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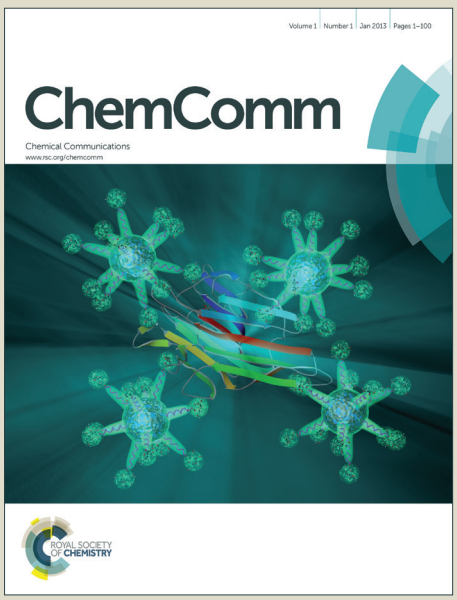

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Journal Name

COMMUNICATION

Copper-Catalyzed Synthesis of *β*-Trifluoromethylated Acrylonitriles and Trifluoromethyl-substituted 2*H*-Azirines

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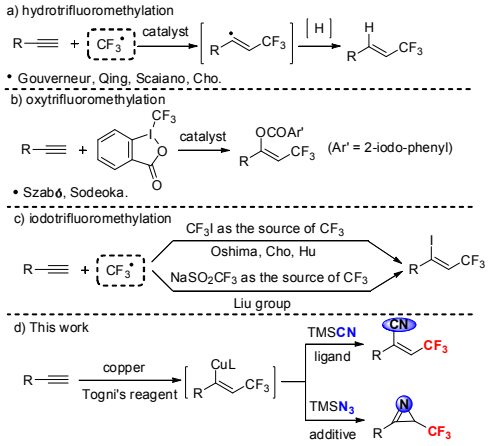
A direct assembly of acrylonitriles and valuable 2*H*-azirines from readily available starting materials is described. This novel alkyne difunctionalization reaction proceeded under mild reaction conditions. Considering the versatile roles of 2*H*-azirines, this work paves the way for further modification into various heterocycles.

The interests in the synthesis of molecules containing the trifluoromethyl (CF_3) group are increasing rapidly, because CF_3 group represents a ubiquitous structural motif which is prevalent in pharmaceutically compounds and functional materials.[1,2] Additionally, owing to its privileged role in modification biological molecules, the synthesis of functionalized trifluoromethyl compounds would help chemists to design lead compounds for drug discovery.[3] A typical procedure for the synthesis of CF_3-containing compounds is the trifluoromethylation of alkynes,[4] especially the reactions based on the intermolecular difunctionalization strategy.[5] Up to now, only three types of reactions have been developed to construct the C(sp^2)-CF_3 bonds from terminal alkynes.[6-8] This is in part because of concerns over the highly reactive of the vinyl radical intermediates generated in situ, which are less stable than their saturated analogs. A second factor is the low activity of CF_3 radical for the fact that the sp-hybridized carbons exert a strong attraction for these π-electrons. In this regard, the hydrotrifluoromethylation of terminal alkynes to construct a C(sp^2)-CF_3 bond were described by the related group (Scheme 1a).[6] In 2012, Szabó and Sodeoka independently reported the Cu-catalyzed oxytrifluoromethylation of alkynes by using Togni's reagent **2a** (Scheme 1b).[7] The groups of Oshima, Cho, Hu, and Liu independently reported 1,2-addition reactions of terminal alkynes for the construction of C-I and C(sp^2)-CF_3 bonds (Scheme 1c).[8] However, the development of an efficient strategy for the synthesis of functionalized CF_3 group containing compounds and the further



Scheme 1 Previous examples and current goals to construct the C(sp^2)-CF_3 bonds from terminal alkynes

exploitation of their synthetic potential is still highly desirable yet a formidable challenge.

Nitriles are readily available feedstock and diversely useful chemicals in organic synthesis.[9] In 2014, a catalytic version of the cyanotrifluoromethylation of alkenes was described by our group.[10] We also proved that the produced cyanotrifluoromethylation products could be transformed to the related amine and *β*-trifluoromethylated carboxylic acid. We envisioned that, *β*-trifluoromethylated acrylonitrile may also be synthesized from alkynes. Furthermore, the same as nitriles, 2*H*-azirines are not only a valuable class of compounds found in nature products,[11] but also versatile intermediates in organic synthesis.[12] As powerful precursors, they participated in a variety of transformations including the synthesis of pyridines,[13] indoles,[14] and pyrroles.[15] Existing procedures for 2*H*-azirines synthesis typically require multiple steps and harsh reaction conditions.[16] Consequently, selective synthetic methods for the construction of functionalization of 2*H*-azirine in an one-pot reaction is of great importance. The groups of Park and Du have independently reported the synthesis of functionalized 2*H*-azirines from *α*-diazo oxime ethers and enamines.[17] In this context, we initiated our synthetic method by using copper catalyst to construct

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† Electronic supplementary information (ESI) available. Experimental procedures and analysis data for new compounds. CCDC reference numbers CCDC 1407790 (**3h**), 1407789(**4q**), 1407786(**5a**), 1407787(**7a**), and 1407788(**9**).
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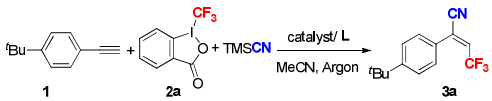
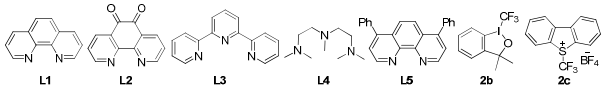
Table 1 Optimization conditions for *β*-trifluoromethylated acrylonitriles[a]



Entry	Catalyst (mol %)	Ligand	Solvent	Yield[b] (%) (E/Z)
1	CuBr (10)	—	1,4-dioxane	trace
2	CuBr (10)	—	DCE	trace
3	CuBr (10)	—	CH_3CN	5 (>20/1)
4	CuBr (10)	L1(20)	CH_3CN	58 (>20/1)
5	$CuCl_2$ (10)	L1(20)	CH_3CN	56 (>20/1)
6	$Cu(OAc)_2$ (10)	L1(20)	CH_3CN	62 (>20/1)
7	$Cu(OAc)_2$ (10)	L2(20)	CH_3CN	58 (>20/1)
8	$Cu(OAc)_2$ (10)	L3(20)	CH_3CN	71 (>20/1)
9	$Cu(OAc)_2$ (10)	L4(20)	CH_3CN	trace
10	$Cu(OAc)_2$ (10)	L5(20)	CH_3CN	57 (>20/1)
11[c]	$Cu(OAc)_2$ (10)	L3(20)	CH_3CN	62
12[d]	$Cu(OAc)_2$ (10)	L3(20)	CH_3CN	35

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), TMSCN (0.4 mmol), 5 h, 70°C. [b]Isolated yield, the ratio of regioisomers was determined by GC-MS. [c]Togni's reagent **2b** was used. [d]Umemoto reagent **2c** was used.

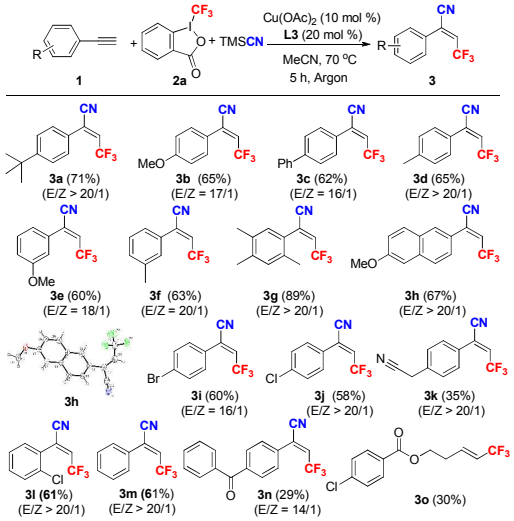


functionalization 2*H*-azirines from readily available alkynes. The work provides rapid assembly of valuable CF_3-containing 2*H*-azirine structures. It also provides a way for further construction of various CF_3-containing heterocycles. On account of the aforementioned, we report herein an unprecedented route to synthesize *β*-trifluoromethylated acrylonitriles and trifluoromethyl-substituted 2*H*-Azirines from alkynes (Scheme 1d). The potential of this trifluoromethyl-substituted 2*H*-azirines for practical synthesis have also been demonstrated. Various pyridines and pyrazines with the CF_3 skeletons were synthesized in high yields. It should be noted that, as the same time as we finish this work, Liu reported the trifluoromethylazidation of alkynes.[18] Nevertheless, the reaction need two steps and requires a high pressure mercury lamp (100 W) as the irradiation source in toluene.

We began our experiment with the model reaction of **1a** with Togni's reagent **2a** and TMSCN at 70°C under argon. Only trace of the acrylonitrile product was formed in our initial investigation. Screening the solvent of 1,4-dioxane, DCE, and CH_3CN, the desired product **3a** could be observed in 5% yield (Table 1, entry 3). With 1,10-phenanthroline **L1** was used, we were pleased to find that the process occurred smoothly and an improved yield (58%) (E/Z > 20/1) of the corresponding product was obtained (entry 4). The brief survey on the ligands indicated that **L3** was the most efficient, which afforded the product **3a** in 71% yield (entry 8).[19]

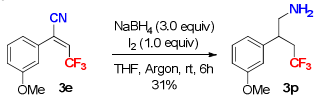
Subsequently, the scope of the cyanotrifluoromethylation was investigated. As depicted in Table 2, excellent E/Z product ratios were obtained in most cases. Alkynes with different substituents on the aromatic ring proceeded smoothly to afford corresponding products **3a–n**. It is worth mentioning that the transformation worked pretty well with 2,4,5-trimethyl substituent phenyl, and gave the corresponding product **3g** in 89% yield. The only unfortunate reality is that linear alkyne failed to give the desired

Table 2 Substrate scope of *β*-trifluoromethylated acrylonitriles from [a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), TMSCN (0.4 mmol), $Cu(OAc)_2$ (10 mol %), ligand (20 mol %), CH_3CN (1.0 mL), isolated yields.

product, but formed a hydrotrifluoromethylation product **3o**. Finally, the produced acrylonitrile **3e** was reduced to the CF_3-containing amine in the presence of I_2 and $NaBH_4$ as reductant (Scheme 2).



Scheme 2 Synthetic transformation

Encouraged by these intriguing results, we wished to further investigate the scope of the azidotrifluoromethylation. However, the desired product was not obtained under the above optimized conditions (Table 3, entry 1). To our delighted, instead of the azidotrifluoromethylation product, an intriguing product **4a** was isolated in 30% yield along with trace of byproducts tetrazole **5a** and nitrile in the absence of **L3** ligand (entry 2). The tetrazole **5a** was obtained through a C-C bond cleavage and a C-N bond formation with the concomitant insertion of four nitrogen atoms.[20] The nitrile was formed through C-C triple bonds cleavage, which has been reported by Jiao group in 2013.[21] When NaOAc was used, we were glad to find that alkyne **1a** was converted into the corresponding product in 51% yield (entry 7). The temperature plays a significant role on the reaction. The yield was improved to 64% at 80 °C. The structure of **5a**, which represented a key molecular motif in medicinal chemistry, was confirmed by X-ray crystallographic analysis. Even if we are not satisfied with the present result, however, any improvement on the yield of **5a** could not be obtained all the time after mulriple attempts.[19]

As shown in Table 4, the scope of alkynes was thoroughly investigated under the optimized reaction conditions. A variety of aromatic alkynes with divergent substituents could efficiently afford the corresponding trifluoromethyl-substituted 2*H*-azirines (**4**). Phenylacetylene with a keto-moiety was employed and gave the desired product **4i** in 55% yield. Sterically congested 2-Cl substituted phenylacetylene slightly decreased the reactivities, offering the corresponding 2*H*-azirine product (**4m**) in 48% yield.

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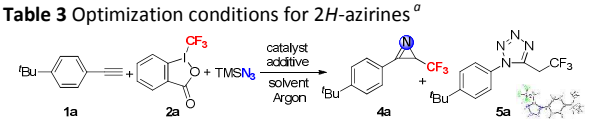
Table 3 Optimization conditions for 2*H*-azirines [a]



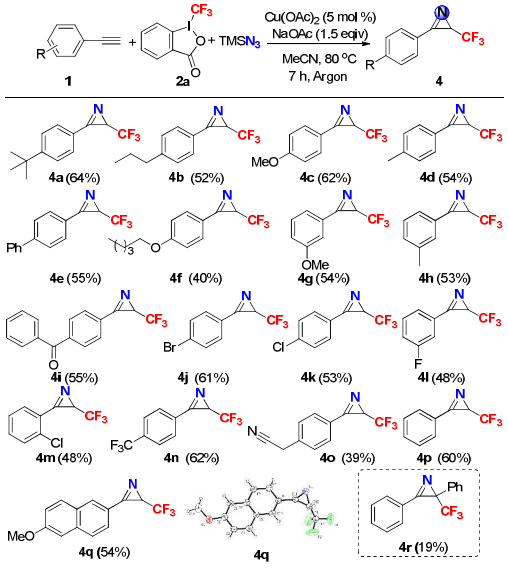
Entry	Catalyst	Base	Solvent	Temp (°C)	Yield **4a** (%)[b]
1	$Cu(OAc)_2$/**L3**	—	CH_3CN	70	trace
2	$Cu(OAc)_2$	—	CH_3CN	70	30
3	CuBr	—	CH_3CN	70	21
4	$Cu(OTf)_2$	—	CH_3CN	70	13
5	$Cu(OAc)_2$	K_2CO_3	CH_3CN	70	41
6	$Cu(OAc)_2$	Na^{t}OBu	CH_3CN	70	45
7	$Cu(OAc)_2$	$NaOA_C$	CH_3CN	70	51
8	$Cu(OAc)_2$	$NaOA_C$	CH_3CN	80	64
9[c]	$Cu(OAc)_2$	$NaOA_C$	CH_3CN	80	61
10[d]	$Cu(OAc)_2$	$NaOA_C$	CH_3CN	80	31

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.26 mmol), $TMSN_3$ (0.36 mmol), catalyst (5 mol %), 7 h. [b]Isolated yield. [c]Togni's reagent **2b** was used. [d]Umemoto reagent **2c** was used.

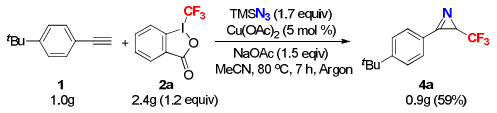
1,2-diphenylethyne (**1r**) was found to be less reactive due to its larger steric hindrance. Only 19% yield of 2*H*-azirine product **4r** was isolated when 1,2-diphenylethyne was employed. An important feature is that the conversion on a gram scale could also be performed (Scheme 3).

To demonstrate the potential of this copper catalyzed synthesis of trifluoromethyl-substituted 2*H*-azirines for practical synthesis. The produced compound **4** was used as an intermediate to synthesize pyridines that are not easy to access traditionally. The 2*H*-azirines **4** reacted with vinyl diazoacetates **6** smoothly in the presence of $[Rh_2(esp)_2]$ in 1,2-dichloroethane followed by exposure to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[22] The yields of the produced CF_3-containing pyridines **7** were good as shown in

Table 4 Scope of the copper-catalyzed synthesis of trifluoromethyl-substituted 2*H*-azirines[a]



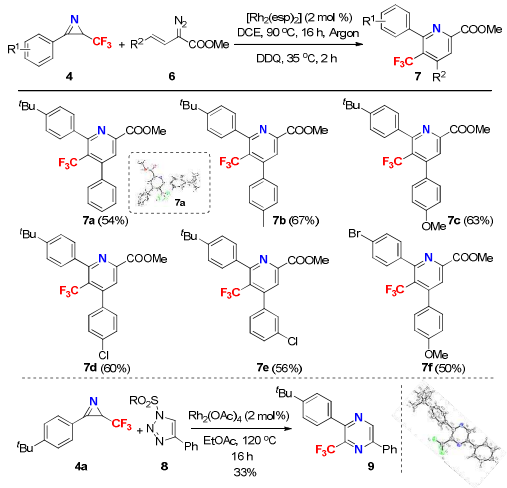
[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.26 mmol), $TMSN_3$ (0.36 mmol), $Cu(OAc)_2$ (5 mol %), CH_3CN (1.0 mL), 80 °C, 7 h, isolated yields.



Scheme 3 Gram-scale reaction

Table 5. Additionally, another particularly useful reaction of this 2*H*-azirines was also occurred, albeit the yield of the obtained pyrazine **9** was only 33%.[23] Pyridines and pyrazines with the CF_3 skeletons are widely embedded in many synthesized biologically active molecules such as those shown in the Figure 1.[24]

Table 5. Further synthetic transformation



In order to gain insight into the mechanism, TEMPO was added and only 10% yield of the product was obtained and 81% of alkyne **1a** was recovered (Scheme 4a). A similar result is also observed in the synthesis of 2*H*-Azirines. When we attempted to use 1,1-diphenylethylene (**10**) to trap the radical, a 89% yield of the azidotrifluoromethylation product **11** was isolated. The 2*H*-azirine product was also obtained in 28% yield. However, no desired product **3a** was detected when 1,1-diphenylethylene was added to the reaction. In addition, the same yields of **12** and **13** were detected whether the reaction was conducted in the presence or absence of alkyne. In 2015, a mechanistic study of aminotrifluoromethylation reaction by means of kinetic studies, NMR and ESI- MS analyses was reported by Sodeoka group.[25] On the basis of Sodeoka's study, the above experiments and related published research studies,[26] we proposed a plausible catalytic cycle (Scheme 5). Togni's reagent **2a** was first activated by $Cu(OAc)_2$ to generate copper(II) complex **A**. Then, the C-C triple bonds of **1a** was activated by copper(II) complex **A** on the activated hypervalent iodine moiety to give intermediate **B**. An addition reaction was occurred via intermediate **C**, leading to the formation of Cu(III) species **D**. Subsequent reductive elimination of Cu(III) species **D** generated the product **3** or intermediate **E**. However, intermediate

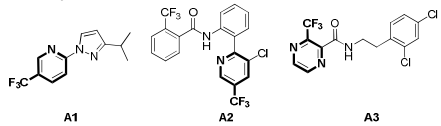


Figure 1 Examples of pyridines and pyrazine containing CF_3 group

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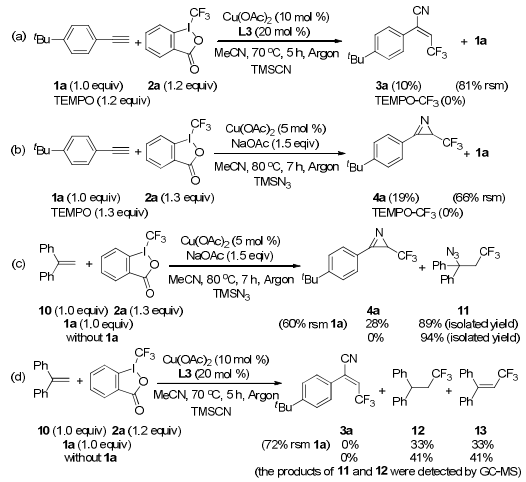
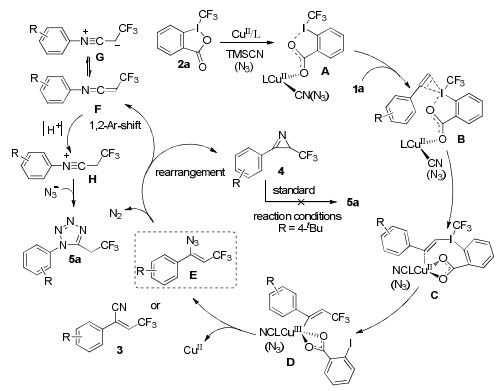


Scheme 4 Trapping experiments

E could not be isolated after considerable efforts due to its highly reactivaty. Finally, the CF_3-containing 2*H*-azirine product **4** was formed via rearrangement of intermediate **E** by losing nitrogen. The 2*H*-azirine **4a** could not rendered tetrazole **5a** under the standard reaction conditions. For another, the intermediate **F**, which is just a resonance structure of the intermediate **G**, could also be formed from intermediate **E** through a 1,2-aryl shift after release of nitrogen. The intermediate **F** forms intermediate **H,** which was attached by azide anion to generate tetrazole **5a**.



Scheme 5 Proposed mechanism

In conclusion, we have developed a copper-catalyzed difunctionalization of alkynes for the synthesis of *β*-trifluoromethylated acrylonitriles and trifluoromethyl-substituted 2*H*-azirines, which are useful compounds in organic synthesis. The potential of this trifluoromethyl-substituted 2*H*-azirines has been demonstrated with wide functional group compatibilities for practical synthesis. Various CF_3-containing pyridines and pyrazines are synthesized in high yields. Further investigation of the reaction scope are currently underway in our laboratory.

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Notes and references

1 (a) K. Uneyama, In *Organofluorine Chemistry*; Blackwell: Oxford, U.K. 2006.
2 (a) M. Hird, *Chem. Soc. Rev.,* 2007, **36**, 2070; (b) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.,* 2011, **111**, 4475;
3 (a) D. T. Wong, K. W. Perry and F. P. Bymaster, *Nat. Rev. Drug Discovery.,* 2005, **4**, 764.
4 Only few reviews involved in trifluoromethylation of alkynes, see: (a) L. Chu and F. L. Qing, *Acc. Chem. Res*., 2014, **47**, 1513; (b) T. Besset, T. Poisson and X. Pannecoucke, *Chem. Eur. J*., 2014, **20**, 16830; (c) P. Gao, X.-R. Song, X.-Y. Liu and Y.-M. Liang, *Chem. Eur. J*., 2015, **21**, 7648.
5 A. Maji, A. Hazra and D. Maiti, *Org. Lett*., 2014, **16**, 4524.
6 (a) T. Kitazume and N. Ishikawa, *J. Am. Chem. Soc*., 1985, **107**, 5186; (b) S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, K. Wheelhouse, G. Rassias, M. Mdebielle and V. Gouverneur, *J. Am. Chem. Soc*., 2013, **135**, 2505; (c) X. Wu, L. Chu and F.-L. Qing, *Angew. Chem., Int. Ed*., 2013, **52**, 2198; (d) S. P. Pitre, C. D. McTiernan, H. Ismaili and J. C. Scaiano, *ACS Catal*., 2014, **4**, 2530; (e) S. Choi, Y. J. Kim, S. M. Kim, J. W. Yang, S. W. Kim and E. J. Cho, *Nat. Commun*., 2014, **5**, 4481.
7 (a) P. G. Janson, I. Ghoneim, N. O. Ilchenko and K. J. Szabó, *Org. Lett*., 2012, **14**, 2882; (b) H. Egami, R. Shimizu and M. Sodeoka, *Tetrahedron Lett*., 2012, **53**, 5503.
8 (a) L. Y. Takeyama, Y. Ichinose, K. Oshima and K. Utimoto, *Tetrahedron Lett*., 1989, **30**, 3159; (b) T. Xu, C. W. Cheung and X. Hu, *Angew. Chem., Int. Ed*., 2014, **53**, 4910; (c) Z. Hang, Z. Li and Z.-Q. Liu, *Org. Lett*., 2014, **16**, 3648; (d) N. Iqbal, J. Jung, S. Park and E. J. Cho, *Angew. Chem., Int. Ed*., 2014, **53**, 539.
9 R. C. Larock, In *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1989, pp 819
10 Y.-T. He, L.-H. Li, Y.-F. Yang, Z.-Z. Zhou, H.-L. Hua, X.-Y. Liu and Y.-M. Liang, *Org. Lett*., 2014, **16**, 270.
11 T. W. Miller, E. W. Tristram and F. J. Wolf, *J. Antibiot*., 1971, **24**, 48.
12 W. F. Berkowitz, *Org. React*., 2011, **78**, 321.
13 C. M. Park and Y. Jiang, *Chem. Sci*., 2014, **5**, 2347.
14 S. Jana, M. D. Clements, B. K. Sharp and N. Zheng, *Org. Lett*., 2010, **12**, 3736.
15 X. X. Qi, X. X. Xu and C. M. Park, *Chem. Commun*., 2012, **48**, 3996.
16 Z. Rappoport and J. F. Liebman, *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; Wiley: Hoboken, NJ, 2008; Vol. 2.
17 (a) X. Li, Y. Du, Z. Liang, X. Li, Y. Pan and K. Zhao, *Org. Lett*., 2009, **11**, 2643; (b) Y. J. Jian, W. C. Chan and C.-M. Park. *J. Am. Chem. Soc*., 2012, **134**, 4104.
18 F. Wang, N. Zhu, P. chen, J. Ye and G. L, DOI: 10.1002/anie.201503412.
19 See ESI† for detailed data.
20 F. Chen, C. Qin, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.,* 2011, **50**, 11487
21 T. Shen, T. Wang, T. Qin and N. Jiao, *Angew. Chem., Int. Ed*., 2013, **52**, 6677.
22 N. S. Y. Loy, A. Singh, X. Xu and C.-M. Park, *Angew. Chem., Int. Ed.,* 2013, **52**, 2212.
23 T. Ryu, Y. Baek and P. H. Lee, *J. Org. Chem*., 2015, **80**, 2376.
24 M. Oda, Y. Matsuzaki, K. Tanaka, E. Takizawa, M. Hasebe, N. Kuroki, A. Suwa and K. Oshima, *PCT Int. Appl*. 2007, WO 2007108483 A1 20070927.
25 S. Kawamura, H. Egami, M. Sodeoka, *J. Am. Chem. Soc*., 2015, **137**, 4865.
26 (a) H. Egami, R. Shintaro, S. Kawamura and M. Sodeoka, *Angew. Chem., Int. Ed*., 2013, **52**. 4000; (b) Y. Yasu, T. Koike and M. Akita, *Chem. Commun*., 2013, **49**, 2037.

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