Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

A Highly Regio- and Stereoselective Syntheses of α-Halo Enamides, Vinyl Thioethers, and Vinyl Ethers with Aqueous Hydrogen Halide in Two-Phase Systems

Wei Cao,[†,∥] Ping Chen,[†,∥] Liang Wang,[§] Hao Wen,[†] Yu Liu,[†] Wanshu Wang,[†] and Yu Tang*[,†,‡]

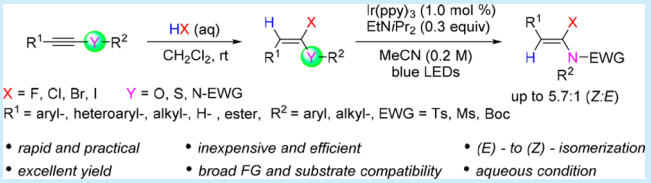
[†]Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Yushan Road, Qingdao 266003, P. R. China

[‡]Laboratory for Marine Drugs and Bioproducts Qingdao National Laboratory for Marine Science and Technology, Qingdao 266237, P. R. China

[§]College of Chemistry and Pharmaceutical Sciences, Qingdao Agricultural University, Qingdao 266109, P. R. China

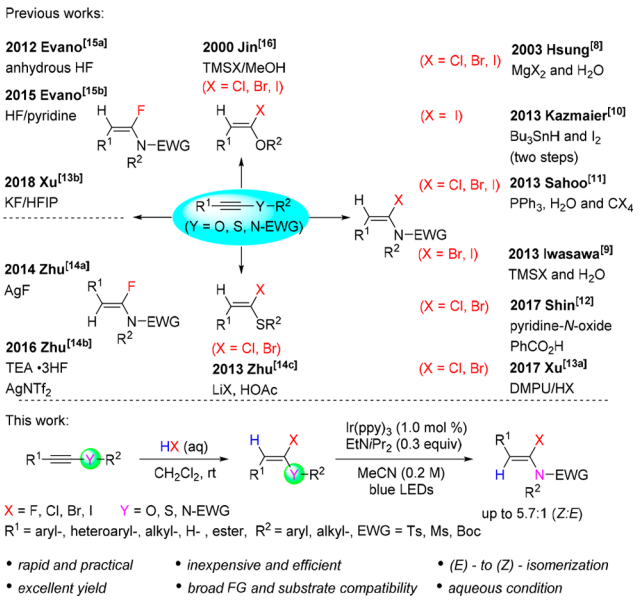
Supporting Information

ABSTRACT: A metal-free regio- and stereoselective method is achieved for the preparation of (*E*)-configured α-halo enamides, vinyl thioethers, and vinyl ethers using aqueous HX (X = F, Cl, Br, I), which features high functional group compatibility and regio- and stereoselectivity, mild conditions, high efficiency, and rapid transformation. Additionally, the isomers could be yielded readily from the (*E*)-configured α-halo enamides via photocatalysis or under Sonogashira coupling conditions.



Enamides are versatile intermediates in organic syntheses, and they are also structural motifs, existing widely in natural products and bioactive molecules.[1,2] Among various enamides, α-haloenamides, e.g., chloro, bromo enamides have received particular attention due to their synthetic usefulness with the C−X bonds and nucleophilic alkenes employed as synthetic handles, providing ample potential for various elaborations,[3] such as halogen−metal exchange and cross-couplings etc., which renders this agent one of the most important building blocks for synthetic chemistry.[4] Its fluoro analogues, i.e., α-fluoroenamides, play significant roles in pharmaceutical chemistry.[5] Similarly, α-halo vinyl thioethers and α-halo vinyl ethers are also ubiquitous building blocks in organic synthesis, material chemistry, and industrial chemicals.[6,7] The development of general synthetic protocols to access these motifs has attracted extensive interest, and a plethora of strategies have been developed (Scheme 1).[8−16] Hsung et al. first reported the stereoselective syntheses of α-haloenamides from ynamides using HX generated in situ.[8] Afterward, some elegant methods have been independently reported by Iwasawa,[9] Kazmaier,[10] Sahoo,[11] and Shin[12] for the syntheses of α-haloenamides. Xu et al. achieved the stereocontrolled hydrochlorination, hydrobromination and hydrofluorination of ynamides using the DMPU/HX system and KF/HFIP system, respectively.[13] In recent years, Zhu and Zhu et al. independently disclosed silver-promoted trans-hydrofluorination of ynamides, giving the (*Z*)-α-fluoroenamides which are inaccessible by conventional methods.[14a,b] Evano and Thibaudeau demonstrated stereoselective hydrofluorination of ynamides using anhydrous HF and HF−pyridine as the fluorination reagents, respectively.[15]

Scheme 1. Synthetic Strategies for α-Alkenyl Halides



Similarly, α-halo vinyl ethers could be furnished by hydrohalogenation of ynol ethers using TMSX and methanol.[16] The α-chloro vinyl thioethers could also be accessed using LiX in the presence of HOAc.[14c] Although these protocols have been well established, they still suffer from

Received: June 11, 2018

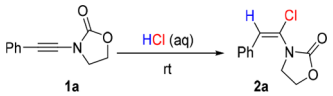
DOI: 10.1021/acs.orglett.8b01809
Org. Lett. XXXX, XXX, XXX−XXX

either rigorous conditions or poor efficiency, such as elevated temperature, toxic reagents, as well as narrow substrate scope, and no general protocol is available for direct hydrofluorination, hydrochlorination, hydrobromination, and hydroiodination of ynamides, ynol ethers, and thioalkynes. Therefore, it is highly desirable to develop a general and straightforward method for the regio- and stereoselective α-halogenation of ynamides.

Inspired by these elegant works and as a continuation of our interest in ynamide chemistry,[8,17] herein we report the direct electrophilic addition of aqueous HX (X= F, Cl, Br, I) to ynamides, ynol ethers and thioalkynes in a two-phase system, affording regio-specific and stereoselective α-halo products in excellent yields with exclusive (E)-configuration at ambient temperature. Additionally, the (Z)-α-chloroenamides could be obtained in good yields via photochemically catalyzed isomerization of the (E)-α-chloroenamides.

At the outset, oxazolidinone ynamide **1a** was selected as the model substrate to investigate the feasibility of the direct hydrohalogenation of ynamides using aqueous HCl (6 M) in EtOAc at ambient temperature (Table 1, entry 1). Gratifyingly,

Table 1. Optimization of Reaction Condition[a]



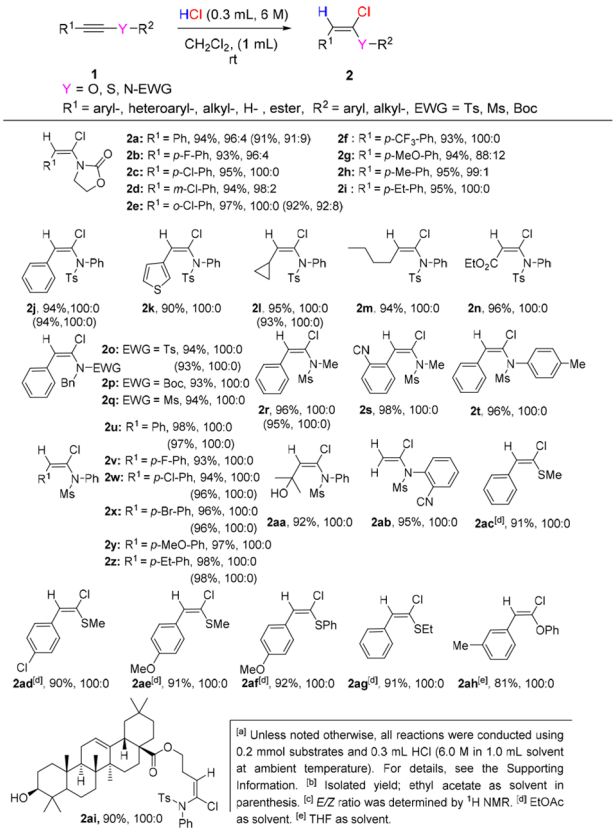
entry	HCl (6.0 M) (mL)	solvent	time (h)	yield[b] (%)	E/Z[c]
1	1.0	EtOAc	0.3	90	91:9
2	1.0	dioxane	0.2	82	83:17
3	1.0	toluene	7.0	75	89:11
4	1.0	THF	0.2	85	83:17
5	1.0	MeOH	0.5	74	83:17
6	1.0	MeCN	0.5	83	90:10
7	1.0	CH_2Cl_2	1.5	92	92:8
8	**0.3**	**CH_2Cl_2**	**2.0**	**94**	**96:4**
9	0.3	H_2O	24	64	87:13

[a]Unless noted otherwise, all reactions were conducted using 0.2 mmol of ynamide **1a** and 1.0 mL of HCl (aq) in 1.0 mL of solvent at ambient temperature. For details, see the Supporting Information. [b]Isolated yield. [c]E/Z ratio was determined by ^{1}H NMR.

the desired (E)-α-chloroenamide **2a** was furnished in 81% yield within 20 min. Encouraged by this result, the reaction parameters were then extensively optimized to improve the efficiency. Afterward, a variety of other solvents were evaluated, the employment of which, however, only resulted in inferior yields (entries 2−6). Notably, the solubility of solvents in water had significant impact on the yield and reaction time (entries 2−6), and higher yield and stereoselectivity were observed using more immiscible CH_2Cl_2, albeit with longer reaction time (entry 7). The impact of HCl loading and concentrations on the reaction were then investigated, and 1.5 equiv of HCl (6 M) was identified as the optimal loading, which furnished **2a** in highest yield (see more details in Table S1). Intriguingly, the desired product **2a** could also be furnished in 55% yield using H_2O as solvent with much longer reaction time (entry 9).

With the optimized conditions in hand, the generality of this protocol was investigated with sterically and electronically diverse ynamides subjected to hydrohalogenation, and the results are presented in Scheme 2. Gratifyingly, all of the substrates were well tolerated to furnish the desired products

Scheme 2. Hydrochlorination of Ynamides, Thioalkynes and Ynol Ethers[a−c]



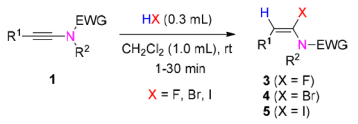
in good to excellent yields (**2a−ai**). As to the aryl groups R^1 substituted on oxazolidinone ynamides **1a−i**, the electronic characteristics had trivial impact on the reaction, giving (E)-chloroenamides in excellent yields (**2a−i**). Remarkably, the stereospecific products **2c**, **2f** and **2i** were furnished under the optimal conditions. In addition to oxazolidinone ynamides, *N*-sulfonylynamides were also ideal substrates, which could be readily hydrochlorinated to produce (E)-chloroenamides in excellent yields as single isomers (**2j−ab**). Remarkably, miscellaneous R^1 substituents, including aryl-, heteroaryl-, alkyl-, H-, and even ester, were all compatible with the hydrochlorination of ynamides, thus allowing the preparation of the corresponding polysubstituted α-chloroenamides, many of which are not readily accessible by conventional condensation methods. In particular, the isopropanolyl was also well tolerated to deliver the corresponding product **2aa** without isomerization even under strong acidic condition. Subsequently, the functional-group compatibility of R^2 was then investigated, and various phenyl, benzyl, and methyl substituents were found to be well tolerated in this hydrochlorination (**2o−t**, **2ab**). Encouraged by these results, hydrohalogenation of more diverse alkynyl substrates, such as thioalkynes, was examined under the optimal conditions, and the reaction proceeded smoothly, yielding the desired (E)-α-chloro vinyl thioethers (**2ac−ag**) as the only isomers in high yields. Similarly, ynol ethers were also subjected to this hydrochlorination with THF as solvent for higher efficiency, which stereospecifically furnished the desired (E)-α-chloro vinyl ether **2ah** in 81% yield. The more complex substrate **1ai** was also subjected to the optimal condition to examine the

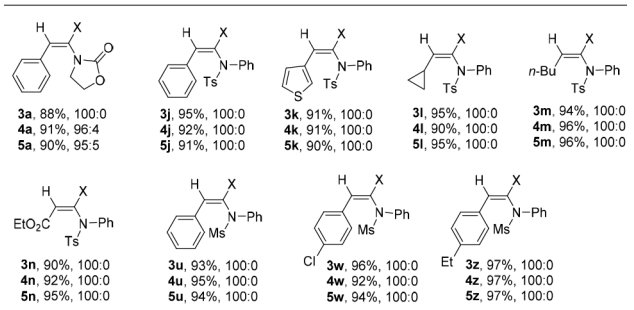
DOI: 10.1021/acs.orglett.8b01809
Org. Lett. XXXX, XXX, XXX−XXX

generality, affording the desired (*Z*)-α-chloroenamides **2ai** in high yield.

To further demonstrate the synthetic utility of this protocol, the hydrofluorination, hydrobromination, and hydroiodination of diverse ynamides were investigated under similar conditions. Gratifyingly, the reactions proceeded smoothly, giving the corresponding (*E*)-configured α-haloenamides (**3a−z**, **4j−z**, **5j−z**) stereospecifically in 88−97% yields (Scheme 3).

Scheme 3. Hydrofluorination, Hydrobromination, and Hydroiodination of Ynamides[a−c]





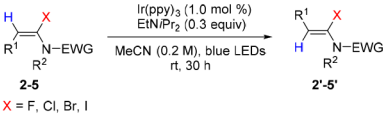
[a]Unless noted otherwise, all reactions were conducted using 0.2 mmol of ynamides and 0.3 mL of HF (48% w/w in water), HBr (48 wt % in water), or HI (55% w/w in water) in 1.0 mL of CH_2Cl_2 at ambient temperature. For details, see the Supporting Information. [b]Isolated yield. [c]*E*/*Z* ratio was determined by ^{1}H NMR.

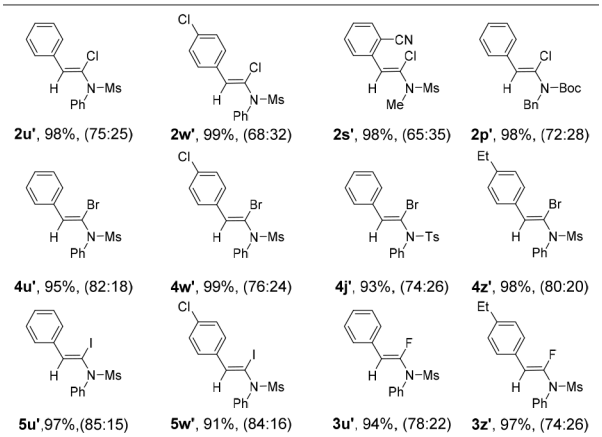
Intriguingly, these hydrohalogenation showed high functional-group compatibility once again, and miscellaneous R^1 substituents and electron-withdrawing groups had trivial impact on the yields, whereas the option of electron-withdrawing group had a significant influence on the stereoselectivity. If oxazolidinone ynamide **1a** was employed as substrate, **4a** and **5a** could be furnished with high stereoselectivity, but not stereospecificity. In sharp contrast, the stereospecific products (**3j−5z**) could be furnished with *N*-sulfonylynamides (**1j−z**) as substrates in which sulfonyl groups serve as the electron-withdrawing groups on nitrogen atom. Notably, hydrobromination showed higher efficiency than other hydrohalogenations, which could be finished in a few minutes.

In recent years, the photocatalytic (*E*)-to (*Z*)-isomerization of alkenes has received considerable attention.[18] As both (*E*)- and (*Z*)-configured haloenamides are useful synthetic intermediates, to further increase the usefulness of this hydrohalogenation, the conversion of (*E*)-configured α-haloenamides to (*Z*)-isomer was tried using $Ir(ppy)_3$ in the presence of DIPEA and blue light, and gratifyingly, the (*Z*)-haloenamides could be formed as the main products with moderate stereoselectivity.

Afterward, the generality of photocatalyzed *E*/*Z*-isomerization was investigated with a variety of (*E*)-α-fluoro, bromo and iodo-enamides employed, and the results are summarized in Scheme 4. All of the substrates were well tolerated, furnishing the (*Z*)-α-haloenamides as the major isomers. Remarkably, the halogen type of α-haloenamides had significant impact on the stereoselectivity, and when chlorine

Scheme 4. (*E*)- to (*Z*)-Isomerization of α-Halo Enamides[a−c]

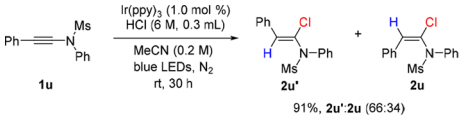




[a]Unless noted otherwise, all reactions were conducted using 1.0 equiv ynamides, 0.3 equiv DIPEA and 1.0 mol % $Ir(ppy)_3$ in MeCN (0.2 M) at 30 °C in the presence of blue light under a nitrogen atmosphere. For details, see the Supporting Information. [b]Isolated yield. [c]*Z*/*E* ratio was determined by ^{1}H NMR.

was replaced with bromine, or even iodine, the *Z*/*E* selectivity could be improved significantly (e.g., **2u′**, **4u′**, **5u′**, **2w′**, **4w′**, **5w′**). Whereas the R^1 and R^2 groups showed little influence on the reaction outcome. Notably, the thermodynamically less stable *Z*-type α-chloroenamide **2u′** could be afforded in one pot in 91% yield with acceptable stereoselectivity by cascade hydrochlorination and photocatalysis, using 0.2 mmol of **1u** and 0.3 mL of HCl (6 M) in 1.0 mL of MeCN (Scheme 5).

Scheme 5. One-Pot Synthesis of *Z*-Type α-Chloroenamide 2u′

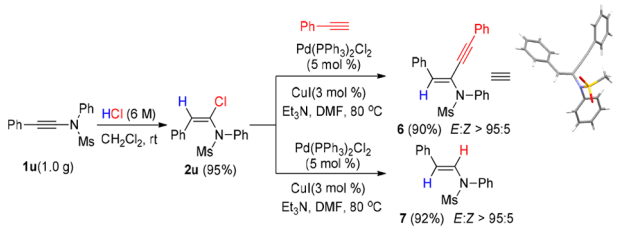


To examine the scalability of the developed protocols, the synthesis of **2u** on a gram scale was performed under the optimal conditions, and the product was furnished in 95% yield with excellent stereoselectivity. Subsequently, Sonogashira coupling was conducted using (*E*)-configured α-chloroenamide **2u**, through which the synthetically versatile alkynyl moiety could be readily installed into enamides, surprisingly yielding the *E*-coulping product **6** in 90% (Scheme 6).[19] To our delight, (*E*)-configured enamide **7** was produced in the absence of phenylacetylene in excellent yield and stereoselectivity (Scheme 6).

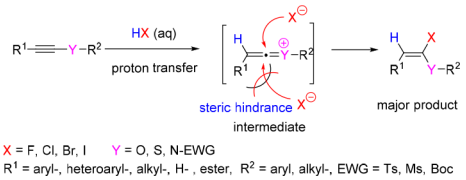
To account for the formation of (*E*)-configured α-haloenamides, a plausible mechanism is proposed, as shown in Scheme 7. Initially, the electron-rich alkynyl motif of ynamide is protonated by hydrogen halide due to the electron-donating ability of the lone pair on nitrogen atom, giving the keteniminium intermediate,[12,13] which then captures a halide anion to afford the *syn*-addition product, namely, (*E*)-

DOI: 10.1021/acs.orglett.8b01809
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 6. Gram-Scale Preparation and Further Synthetic Applications



Scheme 7. Proposed Mechanism



configured α-haloenamides. The high stereoselectivity might be attributed to the steric repulsion shown in the transition state, which blocks halogen anion from approaching the keteniminium intermediate from the R^1 side.

In summary, the synthetically versatile (*E*)-α-halo products were provided directly via hydrohalogenation of ynamides, thioalkynes, ynol ethers, etc., using aqueous hydrogen halides. This method features wide substrate scope, high functional group tolerance, mild conditions, high efficiency, rapid transformation, and high stereoselectivity. In addition, (*Z*)-configured α-haloenamides were readily produced via visible-light-promoted (*E*)- to (*Z*)-isomerization, and the synthetic elaboration of the resultant products further verified the usefulness of this protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01809.

Experimental procedures and NMR spectra and characterizations for all new compounds (PDF)

Accession Codes

CCDC 1844569 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tangyu@ouc.edu.cn.

ORCID

Yu Tang: 0000-0001-8224-4639

Author Contributions

‖W.C. and P.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21572154, 21772181 and 21776148) and NSFC−Shandong Joint Fund for Marine Science Research Centers (U1606403) for financial support. Financial support from the Natural Science Foundation of Shandong Province (ZR2016BM07) and the Fundamental Research Funds for the Central Universities (201612013) is also gratefully acknowledged.

■ REFERENCES

(1) (a) Courant, T.; Dagousset, G.; Masson, G. *Synthesis* **2015**, *47*, 1799−1826. (b) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973−986. (c) Yet, L. *Chem. Rev.* **2003**, *103*, 4283−4306. (d) Lenz, G. R. *Synthesis* **1978**, *1978*, 489−518. (e) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292−301. (f) Kuranaga, T.; Sesoko, Y.; Inoue, M. *Nat. Prod. Rep.* **2014**, *31*, 514−532. (g) Tschesche, R.; Last, H.; Fehlhaber, H. W. *Chem. Ber.* **1967**, *100*, 3937−3943. (h) Okamoto, K.; Sakagami, M.; Feng, F.; Togame, H.; Takemoto, H.; Ichikawa, S.; Matsuda, A. *Org. Lett.* **2011**, *13*, 5240−5243. (i) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599−4657.

(2) (a) Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14−20. (b) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075−1080. (c) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333−1336.

(3) (a) Meier, S.; Würthwein, E. U. *Chem. Ber.* **1990**, *123*, 2339−2343. (b) Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3714−3717. (c) Galli, C.; Rappoport, Z. *Acc. Chem. Res.* **2003**, *36*, 580−587. (d) Minière, S.; Cintrat, J. C. *Synthesis* **2001**, *2001*, 0705−0707.

(4) (a) Endo, N.; Iwasawa, T. *Tetrahedron* **2017**, *73*, 5833−5840. (b) Fujino, D.; Yorimitsu, H.; Osuka, A. *J. Am. Chem. Soc.* **2014**, *136*, 6255−6258. (c) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698−4745. (d) Lemay, A. B.; Vulic, K. S.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 3615−3618. (e) Lander, P. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 8126−8132. (f) Stille, V. J. K. *Angew. Chem.* **1986**, *98*, 504−519. (g) Du, Y. F.; Liu, R. H.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919−5922.

(5) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (b) Li, H. Q.; Lv, P. C.; Yan, T.; Zhu, H. L. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 471−480. (c) Volz, N.; Clayden, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12148−12155.

(6) (a) Chelucci, G. *Chem. Rev.* **2012**, *112*, 1344−1462. (b) Coutrot, P.; Laurenco, C.; Petrova, J.; Savignac, P. *Synthesis* **1976**, *1976*, 107−108. (c) Sacasa, P. R.; Zayas, J.; Wnuk, S. F. *Tetrahedron Lett.* **2009**, *50*, 5424−5427.

(7) (a) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897−1905. (b) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210−7211. (c) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817. (d) Kazankova, M. A.; Chirkov, E. A.; Kochetkov, A. N.; Efimova, I. V.; Beletskaya, I. P. *Tetrahedron Lett.* **1999**, *40*, 573−576. (e) Yu, W. S.; Jin, Z. D. *J. Am. Chem. Soc.* **2001**, *123*, 3369−3370. (f) Yu, W. S.; Jin, Z. D. *J. Am. Chem. Soc.* **2002**, *124*, 6576−6583.

(8) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L. C.; Zificsak, C. *Org. Lett.* **2003**, *5*, 1547−1550.

(9) (a) Sato, A. H.; Ohashi, K.; Iwasawa, T. *Tetrahedron Lett.* **2013**, *54*, 1309−1311. (b) Ohashi, K.; Mihara, S.; Sato, A. H.; Ide, M.; Iwasawa, T. *Tetrahedron Lett.* **2014**, *55*, 632−635. (c) Ide, M.; Ohashi, K.; Mihara, S.; Iwasawa, T. *Tetrahedron Lett.* **2014**, *55*, 2130−2133.

(10) Maity, P.; Klos, M. R.; Kazmaier, U. *Org. Lett.* **2013**, *15*, 6246−6249.

(11) Prabagar, B.; Nayak, S.; Mallick, R. K.; Prasad, R.; Sahoo, A. K. *Org. Chem. Front.* **2016**, *3*, 110−115.

(12) Kim, S. W.; Um, T.-W.; Shin, S. *Chem. Commun.* **2017**, *53*, 2733−2736.

DOI: 10.1021/acs.orglett.8b01809
Org. Lett. XXXX, XXX, XXX−XXX

(13) (a) Zeng, X. J.; Lu, Z. C.; Liu, S. W.; Hammond, G. B.; Xu, B. *J. Org. Chem.* **2017**, *82*, 13179−13187. (b) Zeng, X. J.; Li, J. L.; Ng, C. K.; Hammond, G. B.; Xu, B. *Angew. Chem., Int. Ed.* **2018**, *57*, 2924−2928.
(14) (a) Che, J. W.; Li, Y. L.; Zhang, F.; Zheng, R. W.; Bai, Y. H.; Zhu, G. G. *Tetrahedron Lett.* **2014**, *55*, 6240−6242. (b) He, G. K.; Qiu, S. N.; Huang, H.; Zhu, G. H.; Zhang, D. M.; Zhang, R.; Zhu, H. *Org. Lett.* **2016**, *18*, 1856−1859. (c) Yang, Z. Z.; Chen, X. Y.; Kong, W.; Xia, S. Y.; Zheng, R. W.; Luo, F.; Zhu, G. G. *Org. Biomol. Chem.* **2013**, *11*, 2175−2185.
(15) (a) Compain, G.; Jouvin, K.; Mingot, A. M.; Evano, G.; Marrot, J.; Thibaudeau, S. *Chem. Commun.* **2012**, *48*, 5196−5198. (b) Métayer, B.; Compain, G.; Jouvin, K.; MartinMingot, A.; Bachmann, C.; Marrot, J.; Evano, G.; Thibaudeau, S. J. *J. Org. Chem.* **2015**, *80*, 3397−3410.
(16) Yu, W. S.; Jin, Z. D. *J. Am. Chem. Soc.* **2000**, *122*, 9840−9841.
(17) (a) Chen, P.; Song, C. X.; Wang, W. S.; Yu, X. L.; Tang, Y. *RSC Adv.* **2016**, *6*, 80055−80058. (b) Wang, W. S.; Chen, P.; Tang, Y. *Tetrahedron* **2017**, *73*, 2731−2739.
(18) (a) Singh, K.; Staig, S. J.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 5275−5278. (b) Molloy, J. J.; Metternich, J. B.; Daniliuc, C. G.; Watson, A. J. B.; Gilmour, R. *Angew. Chem., Int. Ed.* **2018**, *57*, 3168−3172.
(19) (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46−49. (b) Gharpure, S. J.; Shelke, Y. G.; Kumar, D. P. *Org. Lett.* **2015**, *17*, 1926−1929.

DOI: 10.1021/acs.orglett.8b01809
Org. Lett. XXXX, XXX, XXX−XXX