Y. Hirai, *Synthesis*, 2007, 3286; (b) P. Finkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, 979.

View Article Online
DOI: 10.1039/C5RA07065A

11 (a) H. Togo, S. Lida, *Synlett*, 2006, 2159; (b) D. Liu and A. Lei, *Chemistry–An Asian Journal*, 2015, **10**, 806.
12 (a) *Angew. Chem*., *Int. Ed*., 2006, **45**, 4402; (b) *Bone*, 2009, **45**, 367; (c) *Chem. Commun*., 2009, 2073; (d) *Org. Lett.*, 2010, **12**, 2841; (e) *Tetrahedron*, 2010, **66**, 5902; (f) *Chem. Commun*., 2014, **50**, 10445; (g) *Org. Lett*., 2014, **16**, 50; (h) *Org. Lett*., 2014, **16**, 3094; (i) *RSC Adv*., 2014, 4, 5357; (j) Chem. Asian. J., 2014, **9**, 950; (k) *Chem. Commun*., 2014, **50**, 14386; (l) *Chem. Commun.*, 2015, **51**, 1371.
13 For select examples of applications of the sulfonyl group: (a) A. V. Ivachtchenko, E. S. Golovina, M. G. Kadieva, V. M. Kysil, O. D. Mitkin, S. E. Tkachenko and I. M. Okun, *J. Med. Chem.* 2011, **54**, 8161; (b) Y. Huang, L. Huo, S. Zhang, X. Guo, C. C. Han, Y. Li and J. Hou, *Chem. Commun*., 2011, **47**, 8904.
14 L. M. Harwood, M. Julia and G. L. Thuillier, *Tetrahedron*, 1980, **36**, 2483.
15 (a) X. Li, X. Xu, P. Hu, X. Xiao, C. Zhou, *J. Org. Chem*., 2013, **78**, 7343; (b) T. Shen, Y. Yuan, S. Song, N. Jiao, *Chem. Commun*., 2014, 4115; (c) W. Wei, J. Wen, D. Yang, J. Du, J. You, H. Wang, *Green Chem*., 2014, **16**, 2988.
16 (a) K. Sun, Y. Li, T. Xiong, J.-P. Zhang and Q. Zhang, *J. Am. Chem. Soc*., 2011, **133**, 1694; (b) G. Li, C.-Q. Jia and K. Sun, *Org. Lett.*, 2013, **15,** 5198; (c) K. Sun, X. Wang, G. Li, Z.-H. Zhu, Y.-Q. Jiang and B.-B. Xiao, *Chem. Commun*., 2014, **50**, 12880; (d) X. Wang, K. Sun, Y.-H. Lv, F.-J. Ma, G. Li, D.-H. Li, Z.-H. Zhu, Y.-Q. Jiang and F. Zhao, *Chem –Asian J*., 2014, **9**, 3413; (e) K. Sun, Y.-H. Lv, Z.-H. Zhu, L.-P. Zhang , H.-K. Wu, L. Liu, Y.-Q. Jiang, B.-B. Xiao and Xin Wang, *RSC Adv*., 2015, **5**, 3094.
17 For sulfonyl radicals generated in situ from sulfonyl hydrazides, see: (a) X. Li, X. Xu and C. Zhou, *Chem. Commun*., 2012, **48**, 12240; (b) X. Li, X. Xu and X. Shi, *Tetrahedron Lett*., 2013, **54**, 3071; (c) *Chem. Commun*., 2013, **49**, 10239 (d) S. Tang, Y. Wu, W. Liao, R. Bai, C. Liu and A. Lei, *Chem. Commun*., 2014, **50**, 4496; (e) X. Li, M. Fang, P. Hu, G. Hong, Y. Tang and X. Xu, *Adv. Synth. Catal*., 2014, **356**, 2103; (f) J. Zhang , Y. Shao, H.-X. Wang , Q. Luo, J.-J. Chen, D.-M. Xu and X.-B. Wan, *Org. Lett.*, 2014, **16**, 3312.