ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: L. Wang, M. Chen, L. Qi, Z. Xu and W. Li, *Chem. Commun.*, 2017, DOI: 10.1039/C7CC00090A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C7CC00090A

Journal Name

COMMUNICATION

Copper-Mediated Oxysulfonylation of Alkenyl Oximes with Sodium Sulfinates: A Facile Synthesis of Isoxazolines Featuring a Sulfone Substituent

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

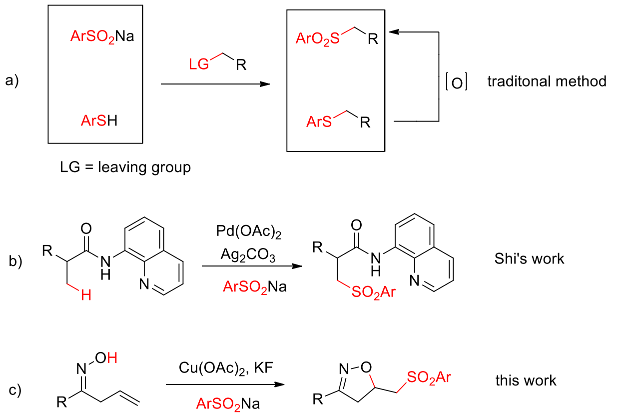
www.rsc.org/

Li-Jing Wang*, Manman Chen, Lin Qi, Zhidong Xu and Wei Li*

A novel and efficient $Cu(OAc)_2$-mediated oxysulfonylation of alkenyl oximes with sodium sulfonates was developed. The reactions are easy to conduct, occur under mild conditions, and form a broad range of sulfone-substituted isoxazolines in good yields.

Aryl alkyl sulfones are an important class of compounds that find widespread applications as pharmaceuticals, bioactive products, and materials.[1] They are also versatile synthetic intermediates in organic chemistry, including in fragment coupling, in Ramberg–Bäcklund reaction, and in Julia olefination.[2] Therefore, the synthesis of organosulfone compounds has received intensive attention and encouraged the development of new synthetic strategies.[3] Traditionally, aryl alkyl sulfones are synthesized via the nucleophilic substitution of carbon electrophiles with sodium sulfinates or thiophenols followed by oxidation (Scheme 1a).[4] These methods suffers from the limitations of requiring multistep sequences to preinstall a leaving group and that they are incompatible with numerous functional groups. In 2015, a more economical and efficient method for the synthesis of aryl alkyl sulfones was developed by Shi and co-workers, which was via a Pd(II)-catalyzed C(sp^3)-H sulfonylation pathway (Scheme 1b). [5] In this reaction, the 8-aminoquinoline auxiliary, stoichiometric silver salts and high reaction temperature were essentially required.

Difunctionalization of unactivated alkenes has emerged as a powerful tool for constructing diversity of chemical structures.[6] Compared with previously reported reactions for constructing aryl alkyl sulfones between alkenes and sulfone reagents,[7] the synthesis of sulfone-substituted heterocycles through a pattern of cyclization has not been well explored. In 2016, Jiang and co-workers reported a copper-catalyzed oxysulfenylation of enolates with sodium sulfinates to construct sulfenylated cyclic ethers, which could be convered to the corresponding sulfone derivatives by the oxidation of *m*-CPBA.[8] Quite recently, Wang and co-workers developed an iodine-promoted cyclization of *N*-propynyl amides via sulfonylation with sulfonyl hydrazides to construct sulfonyloxazoles. But when using *N*-allyl amides, they can only get thiooxazolines.[9] These established methods, however, have disadvantages in that they need a two-step thiolation/oxidation sequence to afford aryl alkyl sulfones. Thus, methods for direct synthesis of sulfone-substituted heterocycles from alkenes and sulfone reagents are indeed desirable.



Scheme 1. Synthesis of aryl alkyl sulfones

Isoxazolines are an important class of heterocycles found in several biologically active agents and versatile precursors in synthetic chemistry.[10] The modification of isoxazoline by introduction of a sulfone group is of great interest both for biology and organic synthesis research. In recent years, difunctionalization of β,γ-unsaturated oximes with a functional group, such as dioxydation,[11] oxy-trifluoromethylation/trifluoromethylthiolation,[12] oxy-fluorination,[13] oxy-azidation,[14] oxy-halogenation,[15] and oxy-amination[16] has become a more straightforward way to construct functionalized isoxazolines. Inspired by these results, we decided to test whether β,γ-unsaturated oximes with

---

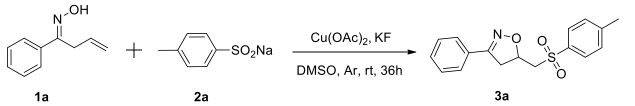
Key Laboratory of Medicinal Chemistry, and Molecular Diagnosis of the Ministry of Education, College of Chemistry & Environmental Science, HeBei University, 180 Wusi Donglu, Baoding 071002, P. R. China.
E-mail: wanglj0405@163.com; liweihebeilab@163.com

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C7CC00090A

sulfone reagents could carry out a direct oxy-sulfonylation and afford the corresponding sulfone-substituted isoxazolines. Herein, we described a tandem preparation of aryl alkyl sulfones through copper-mediated oxygen sulphone functionalization of unactivated alkenes (Scheme 1c).

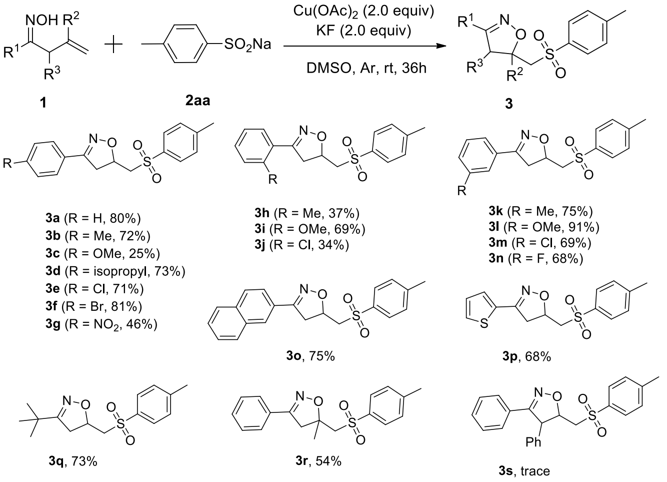
Table 1. Optimization of reaction conditions[a]



entry	[Cu] (equiv)	base (equiv)	oxidant (2.0 equiv)	yield (%)[b]
1	$Cu(OAc)_2$ (0.2)	NaOAc (1.2)	-	35
2	CuI (0.2)	NaOAc (1.2)	-	24
3	$Cu(CF_3SO_3)_2$ (0.2)	NaOAc (1.2)	-	24
4	$CuBr_2$ (0.2)	NaOAc (1.2)	-	26
5	Cu_2O (0.2)	NaOAc (1.2)	-	0
6	CuCl (0.2)	NaOAc (1.2)	-	0
7	$Cu(OAc)_2$ (0.2)	NaOAc (1.2)	$K_2S_2O_8$	0
8	$Cu(OAc)_2$ (0.2)	NaOAc (1.2)	$PhI(OAc)_2$	0
9	$Cu(OAc)_2$ (0.2)	NaOAc (1.2)	DTBP	31
10	$Cu(OAc)_2$ (0.2)	NaOAc (1.2)	$Mn(OAc)_3 \cdot 2H_2O$	45
11	$Cu(OAc)_2$ (1.0)	NaOAc (1.2)	-	50
12	$Cu(OAc)_2$ (2.0)	NaOAc (1.2)	-	64
13[c]	$Cu(OAc)_2$ (2.0)	NaOAc (1.2)	-	55
14	$Cu(OAc)_2$ (2.0)	*t*-BuOK (1.2)	-	52
15	$Cu(OAc)_2$ (2.0)	NEt_3 (1.2)	-	57
16	$Cu(OAc)_2$ (2.0)	KF (1.2)	-	68
17	$Cu(OAc)_2$ (2.0)	KF (0.2)	-	67
18	$Cu(OAc)_2$ (2.0)	KF (2.0)	-	76
19	$Cu(OAc)_2$ (2.0)	KF (2.5)	-	66
20	$Cu(OAc)_2$ (2.0)	-	-	0
21[d]	**$Cu(OAc)_2$ (2.0)**	**KF (2.0)**	**-**	**80**
22[e]	$Cu(OAc)_2$ (2.0)	KF (2.0)	-	80
23	-	KF (2.0)	-	0

[a] All reactions were carried out by using **1a** (0.2 mmol), **2a** (1.5 equiv), copper salts (2.0 equiv), bases (2.0 equiv), oxidants (2.0 equiv) and DMSO (2 mL) under argon and stirred at room temperature for 36 h, except as noted. [b] Isolated yield. [c] under air. [d] 2.0 equiv of **2a** was used. [e] 2.5 equiv of **2a** was used.

At the outset of our studies, we chose oxime **1a** as the substrate, 1.5 equiv of sodium *p*-toluenesulfinate **2a** as sulfone reagent, 20 mol% $Cu(OAc)_2$ as catalyst, 1.2 equiv of NaOAc as the base and DMSO as solvent. The reaction was stirred at room temperature for 36 h under argon atmosphere and gave the desired product **3a** in 35% yield (Table 1, entry 1), the structure of which was unambiguously confirmed by X-ray analysis.[17] Subsequently, We tested other solvents (see the Supporting Information), such as DMF, CH_3CN, and toluene. It was found to be less effective for this reaction. Other copper salts were also examined in the reaction: CuI, $Cu(CF_3SO_3)_2$, and $CuBr_2$ led to lower yields; Cu_2O, and CuCl were completely ineffective for this reaction (entries 2–6). We then turned to oxidizing agents for a trial: $PhI(OAc)_2$ and $K_2S_2O_8$ failed to generate the desired products (entries 7 and 8); Di-tert-butyl peroxide(DTBP) gave a lower yield (31%, entry 9); $Mn(OAc)_3 \cdot 2H_2O$ produced a higher yield (45%, entry 10); Interestingly, increasing the amount of $Cu(OAc)_2$ resulted in much higher yields of 50% and 64%, respectively (entries 11 and 12). However, the reaction under an air atmosphere gave a lower yield (entry 13). The effect of bases was also examined (entries 14–16). The yield of **3a** was increased to 68% when KF was used (entry 16). The loading of the KF was evaluated as well (entries 17-19). The yield was further increased to 76% when using 2.0 equiv of KF (entry 18). In addition, no reaction occurred without KF (entry 20). The screening of the loading of sodium *p*-toluenesulfinate **2a** indicated that 2.0 equiv of **2a** is the best choice for the reaction (entries 21 and 22). The subsequent control experiments revealed that the $Cu(OAc)_2$ was crucial to this transformation (entry 23).



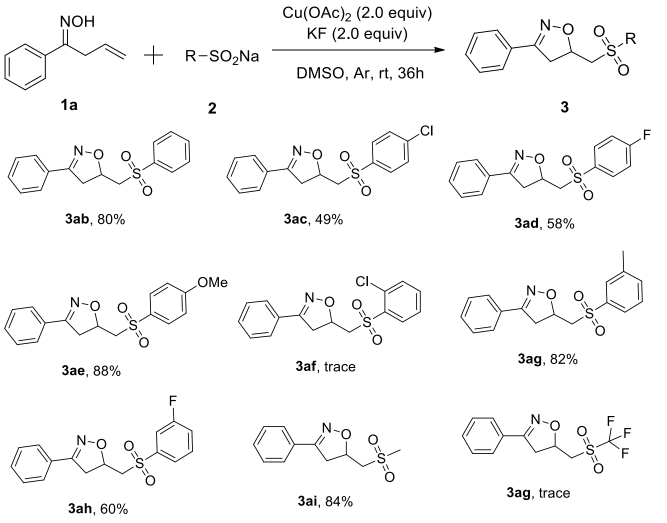
[a] All reactions were carried out by using **1** (0.2 mmol), **2a** (2.0 equiv), $Cu(OAc)_2$ (2.0 equiv), KF (2.0 equiv) and DMSO (2 mL) under argon and stirred at room temperature for 36 h, except as noted. Yields refer to isolated yields.

Scheme 2. Substrate scope of β,γ-unsaturated oximes[a]

With the optimized conditions in hand (Table 1, entry 20), we then examined the scope of this transformation. As shown in Scheme 2, various β,γ-unsaturated oximes were subjected to the standard conditions. First, a series of aromatic oximes with a *para*-substituent on the phenyl ring including some with electrondonating groups (Me, isopropyl) and some with electronwithdrawing groups (Cl, Br) underwent the oxy-sulfonylation smoothly and provided the desired products with good yields (**3b** and **3d-f**). However, compounds **1c** and **1g** having a methoxyl or a nitro group only gave the desired product in yields of 25% and 46%, respectively. Next, substrates with a 2-substituted phenyl were tested. Conversely, **1i** with a methoxy group gave the corresponding products in good yield, while **1h** with a methyl group and **1j** with a chlorine group both gave a lower yield. We have also investigated the effect of *meta*-substituted phenyl ring. To our delight, **1k-n** gave the corresponding products in good to excellent yields. The oxime bearing a naphthyl group was a compatible substrate and gave the product in good yield (**3o**). Thiophene-containing oxime (**1p**) was also transformed into the desired product in 68% yield. We were pleased to find that the aliphatic oximes also provided good conversion to the desired product **3q** under the stated conditions. Then the

View Article Online
DOI: 10.1039/C7CC00080A

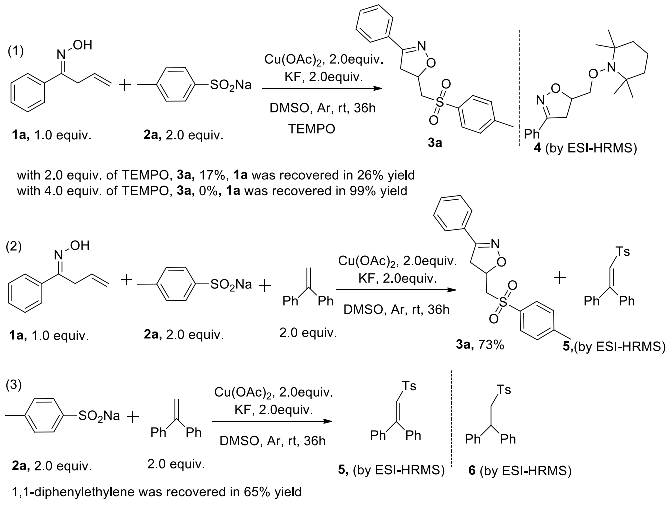
present method was successfully applied to construct the desired product (**3r**) containing a quaternary carbon center. Furthermore, to expand the scope of this reaction, we also investigated α-phenyl oxime **1s**. However, it couldn't work under standard conditions.



[a]All reactions were carried out by using **1a** (0.2 mmol), **2** (2.0 equiv), $Cu(OAc)_2$ (2.0 equiv), KF (2.0 equiv) and DMSO (2 mL) under argon and stirred at room temperature for 36 h, except as noted. Yields refer to isolated yields.

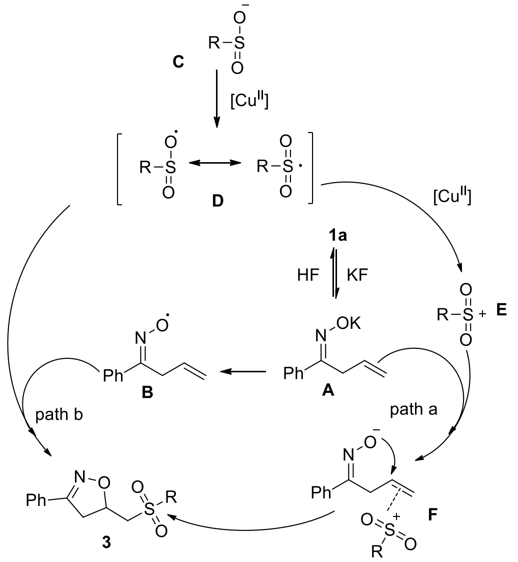
Scheme 3. Substrate scope of sodium sulfinates[a]

To further demonstrate the synthetic potential of this method, various sodium sulfinates were employed in this oxy-sulfonylation reaction (Scheme 3). As expected, sodium benzenesulfinate was worked well under standard conditions (**3ab**). Substrates with electron-donating substituents gave the corresponding products (**3ae**, and **3ag**) in good yields. However, substrates with electron-withdrawing groups only gave the desired products (**3ac, 3ad,** and **3ah**) in medium yields. Compound **2f** with a chlorine group at the *o*- position even failed to obtain the corresponding product. Sodium methanesulphinate (**2i**) could react easily with **1a** to give **3ai** in 84% yield. But when electron-deficient substrate **2g** was used, the oxy-sulfonylation was not found to proceed under standard conditions.



Scheme 4. Mechanistic studies

To have an insight into the mechanism of the chemical reaction, several control experiments were conducted. When the reaction was performed in the presence of a radical scavenger such as TEMPO, the yield of **3a** was decreased significantly to 17% and **1a** was recovered in 26% yield. In addition, **4** was detected by ESI-HRMS measurement of the crude reaction mixture. Increasing the amount of TEMPO to 4.0 equiv, no product was detected and **1a** was recovered in 99% yield (eq 1). The results implied that a radical pathway might be involved in the reaction. However, when we tried to use 1,1-diphenylethylene to trap the radical in the presence or absence of oximes, the yields of the radical coupling products were very low (eq 2 and eq 3). Therefore, we could not overlook a cation pathway in this transformation. On the basis of the above results and literature reports, we propose the following reaction mechanism involving two possible pathways for this transformation (Scheme 5).[12, 14, 18]



Scheme 5. Proposed mechanism.

Initially, intermediate **A** is generated by the reaction of oxime **1a** and KF. And according to the literature[19], intermediate **A** can be converted to the corresponding oxime radical **B**. Meanwhile, the sodium sulfonate is oxidized by Cu^{II} to give sulfonyl radical **D**, and a second oxidation can deliver sulfonyl cation **E**. In path a, the alkene **A** is activated by the electrophilic sulfonyl cation **E** to form intermediate **F**, which is followed by 5-exo-trig cyclization to give the desired isoxazoline **3**. In path b, sulfonyl radical **D** coupled with oxime radical **B** to give the desired product **3**.

Conclusions

In conclusion, we have developed an efficient and practical copper-mediated oxysulfonylation reaction of alkenes with sodium sulfinates for the synthesis of sulfonylated isoxazolines. This reaction proceeds readily at room temperature and is simply performed. Meanwhile, this novel transformation used easily available and stable sodium sulfinates as ideal sulfone reagents. Further studies for a deep understanding of the reaction mechanism and the synthetic methods of other important sulfone-substituted heterocycles are in exploration.

We thank the Hebei Province Science Foundation for Key Program (No. B2016201031), Hebei Province Higher School Science Foundation for High-level personnel (No. GCC2014014), and Hebei university Science Foundation for High-level personnel.

Notes and references

1 (a) C. P. Shcroft, P. Hellier, A. Pettman and S. Wakinson, *Org. Process Res. Dev.* 2011, **15**, 98; (b) R. Ettari, E. Nizi, M. E. D. Franceco, M.-A. Dude, G. Pradel, R. Vičík, T. Schirmeister, N. Micale, S. Grasso and M. Zappalà, *J. Med. Chem.* 2008, **51**, 988-996; (c) F. Reck, F. Zhou, M. Girardot, G. Kern, C. J. Eyermann, N. J. Hales, R. R. Ramsay and M. B. Gravestock, *J. Med. Chem.* 2005, **48**, 499; (d) R. A. Fromtling, *Drugs Future* 1989, **14**, 1165.

2 (a) X. Sun, F. Yu, T. Ye, X. Liang and J. Ye, *Chem. Eur. J.* 2011, **17**, 430-434; (b) A. El-Awa, M. N. Noshi, X. M. du Jourdin and P. L. Fuchs, *Chem. Rev.* 2009, **109**, 2315; (c) K. Plesniak, A. Zarecki and J. Wicha, *Top. Curr. Chem.* 2007, **275**, 163; (d) N. S. Simpkins, *Sulfones in Organic Synthesis, Tetrahedron Organic Chemistry Series;* Pergamon Press: New York, 1993; Vol. **10**.

3 For recent selected examples, see: (a) N.-W. Liu, S. Liang and G. Manolikakes, *Synthesis* 2016, **48**, 1939-1973; (b) J. Meesin, P. Katrun, C. Pareseecharoen, M. Pohmakotr, V. Reutrakul, D. Soorukram and C. Kuhakarn, *J. Org. Chem.* 2016, **81**, 2744-2752; (c) S. Lianga and G. Manolikakes, *Adv. Synth. Catal.* 2016, **358**, 2371-2378; (d) Y. Xi, B. Dong, E. J. McClain, Q. Wang, T. L. Gregg, N. G. Akhmedov, J. L. Petersen and X. Shi, *Angew. Chem., Int. Ed.* 2014, **53**, 4657. (e) Z. Yuan, H.-Y. Wang, X. Mu, P. Chen, Y.-L. Guo and G. Liu, *J. Am. Chem. Soc.* 2015, **137**, 2468; (f) K. Xu, V. Khakyzadeh, T. Bury, B. Breit, *J. Am. Chem. Soc.* 2014, **136**, 16124; (g) X. Tang, L. Huang, Y. Xu, J. Yang, W. Wu and H. Jiang, *Angew. Chem. Int. Ed.* 2014, **53**, 4205; (h) Q. Lu, J. Zhang, G. Zhao, Y. Qi, H. Wang and A. Lei, *J. Am. Chem. Soc.* 2013, **135**, 11481.

4 Solladie, G. *In Comprehensive Organic Synthesis;* B. M. Trost and I. Eds. Fleming, Pergamon Press: Oxford, U.K., 1991; Vol. **6**.

5 W.-H. Rao, B.-B. Zhan, K. Chen, P.-X. Ling, Z.-Z. Zhang and B.-F. Shi, *Org. Lett.* 2015, **17**, 3552-3555.

6 For recent selected examples, see: (a) Y. Sato, S. Kawaguchi, A. Nomoto, A. Ogawa, *Angew. Chem., Int. Ed.* 2016, **55**, 9700-9703; (b) J. Zhao, P. Li, X. Li, C. Xia and F. Li, *Chem. Commun.* 2016, **52**, 3661-3664; (c) H. Cui, X. Liu, W. Wei, D. Yang, C. He, T. Zhang and H. Wang, *J. Org. Chem.* 2016, **81**, 2252-2260; (d) X.-W. Lan, N.-X. Wang, C.-B. Bai, C.-L. Lan, T. Zhang, S.-L. Chen and Y. Xing, *Org. Lett.* 2016, **18**, 5986-5989.

7 (a) Q. Lu, J. Zhang, F. Wei, Y. Qi, H. Wang, Z. Liu and A. Lei, *Angew. Chem. Int. Ed.* 2013, **52**, 7156-7159; (b) W. Wei, C. Liu, D. Yang, J. Wen, J. You, Y. Suo and H. Wang, *Chem. Commun*. 2013, **49**, 10239-10241; (c) A. Kariya, T. Yamaguchi, T. Nobuta, N. Tada, T. Miura and A. Itoh, *RSC Adv.* 2014, **4**, 13191; (d) N. Taniguchi, *J. Org. Chem.* 2015, **80**, 7797-7802; (e) X. Li, X. Xu and C. Zhou, *Chem.Commun.* 2012, **48**, 12240-12242; (f) F. Xiao, S. Chen, Y. Chen, H. Huang and G.-J. Deng, *Chem.Commun.* 2015, **51**, 652-654; (g) K. Sun, Y. Lv, Z. Zhu, Y. Jiang, J. Qi, H. Wu, Z. Zhang, G. Zhang and X. Wang, *RSC Adv.* 2015, **5**, 50701-50704; (h) A. O. Terent'ev, O. M. Mulina, D. A. Pirgach, D. V. Demchuk, M. A. Syroeshkin and G. I. Nikishin, *RSC Adv.* 2016, **6**, 93476-93485; (i) R. Chawla, A. K. Singh and L. D. S. Yadav, *Eur. J. Org. Chem.* 2014, 2032-2036.

8 Y. Gao, Y. Gao, X. Tang, J. Peng, M. Hu, W. Wu and H. Jiang, *Org. Lett.* 2016, **18**, 1158-1161.

9 G. C. Senadi, B.-C. Guo, W.-P. Hu and J.-J. Wang, *Chem. Commun.* 2016, **52**, 11410-11413.

10 Selected examples of biological evaluation of isoxazolines: (a) S. Castellano, D. Kuck, M. Viviano, J. Yoo, F. López-Vallejo, P. Conti, L. Tamborini, A. Pinto, J. L. Medina-Franco and G. J. Sbardella, *J. Med. Chem.* 2011, **54**, 7663; (b) P. K. Poutiainen, T. A. Venäläinen, M. Peräkylä, J. M. Matilainen, S. Väisänen, P. Honkakoski, R. Laatikainen and J. T. Pulkkinen, *Bioorg. Med. Chem.* 2010, **18**, 3437; For synthetic application of isoxazolines, see: (c) I. N. N. Namboothiri and N. Rastogi, Synthesis of Heterocycles via Cycloadditions I. *In Topics in Heterocyclic Chemistry*; Hassner, A., Eds; Springer: Berlin, 2008; p 1; (d) J. W. Bode and E. M. Carreira, *Org. Lett.* 2001, **3**, 1587; (e) D. P. Curran and T. A. Heffner, *J. Org. Chem.* 1990, **55**, 4585; (f) A. P. Kozikowski, *Acc. Chem. Res.* 1984, **17**, 410.

11 (a) B. Han, X.-L. Yang, R. Fang, W. Yu, C. Wang, X.-Y. Duan and S. Liu, *Angew. Chem. Int. Ed.* 2012, **51**, 8816; (b) X.-W. Zhang, Z.-F. Xiao, Y.-J. Zhuang, M.-M. Wang and Y.-B. Kang, *Adv. Synth. Catal.* 2016, **358**, 1942-1945.

12 (a) Y.-T. He, L.-H. Li, Y.-F. Yang, Y.-Q. Wang, J.-Y. Luo, X.-Y. Liu, Y.-M. Liang, *Chem. Commun.* 2013, **49**, 5687; (b) L. Zhu, G. Wang, Q. Guo, Z. Xu, D. Zhang and R. Wang, *Org. Lett.* 2014, **16**, 5390.

13 (a) Y.-Y. Liu, J. Yang, R.-J. Song and J.-H. Li, *Adv. Synth. Catal.* 2014, **356**, 2913-2918; (b) W. Kong, Q. Guo, Z. Xu, G. Wang, X. Jiang and R. Wang, *Org. Lett.* 2015, **17**, 3686-3689.

14 L. Zhu, H. Yu, Z. Xu, X. Jiang, L. Lin and R. Wang, *Org. Lett.* 2014, **16**, 1562.

15 (a) K.-Y. Dong, H.-T. Qin, F. Liu and C. Zhu, *Eur. J. Org. Chem.* 2015, 1419-1422; (b) X.-W. Zhang, Z.-F. Xiao, M.-M. Wang, Y.-J. Zhuang and Y.-B. Kang, *Org. Biomol. Chem.* 2016, **14**, 7275-7281.

16 R.-H. Liu, D. Wei, B. Han and W. Yu, *ACS Catal.* 2016, **6**, 6525-6530.

17 CCDC 1524458

18 (a) H.-S. Li and G. Liu, *J. Org. Chem.* 2014, **79**, 509-516; (b) X. Tang, L. Huang, Y. Xu, J. Yang, W. Wu and H. Jiang, *Angew. Chem. Int. Ed.* 2014, **53**, 4205-4208; (c) L. Kong, M. Wang, F. Zhang, M. Xu and Y. Li, *Org. Lett.* 2016, **18**, 6124-6127; (d) N. Taniguchi, *SYNLETT* 2011, **9**, 1308-1312; (e) Y. Amiel, *J. Org. Chem.* 1974, **39**, 1974; (f) T. W. Bentley and R. O. Jones, *J. Phys. Org. Chem.* 2007, **20**, 1093-1101; (g) K. Miyamoto, S. Iwasaki, R. Doi, T. Ota, Y. Kawano, J. Yamashita, Y. Sakai, N. Tada, M. Ochiai, S. Hayashi, W. Nakanishi and M. Uchiyama, *J. Org. Chem.* 2016, **81**, 3188-3198.

19 (a) Y. Li and A. Studer, *Angew. Chem. Int. Ed.* 2012, **51**, 8221. (b) B. Zhang and A. Studer, *Org. Lett.* 2013, **15**, 4548.