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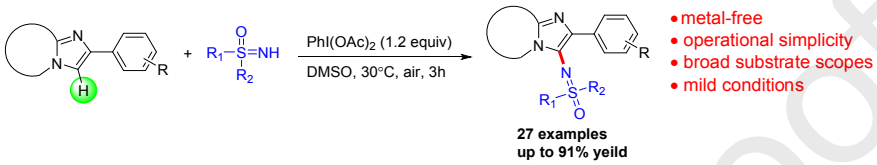

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PhI(OAc)$_2$-Mediated Oxidative C-H Sulfoximination of Imidazopyridines under Mild Conditions

Nannan Luan[a], Zhenwei Liu[a], Shuaijun Han[a], Linhua Shen[a], Jingya Li[b], Dapeng Zou[a,*], Yangjie Wu[a,*] and Yusheng Wu[a,b,c,*]

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Highlights

•The sulfoximination of imidazopyridines at C3 position was firstly achieved
•PhI(OAc)$_2$ was used as oxidant
•The reaction proceeds under air without metal catalyst
•This method features mild conditions and good substrate tolerance

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ABSTRACT

A facile protocol for direct oxidative C-N bond coupling of unactivated imidazo[1,2-a]pyridines with NH-sulfoximines was disclosed using sulfoximines as the nitrogen sources in the presence of (diacetoxy)iodobenzene (PhI(OAc)$_2$). The reaction proceeded smoothly under air without any metal catalyst to give a series of C-3 sulfoximidoyl-functionalized imidazo[1,2-a]pyridines products regioselectively.

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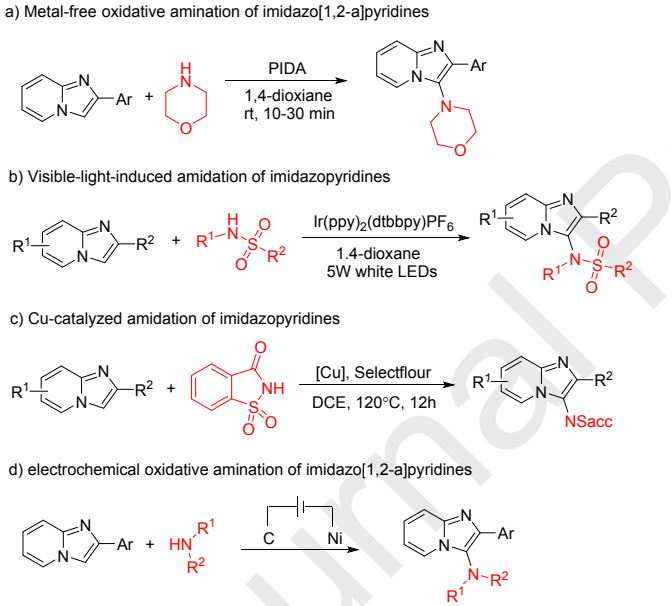
Intr ect

Among numerous nitrogen-containing heterocycles, imidazo[1,2-a]pyridine has been considered as a privileged structural unit found in many natural products and pharmaceuticals.[1] Their derivatives shows highly biological activity, such as antiviral, antitumor, antifungal activities, etc.[2] In particular, amido-substituted imidazo[1,2-a]pyridine is the core structure of several commercially available drugs such as alpidem, zolpidem, saripidem, GSK812397, etc.[1a,3] Therefore, the synthesis methods of amido-substituted imidazopyridines has gained considerable interest of synthetic chemists.[4a-k] In this respect, a direct dehydrogenative C-N coupling between C-H and N-H partners would be the most efficient strategy. In 2017, a radical-type oxidative amination of imidazo[1,2-a]pyridines in the presence of (diacetoxy)iodobenzene was reported by Hajra (Scheme 1a).[4a] Subsequently, Sun group reported a visible-light-induced C(sp^2)-H amidation of imidazopyridines using $Ir(ppy)_2(dtbbpy)PF_6$ as photocatalyst (Scheme 1b).[4b] Later, Sun and co-workers demonstrated a Cu-catalyzed direct C-N bond formation on the C-3 position of imidazo[1,2-a]pyridines using saccharin as an amino source (Scheme 1c).[4c] Recently, Lei reported an electrochemical oxidative C-H/N-H cross-coupling to give C-3 aminated imidazo[1,2-a]pyridines (Scheme 1d).[4d] Despite the above achievements, the diversity of nitrogen sources remains limited.



Scheme 1. Methods for direct dehydrogenative C-N coupling of imidazo[1,2-a]pyridines.

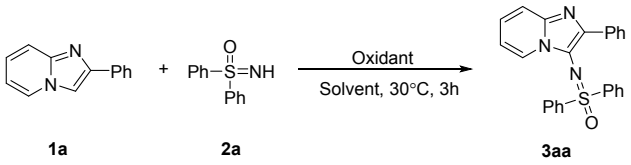
Sulfoximine derivatives are of great significance as their applications in organic synthesis[5] and medicinal chemistry.[6] In drug discovery, they have been used as important pharmacophores to improve specificity[7a-b] or reduce undesired toxicity.[7c-e] In addition, due to the fact that some sulfoximine derivatives showed anticancer activity,[8] the synthesis of N-(hetero)arylsulfoximines has attracted the interest of chemists.[9]

However, since the nucleophilic properties of nitrogen in sulfoximine are lower than that in amines and imines, development of a new C-N bond formation of sulfoximines remains a challenge. In recent years, iodine(III)-mediated oxidative amination of C(sp^2)-H bond has become an important strategy.[10] Several examples of amination of (hetero)arenes using hypervalent iodine have been reported,[11] which prompted us to investigate the feasibility of an iodine(III) reagent in C-N bond construction of C-H functionalization,[12] we herein report the metal-free, regioselective sulfoximination of imidazo[1,2-a]pyridines and other imidazoheterocycles with $PhI(OAc)_2$ as oxidant under mild conditions. This method provides an convenient access to a new type of compounds, C-3 sulfoximidoyl-functionalized imidazo[1,2-a]pyridines, which might have potential value in organic chemistry and drug discovery.

Results and Discussion

The optimization of reaction conditions was started by taking 2-phenylimidazo[1,2-a]pyridine (**1a**) and diphenyl sulfoximine (**2a**) as model substrates. Initially, the reaction was carried out using $PhI(OAc)_2$ as oxidant in acetonitrile (Table 1, entry 1). The target product C-3 sulfoximidoyl-functionalized 2-phenylimidazo[1,2-a]pyridine (**3aa**) was obtained in 29% yield. Then, the effect of different solvents were checked (Table 1, entries 2-10), and DMSO was the most effective one for the reaction, affording 48% of the desired product (Table 1, entry 8). Subsequent oxidants screening indicated that $PhI(OAc)_2$ was the best one. (Table 1, entries 8 vs 11-13). To our delight, when 1.5 equiv of **1a** was used, the yield of desired product was increased to 77% (Table 1, entry 14). Increasing the amount of $PhI(OAc)_2$ to 1.2 equiv, the yield was improved to 82% (Table 1, entries 15). Then, the effect of gaseous environment was also investigated (Table 1, entries 15, 17-18). When the reaction was performed under O_2 atmosphere, almost same results were obtained. Whereas, the yield of the target product decreased dramatically under Ar atmosphere. In the absence of the oxidant, no desired product was observed (Table 1, entry 19). Thus, the optimized reaction conditions were determined as the combination of 2-phenylimidazo [1,2-a]pyridine **1a** (1.5 equiv), diphenyl sulfoximine **2a** (1.0 equiv), $PhI(OAc)_2$ (1.2 equiv) in DMSO at 30 °C for 3 h. The structure of product **3aa** was further confirmed by single-crystal X-ray diffraction analysis (CCDC 1942822).

Table 1. Optimization of the reaction conditions[a]



1a **2a** **3aa**

Entry	Oxidant (equiv)	Solvent	Yield[b] (%)
1	$PhI(OAc)_2$ (1.0)	CH_3CN	29
2	$PhI(OAc)_2$ (1.0)	CH_2Cl_2	14
3	$PhI(OAc)_2$ (1.0)	1,4-dioxane	26
4	$PhI(OAc)_2$ (1.0)	EtOAc	43
5	$PhI(OAc)_2$ (1.0)	CH_3Ph	11
6	$PhI(OAc)_2$ (1.0)	THF	9
7	$PhI(OAc)_2$ (1.0)	DMF	trace
8	$PhI(OAc)_2$ (1.0)	DMSO	48
9	$PhI(OAc)_2$ (1.0)	EtOH	21
10	$PhI(OAc)_2$ (1.0)	*i*-propanol	35
11	$PhI(TFA)_2$ (1.0)	DMSO	trace
12	TBHP (1.0)	DMSO	nd
13	$Na_2S_2O_8$ (1.0)	DMSO	nd
14[c]	$PhI(OAc)_2$ (1.0)	DMSO	77
15[c]	$PhI(OAc)_2$ (1.2)	DMSO	82
16[c]	$PhI(OAc)_2$ (1.5)	DMSO	81

17[c]			
18[c,e]	$PhI(OAc)_2$ (1.2)	DMSO	14
19[c]	-	DMSO	nd

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $PhI(OAc)_2$ (1.0 equiv), solvent (1.0 mL) at 30 ºC for 3 h, sealed tube, nd = not detected.

[b]HPLC yield.

[c]**1a** (0.3 mmol), **2a** (0.2 mmol).

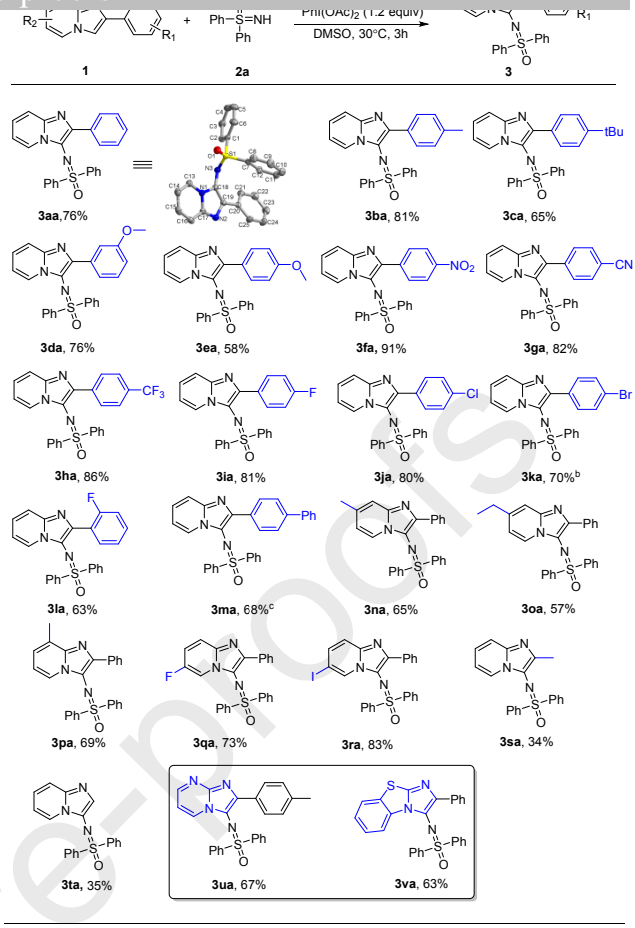
[d]under O_2 atmosphere.

[e]under argon atmosphere.

Under the optimized conditions, imidazo[1,2-a]pyridines (**1**) were reacted with diphenyl sulfoximine (**2a**) to give the desired products in moderate to good yields (Table 2, **3aa-3ta**). Initially, the effect of substituents on the benzene ring of imidazo[1,2-a]pyridines was explored. Imidazo[1,2-a]pyridines with electron-withdrawing groups on the benzene ring worked comparatively well than the substrates possessing electron-donating groups (**3fa-3ha** vs **3ba-3ea**). The halogen groups containing substrates were tolerated in the reaction to give the corresponding products in good yields (**3ja-3la**). When the substrate bearing phenyl group at the 2-phenyl moiety was checked, the desired **3ma** was obtained in 63% yield. The effect of various groups on the pyridyl ring was also investigated. The substrates with halogen groups proceeded well (**3qa-3ra**), whereas, alkyl substituents reduced the yields (**3na-3pa**). When 2-phenyl moiety was switched to methyl or hydrogen, the yields of the target product dramatically decreased (**3sa-3ta**). Other imidazoheterocycles, such as 2-(p-tolyl) imidazo[1,2-a]pyrimidine and 2-phenylbenzo[d]imidazo[2,1-b]thiazole were also compatible to this catalytic system, giving the desired **3ua**, **3va** in 67% and 63% yield, respectively.

To establish the scope of the protocol, several NH-sulfoximines (**2**) were then examined under the optimized reaction conditions (Table 3). It was found that most alkyl aryl sulfoximines reacted smoothly with **1a** under the optimum conditions (**3ab-3af**). Sulfoximine bearing halogen (Br), electron-donating substituent (OMe) or a strong electron-withdrawing group (NO_2) on the phenyl ring all worked well to give **3ac**, **3ad** and **3ae** in good yields. It is noteworthy that cycloalkyl sulfoximine, S,S-tetramethylenesulfoximine also afforded the corresponding product **3af** in reasonable yield of 62%.

Table 2. Substrate Scope of Imidazo[1,2-a]pyridines[a]

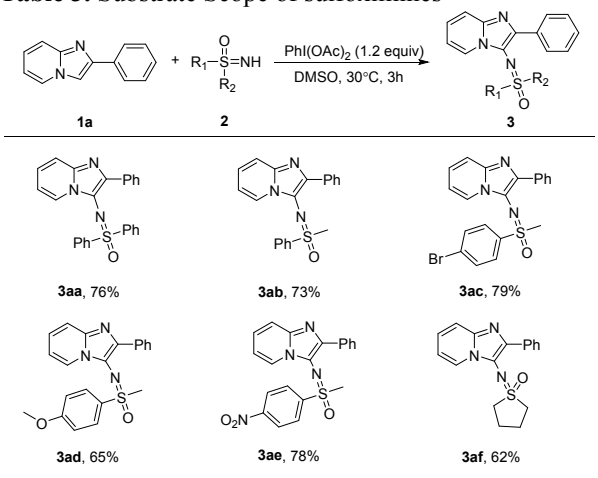


[a]Reaction conditions: 1 (0.3 mmol), 2a (0.2 mmol), $PhI(OAc)_2$ (1.2 equiv), DMSO (1.0 mL) at 30 °C for 3 h. Sealed tube. Isolated yields.

[b]DMSO (3.0 mL).

[c]DMSO (4.0 mL).

Table 3. Substrate Scope of sulfoximines[a,b]



[a]Reaction conditions: 1 (0.3 mmol), 2a (0.2 mmol), $PhI(OAc)_2$ (1.2 equiv), DMSO (1.0 mL) at 30 °C for 3 h. Sealed tube.

[b]Isolated yields.

Several control experiments were carried out to provide further insights into the mechanism of this reaction (Scheme 2). When a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added under the optimized reaction conditions, only trace amount of product was detected. In the presence of 2,6-di-tert-butyl-4-methyl phenol (BHT), the reaction was also suppressed

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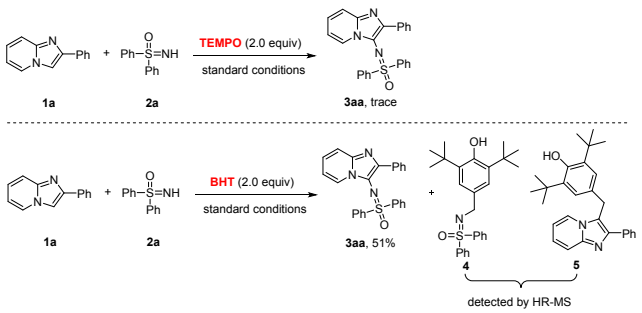
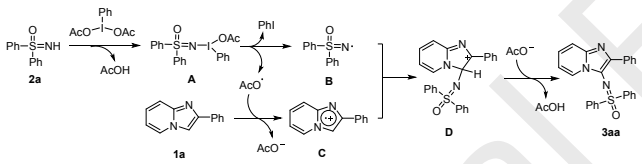
detected by HRMS. These observations suggest that the reaction probably proceeds through a radical pathway.

Scheme 2. Control Experiments.



Based on the above results as well as previous reports,[4a,4e,12a,13] a possible mechanism for this direct C-H sulfoximination of imidazopyridines is proposed in Scheme 3. At first, NH-sulfoximine (**2a**) produces N-iodoamino species **A** in the presence of $PhI(OAc)_2$, which subsequently generates the corresponding N-centered radical species **B** and acetoxy radical. The imidazopyridine radical cation (**C**) is obtained from 2-phenylimidazo[1,2-a]pyridine (**1a**) through a single electron transfer process in the presence of acetoxy radical. Then, the N-centered radical **B** coupled with the imidazopyridine radical cation (**C**) regioselectively to produce the intermediate **D**. The intermediate **D** consequently affords the product (**3aa**) through further deprotonation by the acetate anion, together with the elimination of AcOH.

Scheme 3. Plausible Mechanism.



Conclusion

In summary, an efficient method for $PhI(OAc)_2$-mediated regioselective sulfoximination of imidazopyridines via $C(sp^2)$-H bond functionalization has been developed. The reaction proceeded smoothly with a wide range of substrates and provided the coupling products in moderate to good yield. Other imidazoheterocycles, such as 2-phenylbenzo[d]imidazo[2,1-b]thiazole and 2-(p-tolyl) imidazo[1,2-a]pyrimidine were also compatible to this system. Broad substrate scopes, operational simplicity and mild conditions are the prominent advantages of this methodology. We believe this strategy possesses great potential in organic chemistry and pharmaceutical research.

References and notes

1. (a) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem.* **2007**, *7*, 888-899. (b) Liu, J.; Chen, Q. *Progress in Chemistry*, **2010**, *22*, 631-638.
2. (a) Lhassani, M.; Chavignon, O.; Chezal, J. M.; Teulade, J. C.; Chapat, J. P.; Snoeck, R.; Andrei, G.; Balzarini, J.; Clercq, E.; Gueiffier, A. *Eur. J. Med. Chem.* **1999**, *34*, 271-274. (b) Gueiffier, A.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J. C.; Kerbal, A.; Essassi, E. M.; Debouzy, J. C.; Witvrouw, M.; Blache, Y.; Balzarini, J.; Clercq,E.; Chapat, J. P. *J. Med. Chem.* **1996**, *39*, 2856-2859. (c) Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *Eur. J. Med. Chem.* **1991**, *26*, 13-18. (d) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; *8*, 305-312.
3. (a) Du, B.; Shan, A.; Zhong, X.; Zhang, Y.; Chen, D.; Cai, K. *Am. J. Med. Sci.* **2014**, *347*, 178-182. (b) Boggs, S.; Elitzin, V. I.; Gudmundsson, K.; Martin, M. T.; Sharp, M. *J. Org. Process Res. Dev.* **2009**, *13*, 781-785.
4. (a) Mondal, S.; Samanta, S.; Jana, S.; Hajra, A. *J. Org. Chem.* **2017**, *82*, 4504-4510. (b) Gao, Y.; Chen, S.; Lu, W.; Gu, W.; Liu, P.; Sun, P. *Org. Biomol. Chem.* **2017**, *15*, 8102-8109. (c) Sun, K.; Mu, S.; Liu, Z.; Feng, R.; Li, Y.; Pang, K.; Zhang, B. *Org. Biomol. Chem.* **2018**, *16*, 6655-6658. (d) Yu, Y.; Yuan, Y.; Liu, H.; He, M.; Yang, M.; Liu, P.; Yu, B.; Dong, X.; Lei, A. *Chem. Commun.* **2019**, *55*, 1809-1812. (e) Singsardar, M.; Mondal, S.; Sarkar, R.; Hajra, A. *ACS Omega* **2018**, *3*, 12505-12512. (f) Lu, S.; Tian, L.; Cui, T.; Zhu, Y.; Zhu, X.; Hao, X.; Song, M.; *J. Org. Chem.* **2018**, *83*, 13991-14000. (g) Samanta, S.; Ravi, C.; Rao, S.; Joshi, A.; Adimurthy, S. *Org. Biomol. Chem.* **2017**, *15*, 9590-9594. (h) Chen, H.; Yi, H.; Tang, Z.; Bian, C.; Zhang, H.; Lei, A. *Adv. Synth. Catal.* **2018**, *360*, 3220-3227. (i) Samanta, S.; Mondal, S.; Ghosh, D.; Hajra, A. *Org. Lett.* **2019**, *21*, 4905-4909. (j) Wang, Y.; Frett, B.; McConnell, N.; Li, H. *Org. Biomol. Chem.* **2015**, *13*, 2958-296. (k) DiMauro, E. F.; Kennedy, J. M. *J. Org. Chem.* **2007**, *72*, 1013-1016.
5. (a) Bizet, V.; Kowalczyk, R.; Bolm, C. *Chem. Soc. Rev.* **2014**, *43*, 2426-2438. (b) Rémy, P.; Langner, M.; Bolm, C. *Org. Lett.* **2006**, *8*, 1209-1211. (c) Langner, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 5984-5987. (d) Sedelmeier, J.; Hammerer, T.; Bolm, C. *Org. Lett.* **2008**, *10*, 917-920. (e) Frings, M.; Thomé, I.; Bolm, C. *Beilstein J. Org. Chem.* **2012**, *8*, 1443-1451. (f) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Chem. Eur. J.* **2012**, *18*, 5541-5545.
6. (a) Lücking, U. *Angew. Chem. Int. Ed.* **2013**, *52,* 9399-9408. (b) Frings, M.; Bolm, C.; Blum, A. Gnamm, C. *Eur. J. Med. Chem.* **2017**, *126*, 225-245. (c) Sirvent, J. A.; Lücking, U. *ChemMedChem* **2017**, *12*, 487-501. (d) Lücking, U. *Org. Chem. Front.* **2019**, *6*, 1319-1324.
7. (a) Griffith, O. W.; Meister, A. *J. Biol. Chem.* **1979**, *254*, 7558-7560. (b) Griffith, O. W.; Anderson, M. E.; Meister, A. *J. Biol. Chem.* **1979**, *254*, 1205-1210. (c) Walker, D. P.; Zawistoski, M. P.; McGlynn, M. A.; Li, J.; Kung, D. W.; Bonnette, P. C.; Baumann, A.; Buckbinder, L.; Houser, J. A.; Boer, J.; Mistry, A.; Han, S.; Guzman-Perez, L. X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3253-3258. (d) Park, S. J.; Buschmann, H.; Bolm, C. *Bioorg. Med.Chem. Lett.* **2011**, *21*, 4888-4890. (e) Park, S. J.; Baars, H.; Mersmann, S.; Buschmann, H.; Baron, J. M.; Amann, P. M.; Czaja, K.; Hollert, H.; Bluhm, K.; Redelstein, R.; Bolm, C. *ChemMedChem* **2013**, *8*, 217-220.
8. (a) Lücking, U..; Siemeister, G.; Jautelat, R WO Patent WO 2006/099974, A1 **2006**. (b) Shetty, S. J.; Patel, G. D.; Lohray, B. B.; Lohray, V. B.; Chakrabarti, G.; Chatterjee, A.; Jain, M. R.; Patel, P. R. WO Patent WO 2007/077574, A2 **2006**.
9. (a) Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359-361. (b) Sumunnee, L.; Pimpasri, C.; Noikham, M.; Yotphan, S. *Org. Biomol. Chem.* **2018**, *16*, 2697-2704. (c) Aithagani, S.; Kumar, M.; Yadav, M.; Vishwakarma, R. A.; Singh, P. *J. Org. Chem.* **2016**, *81*, 5886-5894. (d) Yu, H.; Dannenberg, C.; Li, Z.; Bolm, C. *Chem. Asian J.* **2016**, *11*, 54-57. (e) Yang, Q.; Choy, P.; Zhao, Q.; Leung, M.; Chan, H.; So, C.; Wong, W.; Kwong, F. *J. Org. Chem.* **2018**, *83*, 11369-11376. (f) Wimmer, A.; König, B.; *Org. Lett.* **2019**, *21*, 2740-2744. (g) Jiang, Y.; You, Y.; Dong, W.; Peng, Z.; Zhang, Y.; An. D. *J. Org. Chem.* **2017**, *82*, 5810-5818. (h) Aithagani, S.; Dara, S.; Munagala, G.; Aruri, H.; Yadav, M.; Sharma, S.; Vishwakarma, R. A.; Singh, P. *Org. Lett.* **2015**, *17*, 5547-5549. (i) Kim, J.; Ok, J.; Kim, S.; Choi, W.; Lee, P. *Org. Lett.* **2014**, *16*, 4602-4605. (j) Wang, L.; Priebbenow, D. L.; Dong, W.; Bolm, C. *Org. Lett.* **2014**, *16*, 2661-2663. (k) Moessner, C.; Bolm, C. *Org. Lett.* **2005**, *7*, 2667-2669.
10. (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299-5358. (b) Manna, S.; Matcha, K.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 8163-8166. (c) Sun, C.; Shi, Z. *Chem. Rev.* **2014**, *114*, 9219-9280. (d) Kalbandhe, A. H.; Kavale, A. C.; Karade, N. N. *Eur. J. Org. Chem.* **2017**, *2017*, 1318-1322.
11. (a) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382-16385. (b) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960-19965. (c) Manna, S.; Serebrennikova, P. O.; Utepova, I. A.; Antonchick, A. P.; Chupakhin, O. N. *Org. Lett.* **2015**, *17*, 4588-4591.
12. (a) Han, S.; Gao, X.; Wu, Q.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Adv. Synth. Catal.* **2019**, *361*, 1559-1563. (b) Mu, B.; Li, J.; Zou, D.; Wu,

Geng, Y.; Han, S.; Liang, A.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron Lett.* **2018**, *59*, 1551-1554. (d) Han, S.; Liang, A.; Ren, X.; Gao, X.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron Lett.* **2017**,

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Wu, Y.; Wu, Y. *Tetrahedron Lett.* **2016**, *57*, 3067-3070.

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