OL Organic Letters

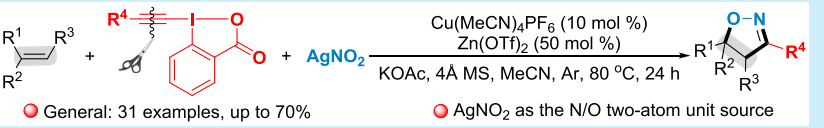
pubs.acs.org/OrgLett Letter

[2 + 2 + 1] Heteroannulation of Alkenes with Enynyl Benziodoxolones and Silver Nitrite Involving C≡C bond Oxidative Cleavage: Entry to 3-Aryl-Δ^2-isoxazolines

Cheng-Yong Wang, Fan Teng, Yang Li,* and Jin-Heng Li*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01285 Read Online

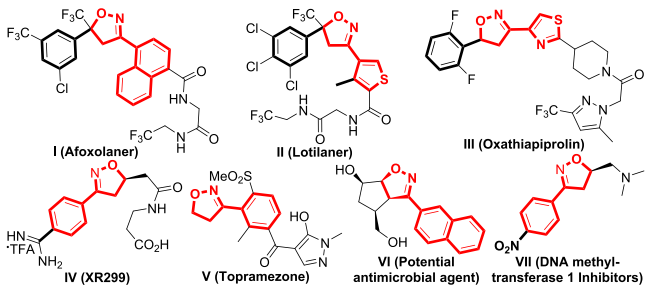
ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A copper-catalyzed [2 + 2 + 1] heteroannulation of alkenes with enynyl benziodoxolones and $AgNO_2$ involving oxidative cleavage of the C≡C bond promoted by cooperative $Zn(OTf)_2$, KOAc, and 4 Å MS for producing 3-aryl Δ^2-isoxazolines is reported. Mechanistic studies indicate that $AgNO_2$ serves as the N/O two-atom unit source, enabling the formation of three bonds through NO_2 addition across the C≡C bond, NO-transfer, C≡C bond cleavage, and annulation cascades.

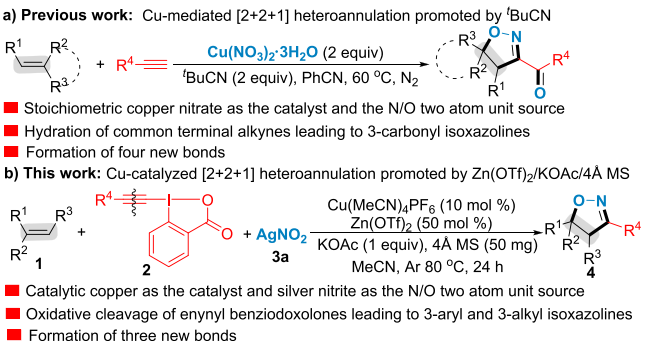
Isoxazolines are ubiquitous core structures that exist in many natural products, pharmaceuticals, and organic materials and serve as ligands and versatile synthetic intermediates.[1,2] Among them, Δ^2-isoxazolines, especially 3-aryl-substituted systems (Scheme 1), have discovered broad applications as agrochemicals, pharmaceuticals, and organic materials.[2] For example, both afoxolaner (**I**) and lotilaner (**II**) show highly insecticidal activity and have been used commercially for animal health.[2a,b] Oxathiapiprolin (**III**) is an antifungal agent as discovered by DuPont that is used for control of plant diseases caused by oomycetes.[2c,d] For these reasons, the development of efficient synthetic processes to the assembly of functionalized Δ^2-isoxazolines in a modular and selectivity-controlled manner remains a great significance.

Scheme 1. Examples of Important 3-Aryl-Δ^2-isoxazolines



Traditionally, typical methods to build such isoxazoline skeletons focus on the use of nitrile oxides and their precursors as reactants[3−6] via intermolecular 1,3-dipolar [3 + 2] cycloaddition of nitrile oxide intermediates with unsaturated compounds (e.g., alkenes, enols and alkynes)[4,5] or intramolecular cyclization of γ,δ-unsaturated oximes[6] by electrophilic addition or transition-metal catalysis.[3−6] However, most of which are restrict to special unsaturated compounds under harsh conditions. In particular, approaches for preparing Δ^2-isoxazolines are much less developed, and such versions that are general to alkenes, especially unactivated alkenes, are rare.[3−6] In 2015, Xu and co-workers developed a multicomponent strategy to regioselectively access 3-carbonyl Δ^2-isoxazolines via ^{t}BuCN-promoted [2 + 2 + 1] heteroannulation of terminal alkynes with alkenes and $Cu(NO_3)_2$ (Scheme 2a).[5] By employing stoichiometric $Cu(NO_3)_2$ as both the catalyst and the N/O two-atom unit source, this process enables the

Scheme 2. [2 + 2 + 1] Heteroannulation



Received: April 12, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01285
Org. Lett. XXXX, XXX, XXX−XXX

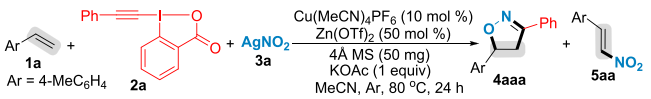
formation of four new bonds in a single reaction involving an alkyne hydration process. However, this method is limited to the activated electron-poor alkenes and alkylalkenes leading to the 3-carbonyl-substituted skeleton. Thus, unremitting discovery of new general multicomponent strategies that accommodate to broad alkenes and readily introduce functional groups for building functionalized Δ^2-isoxazolines, especially the important 3-aryl-susbtituted system, is highly desirable.

Herein, we report a new $Cu(MeCN)_4PF_6$-catalyzed three-component [2 + 2 + 1] heteroannulation of alkenes and enynyl benziodoxolones (EBXs) and $AgNO_2$ promoted by the $Zn(OTf)_2$/KOAc/4 Å MS system for producing functionalized Δ^2-isoxazolines, especially including pharmacologically relevant 3-aryl-substituted variants (Scheme 2b). The reaction employs $AgNO_2$ as the N/O two-atom unit source[7] to allow the formation of three new bonds, a C−C bond, a C−O bond, and a C═N bond, through NO_2 addition across the C≡C bond, NO-transfer, C≡C bond cleavage, and annulation cascades and features a broad scope of alkenes, including unactivated alkenes.

We initiated our efforts to explore a multicomponent [2 + 2 + 1] heteroannulation strategy for the synthesis of Δ^2-isoxazoline using 4-methoxystyrene (**1a**), phenylenynyl benziodoxolone (Ph-EBX; **2a**), and $AgNO_2$ (**3a**) as model substrates (Table 1). Gratifyingly, treatment of alkene **1a** with Ph-EBX **2a**, $AgNO_2$ **3a**, $Cu(MeCN)_4PF_6$, $Zn(OTf)_2$, KOAc, and 4 Å MS afforded the desired product **4aaa** in 70% yield (entry 1). A very small amount of product was obtained without $Cu(MeCN)_4PF_6$ (entry 2). Several other Cu salts, namely CuI, CuBr, copper(I) thiophene-2-carboxylate (CuTc), and $Cu(OTf)_2$, showed high catalytic activity, but they all were less efficient than $Cu(MeCN)_4PF_6$ (entries 3−6). We found that $Zn(OTf)_2$, 4 Å MS or KOAc acted as a promoter since omission of each the reaction could occur (entries 7−9). Using DBU or K_2CO_3 instead of KOAc was proven to be disfavored (entries 10 and 11). Both DMF and toluene both were inferior to MeCN (entries 12 and 13). While a lower temperature (60 °C) had a negative effect (entry 14), a higher reaction temperature (100 °C) gave a yield identical to that of 80 °C (entry 15). A series of other N/O two-atom unit sources, including $NaNO_2$ **2b**, $NaNO_2$ **2b**/AgOAc, $AgNO_3$ **2c**, $^tBuNO_2$ (TBN; **2d**), and $Cu(NO_3)_2$ **2e**, were evaluated (entries 16−19). Three sources, $NaNO_2$, $NaNO_2$//AgOAc, and $AgNO_3$, were less reactive than $AgNO_2$ attributed to a lower conversion of alkene **1a** (entries 16 and 17). Similarly, both TBN and $Cu(NO_3)_2$, the reported effective N/O two-atom unit source,[5] had no reactivity for the [2 + 2 + 1] heteroannulation reaction, but vinyl C−H nitration formed **5aa** (entries 18 and 19). Notably, no [2 + 2 + 1] heteroannulation of **1a** with **2a** occurred under the Xu conditions (entry 20).[5] These results suggest a different mechanism from the Xu reaction[5] probably because the current reaction utilized EBXs that are internal alkynes with internal oxidation to replace common terminal alkynes used by Xu group. Delightedly, the reaction with a scale up to 1 mmol of **1a** was successful to afford **4aaa** in 65% yield (entry 21).

The scope of this [2 + 2 + 1] heteroannulation protocol with respect to alkenes **1** and EBXs **2** was investigated (Schemes 3 and 4). A wide range of alkenes, including arylalkenes, alkylalkenes and acrylates, were compatible with the optimal conditions (**4baa**−**taa**). For arylalkenes, several substituents,

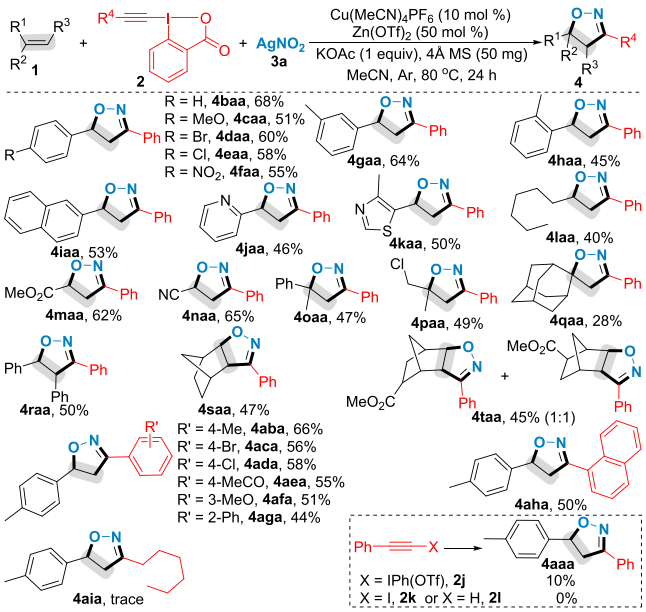
Table 1. Optimization of the Reaction Conditions[a]



entry	variation from the standard conditions	yield[b] (%) 4aaa	5aa
1	none	70	0
2	without $Cu(MeCN)_4PF_6$	10	0
3	CuI instead of $Cu(MeCN)_4PF_6$	55	0
4	CuBr instead of $Cu(MeCN)_4PF_6$	59	0
5	CuTc instead of $Cu(MeCN)_4PF_6$	57	0
6	$Cu(OTf)_2$ instead of $Cu(MeCN)_4PF_6$	55	0
7	without $Zn(OTf)_2$	30	0
8	without molecular sieve	42	0
9	without KOAc	50	0
10	DBU instead of KOAc	31	0
11	K_2CO_3 instead of KOAc	47	0
12	DMF instead of MeCN	54	0
13	toluene instead of MeCN	50	0
14	60 °C	53	0
15	100 °C	66	0
16[b]	$NaNO_2$ (**2b**) instead of $AgNO_2$	15	0
17[c]	$AgNO_3$ (**2c**) instead of $AgNO_2$	6	0
18	$^tBuNO_2$ (**2d**) instead of $AgNO_2$	trace	82
19	$Cu(NO_3)_2$ (**2e**) instead of $AgNO_2$	trace	80
20[d]	Xu conditions[5]	0	30
21[e]	none	65	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (2 equiv), $AgNO_2$ (2 equiv), $Cu(MeCN)_4PF_6$ (10 mol %), $Zn(OTf)_2$ (50 mol %), KOAc (1 equiv), 4 Å MS (50 mg), MeCN (1 mL), argon, 80 °C, and 24 h. [b]>80% of **1a** was recovered in the presence/absence of AgOAc (2 equiv). [c]>90% of **1a** was recovered. [d]$Cu(NO_3)_2{\cdot}3H_2O$ (2 equiv), ^{t}BuCN (2 equiv), PhCN (1.5 mL), 60 °C and N_2. [e]**1a** (1 mmol) and 36 h.

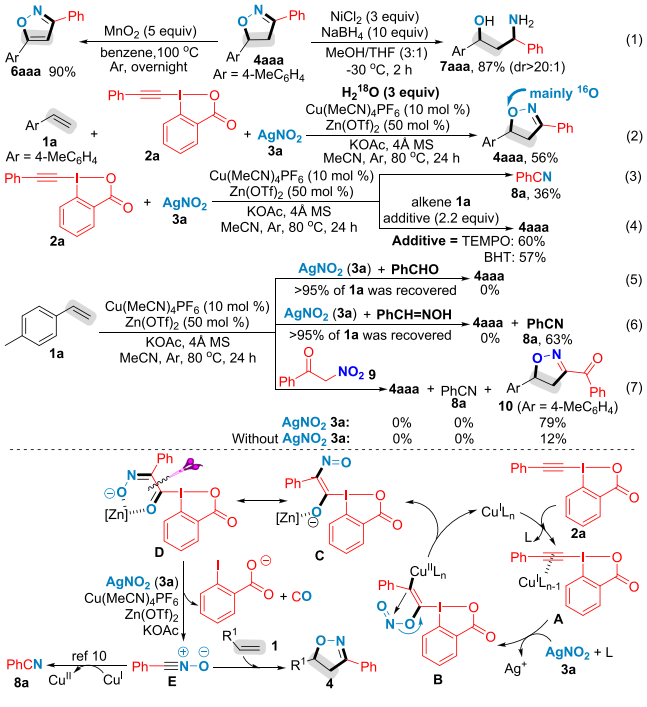
Scheme 3. Variation of the Alkenes (1) and EBXs (2)[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (2 equiv), $AgNO_2$ (2 equiv), $Cu(MeCN)_4PF_6$ (10 mol %), $Zn(OTf)_2$ (50 mol %), KOAc (1 equiv), 4 Å MS (50 mg), MeCN (1 mL), argon, 80 °C, and 24 h.

https://dx.doi.org/10.1021/acs.orglett.0c01285
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Synthetic Utilizations, Control Experiments, and Possible Mechanisms



such as MeO, Br, Cl, and NO_2, on the aryl ring at the terminal alkene were perfectly tolerated, and their electronic and position nature affected the reaction (**4baa**−**kaa**). While styrene **1b** was converted to **4baa** in 63% yield, alkene **1f** with a strong electron-withdrawing NO_2 group gave **4faa** in diminishing yield. Fascinatingly, the halogen (Br and Cl) groups were retained in the resulting products **4daa**−**eaa**, which would be used as a vehicle for further manipulations. We found that *m*-Me-substituted arylalkene **1g** was more reactive than *o*-Me-substituted **1h** (**4gaa**,**haa**). Functionalized arylalkenes, 2-vinylnaphthalene (**1i**), 2-vinylpyridine (**1j**), and 4-methyl-5-vinylthiazole (**1k**), were subjected to the reaction (**4iaa**−**kaa**). Oct-1-ene (**1l**), a terminal aliphatic alkene, was a suitable substrate (**4laa**). Using electron-poor alkenes **1m**,**n** efficiently furnished **4maa**,**naa** in good yields. Bulky 1,1-disubstituted alkenes **1o**−**q** also worked well to give **4oaa**−**qaa**, respectively. The reaction accommodated internal alkenes (norbornene and its derivatives) **1r**−**t**, which makes this reaction more attractive in synthetic applications (**4raa**−**taa**).

The generality of this [2 + 2 + 1] heteroannulation protocol to the EBXs **2** was next exploited. The reaction was affected by the substitution effect at the terminal alkyne. While electron-donating Me-substituted aryl-EBX **2b** furnished **4aba** with 66% yield, electron-withdrawing Br-, Cl-, and MeCO-substituted aryl-EBXs **2c**−**e** assembled **4aca**−**aea**, respectively, in 55%−58% yields. Aryl-EBXs **2f**−**h** bearing a *m*-MeO, an *o*-Ph or a naphthalen-1-yl group were also viable to assemble **4afa**−**aha**. Unfortunately, aliphatic EBX **2i** was inert for the heteroannulation (**4aia**). Another alkynyl hypervalent iodine (**2j**) exhibited lower reactivity, giving **4aaa** in 10% yield. However, (iodoethynyl)benzene (**2k**) and phenylacetylene (**2l**) had no reactivity.

Gratifyingly, isoxazoline **4aaa** is a versatile intermediate and could be readily converted into valuable isoxazole **6aaa**[8a] or 3-amino-propan-1-ol **7aaa**[8b] in high yields (eq 1; Scheme 4). The ^{18}O-labeled experiment was conducted and indicated that the oxygen atom in **4aaa** was not from water (eq 2). Omission of alkenes **1** led to the formation of benzonitrile **8a** from the reaction of Ph-EBX **2a** with $AgNO_2$ **3a** (eq 3). The reaction still proceeded smoothly when a stoichiometric radical inhibitor, TEMPO or 2,6-di-*tert*-butyl-4-methylphenol (BHT), was used, thus ruling out a free-radical process (eq 4). Replacement of Ph-EBX **2** by benzaldehyde or benzaldehyde oxime (the previous reported effect reagent[3−6]) indicated that benzaldehyde was inert (eq 5), and benzaldehyde oxime furnished benzonitrile **8a**, not the expected isoxazoline **4aaa** (eq 6). The results suggest that $AgNO_2$ first reacts with EBXs, and either benzaldehyde or benzaldehyde oxime was not the intermediates. Employing 2-nitro-1-phenylethan-1-one **9** instead of EBXs **2** promoted by $AgNO_2$ **3a** afforded 3-carbonyl isooxazoline **10**,[5] not **4aaa**, implying that substrate **9** is not the intermediate (eq 7).

The possible mechanism of the [2 + 2 + 1] heteroannulation protocol was proposed on the basis of the present results and literature results (Scheme 4).[3−7] Complexation of Ph-EBX **2a** with the active $L_nCu(I)$ species affords the intermediate **A**, followed by addition across the C≡C bond to afford the intermediate **B**. Reductive elimination and NO transfer of the intermediate **B** forms the intermediates **C** or **D** and regenerate the active $L_nCu(I)$ species.[3−5,7] The C−C bond cleavage[9] of the intermediate **D** by a combined effect of **2a**, $AgNO_2$, $Cu(MeCN)_4PF_6$, $Zn(OTf)_2$, KOAc, and 4 Å MS delivers the dipolar nitrile oxide intermediate **E** and releases CO (Figure S1, Supporting Information). Finally, annulation of the intermediate **E** with alkene **1** furnished product **4**.

On the other hand, the intermediate **E** might undergo the reduction reaction with the active LnCu(I) species to afford benzonitrile **8**.[10] The role of 4 Å MS might play a drying effect to avoid hydration of alkynes.

In conclusion, we have developed a novel copper-catalyzed [2 + 2 + 1] heteroannulation of alkenes, EBXs, and $AgNO_2$ for the synthesis of 3-aryl Δ^2-isoxazolines involving the C≡C bond cleavage. The reaction is facilitated by the $Zn(OTf)_2$/KOAc/4 Å MS system and features a broad alkene scope with exquisite selectivity control and excellent functional group tolerance. Importantly, $AgNO_2$ serves as the efficient N/O two-atom unit source to access polysubstituted Δ^2-isoxazolines, which had been applied as versatile synthetic intermediates in preparing highly valuable compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01285.

Experimental details, NMR spectra, and details of the experiments (PDF)

Accession Codes

CCDC 1040053 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

https://dx.doi.org/10.1021/acs.orglett.0c01285
Org. Lett. XXXX, XXX, XXX−XXX

AUTHOR INFORMATION

Corresponding Authors

Yang Li − *Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China*; Email: liyang8825490@126.com

Jin-Heng Li − *Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China; State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China; Key Laboratory of Functional Metal−Organic Compounds of Hunan Province, Key Laboratory of Functional Organometallic Materials, University of Hunan Province, Hengyang Normal University, Hengyang 421008, China*; orcid.org/0000-0001-7215-7152; Email: jhli@hnu.edu.cn

Authors

Cheng-Yong Wang − *Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China; Key Laboratory of Functional Metal−Organic Compounds of Hunan Province, Key Laboratory of Functional Organometallic Materials, University of Hunan Province, Hengyang Normal University, Hengyang 421008, China*

Fan Teng − *Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01285

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21625203 and 21871126) for financial support.

REFERENCES

(1) For selected reviews and papers, see: (a) Kaur, K.; Kumar, V.; Sharma, A. K.; Gupta, G. K. *Eur. J. Med. Chem.* **2014**, *77*, 121−133. (b) Weber, T.; Selzer, P. M. *ChemMedChem* **2016**, *11*, 270−276. (c) Long, A. *Drug Discovery Infect. Diseas.* **2018**, *8*, 319−351. (d) Avupati, V. R. *World J. Pharm. Res.* **2019**, *8*, 586−601. (e) Lamberth, C. *J. Heterocycl. Chem.* **2018**, *55*, 2035−2045. (f) Kotian, S. Y.; Mohan, C. D.; Merlo, A. A.; Rangappa, S.; Nayak, S. C.; Rai, K. M. L.; Rangappa, K. S. *J. Mol. Liq.* **2020**, *297*, 111686. (g) Arai, M. A.; Arai, T.; Sasai, H. *Org. Lett.* **1999**, *1*, 1795−1797. (h) Vitale, P.; Scilimati, A. *Adv. Heterocycl. Chem.* **2017**, *122*, 1−41. (i) Tangara, S.; Kanazawa, A.; Py, S. *Eur. J. Org. Chem.* **2017**, *2017*, 6357−6364.

(2) (a) Letendre, L.; Larsen, D.; Mark, M. *Drug Discovery Infect. Diseas.* **2018**, *8*, 273. (b) Zhang, Y.-b. *World Pesticide* **2015**, *37*, 4. (c) Jeanmart, S.; Edmunds, A. J. F.; Lamberth, C.; Pouliot, M. *Bioorg. Med. Chem.* **2016**, *24*, 317−341. (d) Wang, W.; Teng, P.; Liu, F.; Fan, T.; Peng, Q.; Wang, Z.; Hou, T. *J. Agric. Food Chem.* **2019**, *67*, 12904−12910. (e) Sielecki, T. M.; Wityak, J.; Liu, J.; Mousa, S. A.; Thoolen, M.; Wexler, R. R.; Olson, R. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 449−452. (f) Tiwari, D. K.; Paradkar, V. K.; Dubey, R.; Dwivedi, R. K. *Int. J. Agric. Sci.* **2018**, *10*, 5079−5081. (g) Kenanda, E. O.; Omosa, L. K. *Pharmacogn. Commun.* **2017**, *7*, 47−52. (h) Imran, M.; Khan, S. A.; Siddiqui, N. *Indian J. Pharm. Sci.* **2004**, *66*, 377−381.

(3) For selected reviews, see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002. (b) Rück-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507−516. (c) Vitale, P.; Scilimati, A. *Synthesis* **2013**, *45*, 2940−2948. (d) Rai, K. M. L. *Top. Heterocycl. Chem.* **2008**, *13*, 1−69. (e) Drosik, O. K.; Suwinski, J. W. *Curr. Org. Chem.* **2018**, *22*, 345−361.

(4) For representative papers, see: (a) Basel, Y.; Hassner, A. *Synthesis* **1997**, *1997*, 309−312. (b) Kunetsky, R. A.; Dilman, A. D.; Ioffe, S. L.; Struchkova, M. I.; Strelenko, Y. A.; Tartakovsky, V. A. *Org. Lett.* **2003**, *5*, 4907−4909. (c) Gao, M.; Gan, Y.; Xu, B. *Org. Lett.* **2019**, *21*, 7435−7439. (d) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082−2085. (e) Li, C.; Deng, H.; Li, C.; Jia, X.; Li, J. *Org. Lett.* **2015**, *17*, 5718−5721. (f) Wang, G.-W.; Cheng, M.-X.; Ma, R.-S.; Yang, S.-D. *Chem. Commun.* **2015**, *51*, 6308−6311. (g) Tang, Z.; Zhou, Y.; Song, Q. *Org. Lett.* **2019**, *21*, 5273−5276. (h) Kesornpun, C.; Aree, T.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. *Angew. Chem., Int. Ed.* **2016**, *55*, 3997−4001. (i) Chen, R.; Zhao, Y.; Fang, S.; Long, W.; Sun, H.; Wan, X. *Org. Lett.* **2017**, *19*, 5896−5899. (j) Chen, R.; Ogunlana, A. A.; Fang, S.; Long, W.; Sun, H.; Bao, X.; Wan, X. *Org. Biomol. Chem.* **2018**, *16*, 4683−4687. (k) Dai, P.; Tan, X.; Luo, Q.; Yu, X.; Zhang, S.; Liu, F.; Zhang, W.-H. *Org. Lett.* **2019**, *21*, 5096−5100. (l) Lai, Z.; Li, Z.; Liu, Y.; Yang, P.; Fang, X.; Zhang, W.; Liu, B.; Chang, H.; Xu, H.; Xu, Y. *J. Org. Chem.* **2018**, *83*, 145−153. (m) Shang, X.; Liu, K.; Zhang, Z.; Xu, X.; Li, P.; Li, W. *Org. Biomol. Chem.* **2018**, *16*, 895−898. (n) Lin, Y.; Zhang, K.; Gao, M.; Jiang, Z.; Liu, J.; Ma, Y.; Wang, H.; Tan, Q.; Xiao, J.; Xu, B. *Org. Biomol. Chem.* **2019**, *17*, 5509−5513. (o) Wang, D.; Zhang, F.; Xiao, F.; Deng, G.-J. *Org. Biomol. Chem.* **2019**, *17*, 9163−9168.

(5) Gao, M.; Li, Y.; Gan, Y.; Xu, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 8795−8799.

(6) (a) Eisenhauer, B. M.; Wang, M.; Labaziewicz, H.; Ngo, M.; Mendenhall, G. D. *J. Org. Chem.* **1997**, *62*, 2050−2053. (b) Han, B.; Yang, X.-L.; Fang, R.; Yu, W.; Wang, C.; Duan, X.-Y.; Liu, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 8816−8820. (c) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Wang, Y.-Q.; Luo, J.-Y.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 5687−5689. (d) Zhu, L.; Wang, G.; Guo, Q.; Xu, Z.; Zhang, D.; Wang, R. *Org. Lett.* **2014**, *16*, 5390−5393. (e) Liu, Y.-Y.; Yang, J.; Song, R.-J.; Li, J.-H. *Adv. Synth. Catal.* **2014**, *356*, 2913−2918. (f) Liu, Y.-Y.; Yang, X.-H.; Yang, J.; Song, R.-J.; Li, J.-H. *Chem. Commun.* **2014**, *50*, 6906−6908. (g) Wei, Q.; Chen, J.-R.; Hu, X.-Q.; Yang, X.-C.; Lu, B.; Xiao, W.-J. *Org. Lett.* **2015**, *17*, 4464−4467. (h) Zhang, W.; Su, Y.; Wang, K.-H.; Wu, L.; Chang, B.; Shi, Y.; Huang, D.; Hu, Y. *Org. Lett.* **2017**, *19*, 376−379. (i) Jimoh, A. A.; Hosseyni, S.; Ye, X.; Wojtas, L.; Hu, Y.; Shi, X. *Chem. Commun.* **2019**, *55*, 8150−8153. (j) Li, X.-T.; Gu, Q.-S.; Dong, X.-Y.; Meng, X.; Liu, X.-Y. *Angew. Chem., Int. Ed.* **2018**, *57*, 7668−7672. (k) Wang, L.; Zhang, K.; Wang, Y.; Li, W.; Chen, M.; Zhang, J. *Angew. Chem., Int. Ed.* **2020**, *59*, 4421−4427.

(7) For reviews on the use of nitrates and nitrite reagents in the synthesis of nitrogen-containing heterocycles, especially isoxazolines, see: (a) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; VCH: New York, 1989. (b) Yan, G.; Yang, M. *Org. Biomol. Chem.* **2013**, *11*, 2554−2566. (c) Gao, M.; Xu, B. *Chem. Rec.* **2016**, *16*, 1701−1714. (d) Gao, M.; Ye, R.; Shen, W.; Xu, B. *Org. Biomol. Chem.* **2018**, *16*, 2602−2618. (e) Zhang, K.; Jelier, B.; Passera, A.; Jeschke, G.; Katayev, D. *Chem. - Eur. J.* **2019**, *25*, 12929−12939.

(8) (a) Vilela, G. D.; da Rosa, R. R.; Schneider, P. H.; Bechtold, I. H.; Eccher, J.; Merlo, A. A. *Tetrahedron Lett.* **2011**, *52*, 6569−6572. (b) Zhu, M. K.; Zhao, J. F.; Loh, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 6284−6285.

(9) (a) Gaydou, M.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 13468−13471. (b) Wang, T.; Jiao, N. *Acc. Chem. Res.* **2014**, *47*, 1137−1145. (c) Shen, T.; Zhang, Y.; Liang, Y.-F.; Jiao, N. *J. Am. Chem. Soc.* **2016**, *138*, 13147−13150. (d) Qin, C.; Su, Y.; Shen, T.; Shi, X.; Jiao, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 350−354. (e) Shen, T.; Wang, T.; Qin, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 6677−6680. (f) Qin, C.; Shen, T.; Tang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 6971−6975. (g) Okamoto, N.; Ishikura, M.; Yanada, R. *Org.*

Lett. **2013**, *15*, 2571−2573. (h) Shen, T.; Zhu, B.; Lin, F.; Pan, J.; Wei, J.; Luo, X.; Liu, J.; Jiao, N. *Chin. J. Chem.* **2018**, *36*, 815−818.
(10) (a) Smith, L. I. *Chem. Rev.* **1938**, *23*, 193−285. (b) Grundmann, C. J.; Frommeld, H. D. *J. Org. Chem.* **1965**, *30*, 2077−2078. (c) Genco, N. A.; Partis, R. A.; Alper, H. *J. Org. Chem.* **1973**, *38*, 4365−4367.

https://dx.doi.org/10.1021/acs.orglett.0c01285
Org. Lett. XXXX, XXX, XXX−XXX