Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

pubs.acs.org/OrgLett

DPPF-Catalyzed Atom-Transfer Radical Cyclization via Allylic Radical

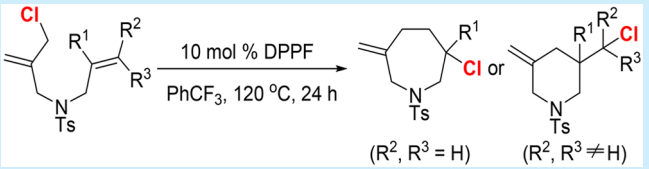
Longlei Hou,[†] Zhaozhao Zhou,[‡] Dong Wang,[‡] Yuwen Zhang,[‡] Xin Chen,[‡] Lijin Zhou,[‡] Yang Hong,[‡] Wei Liu,[‡] Yading Hou,[‡] and Xiaofeng Tong*[,†,‡]

[†]Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

[‡]School of Petrochemical Engineering, Changzhou University, 1 Gehu Road, Changzhou 213164, China

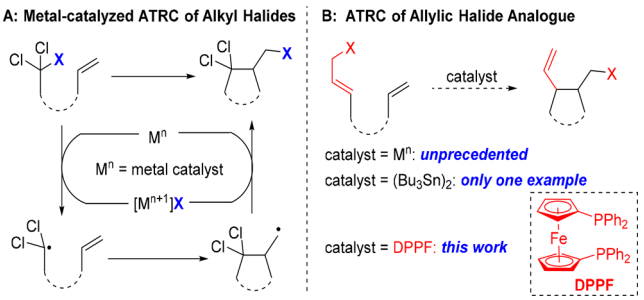
Supporting Information

ABSTRACT: A general iron-catalyzed strategy for the atom-transfer radical cyclization (ATRC) of allylic halide is reported. Critical to this strategy is the use of DPPF [1,1′-bis(diphenylphosphino)ferrocene] as catalyst, which allows for efficient generation of the allylic radical species via a single-electron transfer (SET) process. The feasibility of achieving ATRC reactions of propargyl chlorides is also demonstrated, which affords products with an exocyclic allene moiety.



Since the Kharasch reaction (addition of CX_4 across alkene via radical mechanism) was discovered in 1945,[1] its intramolecular version (Scheme 1A), known as atom-transfer radical cyclization (ATRC), has been extensively exploited and refined into a versatile and powerful tool for organic synthesis.[2] It has long been known that a wide range of metal complexes, such as copper,[3] iron,[4] ruthenium,[5] palladium,[6] and nickel,[7] can catalyze such ATRC reactions. The redox ability of these metal catalysts not only allows homolytic cleavage of the C−X bond to generate an alkyl radical via a single-electron transfer (SET) process but also is able to terminate the newly generated alkyl radical after cyclization to form a new C−X bond, thus furnishing the ATRC reaction (Scheme 1A). In order to ensure the success of an initial halogen atom abstraction, an activated C−X bond is generally required.[8] In light of these advances, one can anticipate that the ATRC reaction of allylic halide analogue would follow a similar pathway; the relatively lower bond dissociation energy of allylic halide would make the corresponding SET process more feasible to generate the allylic radical (Scheme 1B).[9] This extension is particularly appealing since the retained alkene residue has the potential for further chemical manipulations along with the group of alkyl halide.

Scheme 1. Overview of ATRC



However, the metal-catalyzed ATRC reaction of allylic halide bearing a pendant alkene has not been developed yet and is a long-standing problem in organic chemistry. Logically, the proposed ATRC reaction would also require the efficient generation of allylic radical species via a SET process. Unfortunately, the interaction of allylic halide and metal catalyst, not like the alkyl halide counterpart,[10] is dominated by the oxidative addition process, thus leading to the π-allyl metal intermediate rather than the desired allylic radical species.[11] To date, only one example of ATRC variant of allylic halide was reported by the group of Curran in 1989, in which hexabutylditin was used as the catalyst.[12] While this precedent provides the proof-of-concept of the ATRC reaction of allylic halide, the use of organostannane reagent is apparently complicated by high toxicity and tough purification problems. Moreover, some questions, such as the reactivity of allylic radical,[13] reaction selectivity, and so on, need to be further addressed. Therefore, the development of tin-free metal-catalyzed ATRC of allylic halide is highly desired from the synthetic, fundamental, and environmental viewpoints.

Apparently, the key challenge in developing the ATRC reaction of the allylic halide variant is to harness the interaction of allylic halide with metal catalyst from reliable oxidative addition to unfavorable SET process. To achieve this goal, we turned our attention to ferrocene derivatives. We envisioned that their fully coordinated sandwich structures could intrinsically exclude the π-allyl metal formation, which, in turn, would open up a new avenue for the SET process (Scheme 1B). In conjunction with our efforts with metal-catalyzed halogen-transfer cyclization,[14] we report herein the first tin-free ATRC reaction of allylic halide analogue by using ferrocene derivative as the catalyst, which proceeds with several different categories

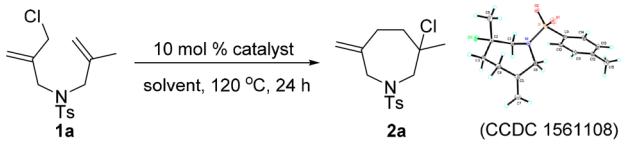
Received: October 9, 2017

DOI: 10.1021/acs.orglett.7b03135
Org. Lett. XXXX, XXX, XXX−XXX

of allylic and propargyl halides and is compatible with chloroalkene as the acceptor of allylic radical. This reaction takes advantage of the incorporation of either the alkene or allene group into products.

The ATRC reaction of alkyl halide can be readily achieved by using a wide range of metal complexes. Among these catalysts, $FeCl_2[P(OEt)_3]_2$, $Pd(PPh_3)_4$, $RuCl_2(PPh_3)_2$, and CuCl/bpy have been proven to be highly efficient. Thus, we began our investigation by examining the catalytic activity of these common catalysts toward the ATRC reaction of allylic halide **1a** in refluxing toluene (Table 1, entries 1–4). Not surprisingly,

Table 1. Catalyst Screening and Condition Optimization[a]



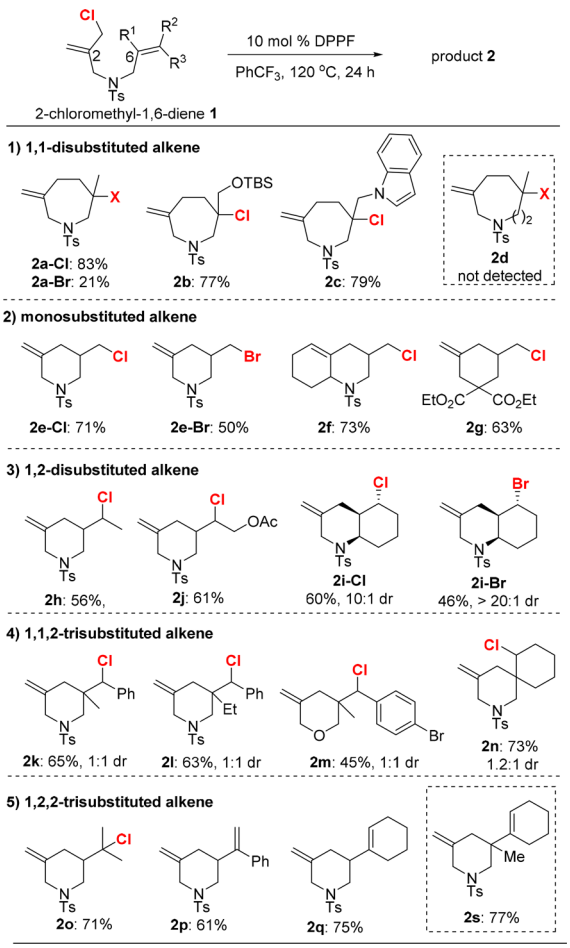
entry	catalyst	solvent	yield (%)[b]
1	$FeCl_2[P(OEt)_3]_2$	toluene	0
2	$Pd(PPh_3)_4$	toluene	0
3	$RuCl_2(PPh_3)_2$	toluene	0
4	CuCl/Bipy	toluene	0
5	R = H	toluene	0
6	R = Me	toluene	0
7	R = Ph	toluene	0
8	R = $P(Ph)_2$	toluene	62
9	R = $P(4\text{-}MeOC_6H_4)_2$	toluene	60
10	R = $P(4\text{-}FC_6H_4)_2$	toluene	59
11	R = $P(tBu)_2$	toluene	60
12	DPPE or DPPB or XantPhos	toluene	0
13	(DPPF)	xylene	76
14		$PhCF_3$	83
15		DMF	77
16		dioxane	<5

[a]Reactions conducted on 0.2 mmol scale. [b]Isolated yield.

no ATRC product was observed, and compound **1a** was recovered in >90% yield in some cases. These results are consistent with Curran's observation.[12] Then, we turned our attention to ferrocene derivatives. However, use of the simplest ferrocene as the catalyst did not provide the desired ATRC product (Table 1, entry 5). Neither dimethylferrocene nor diphenylferrocene also showed any catalytic activity (Table 1, entries 6 and 7). To our delight, DPPF exhibited good activity, enabling the isolation of product **2a** in 62% yield (Table 1, entry 8). Several bis(diphosphino)ferrocenes were then examined, which disclosed that both of the electronic and steric characters of substitutions on the phosphine exerted ignorable influence on the reaction performance (Table 1, entries 9–11). As evidence for the crucial role of ferrocene moiety, control reactions in the presence of various diphosphines did not afford any detectable products (Table 1, entry 12). We then briefly examined the reaction solvent and found that $PhCF_3$ was optimal, resulting in 83% isolated yield of **2a** (Table 1, entries 13–16).

The optimized conditions were then tested with a number of 2-chloromethyl-1,6-dienes **1** bearing diverse alkene moieties (Scheme 2). For the substrates **1a–d** bearing a 6,6′-

Scheme 2. Reaction Scope of 2-Chloromethyl-1,6-diene 1



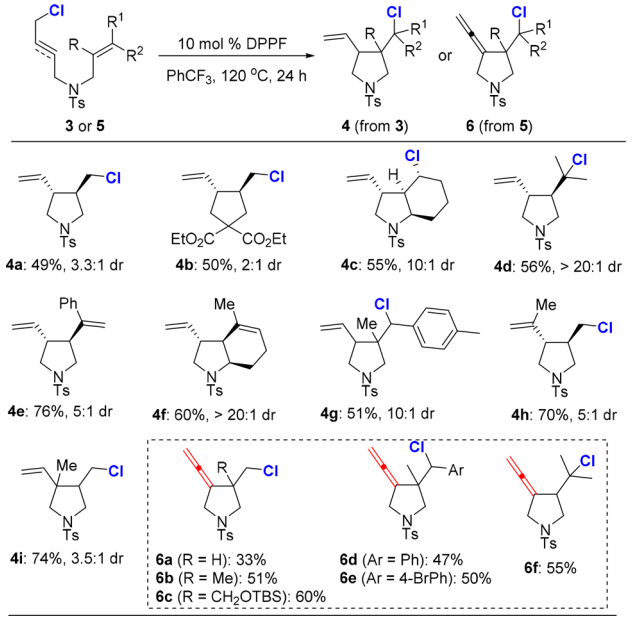
disubstituted alkene, the ATRC occurred in a 7-endo fashion to give the corresponding 7-membered products **2a–d**, which can be explained by the involvement of thermodynamically stable tertiary radical. Likely due to its instability at high temperature, allylic bromine **1a-Br** gave product **2a-Br** only in 21% yield. It should be mentioned that no 8-membered ring product **2d** was detected for the reaction of 1,7-diene **1d**, and the starting material was recovered in 95% yield. This result reflects one of the limitations of this reaction. The conversion of relatively stable allylic radical[15] into less stable alkyl radical would require rapid exothermic cyclization. As expected, the reactions of substrates **1e–g** bearing a monosubstituted alkene took place in a 6-exo fashion. In addition to the N-linkage, the C-linkage was proven to be competent, affording product **2g** in 63% yield. Although the reactions of substrates **1h** and **1j** bearing a 6,7-disubstituted alkene were found to be somewhat complex, only one diastereoisomer could be obtained via the preparative layer chromatography. Moreover, **1i-Cl** with an endocyclic alkene could be readily converted into fused bicycle **2i-Cl** in 60% yield with 10:1 diasteroselectivity. The reaction of bromine analogue **1i-Br** showed much better stereoselectivity to give product **2i-Br** as a single isomer, which might arise from the bulkiness of the bromine atom. For the cases of substrates **1k–m** with a 6,6′,7-trisubstituted alkene, products **2k–m** with an all-carbon quaternary center could be obtained in moderate yields with 1:1 dr. Interestingly, this method was found to be suitable to construct spirocycle. Indeed, spirocyclic product **2n** was isolated in 73% yield with 2:1 dr. Moreover, compound **1o**

DOI: 10.1021/acs.orglett.7b03135
Org. Lett. XXXX, XXX, XXX–XXX

bearing a 6,7,7′-trisubstituted alkene was also a suitable substrate, undergoing 6-exo cyclization to afford product **2o** in 71% yield. On the other hand, substrates **1p** and **1q** underwent Heck-type reaction, delivering diene products **2p** and **2q** in good yields. While a great deal of HCl was concomitantly produced, these two reactions seemed unaffected. Finally, the reaction was found to be applicable to substrate **1s** with a tetrasubstituted alkene, and the diene product **2s** was isolated in 77% yield.

In addition to allylic halides **1**, the 1-chloromethyl ones **3**, such as N-tethered substrate **3a** and C-tethered substrate **3b**, could also readily undergo chlorine-transfer cyclization, affording 5-membered cycles **4a** and **4b** with a vinyl group (Scheme 3). These results provided strong evidence to support

Scheme 3. Reaction Scope of 1,6-Diene 3 and 1,6-Enyne 5

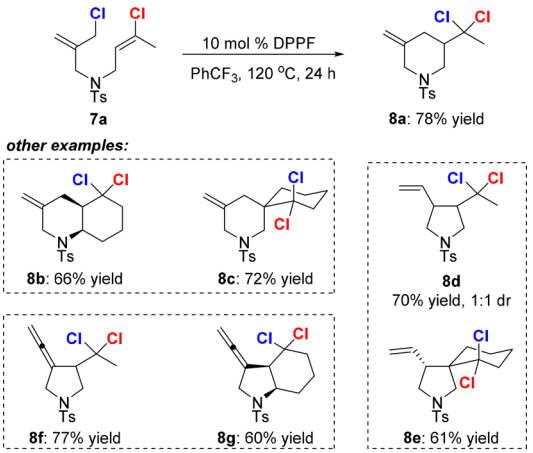


the reaction pathway via allylic isomerization.[16] A fused bicycle **4c** with four contiguous stereogenic centers was obtained with high diastereoselectivity (10:1). It should be mentioned that 2-methyl and 3-methyl 1,6-dienes **3i** and **3j** were also suitable candidates, delivering products **4i** and **4j** in good yields albeit with low diastereoselectivity. In the latter case, an all-carbon quaternary center was formed. Notably, this DPPF-catalyzed cyclization could be successfully extended to propargyl chloride variants **5a**–**f**, affording products **6a**–**f** with an exocyclic allene group in moderate yields.[17]

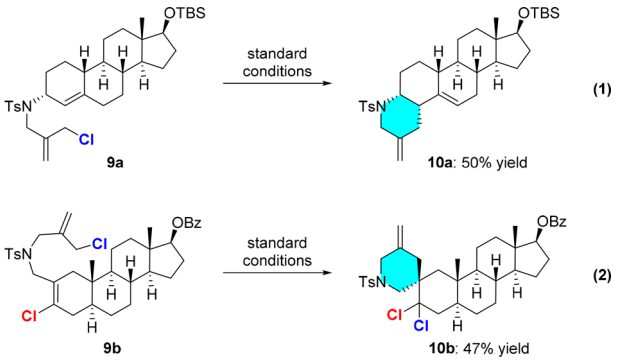
To further extend the substrate scope of this method, substrate **7a** with chloroalkene as the radical acceptor[18] was examined. Gratefully, the reaction of **7a** was still workable, affording *gem*-dichloride product **8a** in 78% yield (Scheme 4). This result is remarkable due to the fact that poly-haloalkane commonly cannot survive under the classical metal-catalyzed ATRC systems. The importance of this transformation was readily seen from the construction of polycyclic molecules. For instance, fused bicycles **8b** and **8g** could be produced with excellent stereoselectivity, while spirocycles **8c** and **8e** were obtained in good yields.

Finally, we explored the feasibility of this method to the late-stage modification of complex compounds. As shown in eqs 1 and 2, the standard conditions was compatible to structurally

Scheme 4. Reaction Scope of Chloroalkene 7



complex compounds **9a** and **9b**, giving products **10a** and **10b** in synthetically useful yields, respectively.

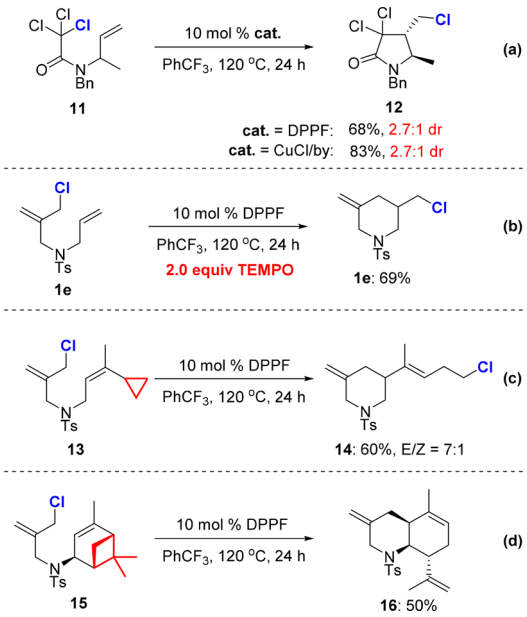


Mechanistic details, especially the essential role of diphenylphosphanyl substitution, are the focus of our ongoing investigations, but several observations are worth noting. As might be expected, this DPPF-catalyzed halogen-atom-transfer cyclization likely proceeds via a radical process. The potential of DPPF toward a SET process is readily evident from the reactions of trichloroacetamide **11**. The copper-catalyzed isomerization of compound **11** has been convincingly established to proceed through an ATRC mechanism.[19] In comparison, compound **11** was exposed to the well-known CuCl/bpy system under otherwise identical conditions, which smoothly proceeded in 83% yield to give predominately (2.7:1) *trans*-lactam **12** (Scheme 5a). It was of considerable interest that the present DPPF catalysis also produced *trans*-lactam **12** with 2.7:1 diastereoselectivity albeit in somewhat lower yield (Scheme. 5a). Thus, the virtually identical stereochemical outcome essentially reflected the capability of DPPF as an ATRC catalyst. Furthermore, the DPPF-catalyzed reaction of **1e** was not inhibited by radical scavengers such as TEMPO and hydroquinone (Scheme 5b). The results are in line with the copper-catalyzed cyclization of allyl trichloroacetates,[20] indicating that the ATRC mechanism would be operative for this reaction.

To further elucidate the radical-involved reaction pathway, two radical probe experiments were designed on the basis of compounds **13** and **15**, wherein the cyclopropyl and cyclobutyl radical clocks were installed at the alkenyl ends, respectively.[21] Subjecting **13** to the standard conditions resulted in cyclopropane ring-opening product **14** in 60% yield (Scheme 5c),

DOI: 10.1021/acs.orglett.7b03135
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Mechanistic Investigations



indicating the involvement of cyclopropylmethyl radical, which is rapidly rearranged to the homoallyl radical before formation of a C−Cl bond. The reaction of **15** also led to rearrangement product **16** in 50% yield (Scheme 5d). These two experiments clearly demonstrate that this reaction proceeds via a radical process.

In summary, we have developed an efficient tin-free ATRC reaction of allylic halide bearing a pendant alkene using DPPF as catalyst. The key feature is the generation of an allylic radical via the reaction of allylic halide and DPPF. The developed method shows a very broad substrate scope on both the allylic halide donors and the olefin acceptors. This work illustrates an advancement of the metal-catalyzed ATRC reaction and would be highly valuable in the construction of structurally complex molecules from readily available starting materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03135.

General procedures, data, and NMR spectra of products, and X-ray data of compound **2a** (PDF)

Accession Codes

CCDC 1561108 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: txf@cczu.edu.cn.

ORCID

Xiaofeng Tong: 0000-0002-6789-1691

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the NSFC (Nos. 21472042 and 21772016), Jiangsu Province Funds for Distinguished Young Scientists (BK20160005), and the Qing-Lan Project.

■ REFERENCES

(1) (a) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *Science* **1945**, *102*, 128. (b) Kharasch, M. S.; Urry, W. H.; Jensen, E. V. *J. Am. Chem. Soc.* **1945**, *67*, 1626.

(2) (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (b) Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 5533. (c) Curran, D. P. *Synthesis* **1988**, *1988*, 489. (d) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1. (e) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (f) Rowlands, G. *Tetrahedron* **2010**, *66*, 1593.

(3) Nagashima, H.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2395.

(4) Lee, G. M.; Parvez, M.; Weinreb, S. M. *Tetrahedron* **1988**, *44*, 4671.

(5) (a) Severin, K. *Curr. Org. Chem.* **2006**, *10*, 217. (b) Quayle, P.; Fengas, D.; Richards, S. *Synlett* **2003**, *12*, 1797.

(6) Monks, B. M.; Cook, S. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 14214.

(7) Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 5629.

(8) Shen, Y.; Cornella, J.; Juliá-Hernández, F.; Martin, R. *ACS Catal.* **2017**, *7*, 409.

(9) (a) Stork, G.; Reynolds, M. E. *J. Am. Chem. Soc.* **1988**, *110*, 6911. (b) Kaliappan, K.; Rao, G. S. R. S. *Chem. Commun.* **1996**, 2331.

(10) (a) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (c) Glasspoole, B. W.; Crudden, C. M. *Nat. Chem.* **2011**, *3*, 912.

(11) (a) Rideau, E.; You, H.; Sidera, M.; Claridge, T. D. W.; Fletcher, S. P. *J. Am. Chem. Soc.* **2017**, *139*, 5614. (b) Holzwarth, M.; Dieskau, A.; Tabassam, M.; Plietker, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 7251. (c) Bartholomew, E. R.; Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 11244. (d) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(12) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 933.

(13) (a) Pratsch, G.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 11388. (b) Kippo, T.; Hamaoka, K.; Ryu, I. *J. Am. Chem. Soc.* **2013**, *135*, 632.

(14) (a) Liu, Q.; Chen, C.; Tong, X. *Tetrahedron Lett.* **2015**, *56*, 4483. (b) Liu, H.; Li, C.; Qiu, D.; Tong, X. *J. Am. Chem. Soc.* **2011**, *133*, 6187. (c) Chen, C.; Hou, L.; Cheng, M.; Su, J.; Tong, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 3092.

(15) Korth, H.-G.; Trill, H.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483.

(16) Walling, C.; Thaler, W. *J. Am. Chem. Soc.* **1961**, *83*, 3877.

(17) (a) Wartenberg, F.-H.; Junga, H.; Blechert, S. *Tetrahedron Lett.* **1993**, *34*, 5251. (b) Denieul, M.-P.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5495. (c) Alameda-Angulo, C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2006**, *47*, 913.

(18) Song, L.; Fang, X.; Wang, Z.; Liu, K.; Li, C. *J. Org. Chem.* **2016**, *81*, 2442.

(19) Nagashima, H.; Ozaki, N.; Seki, K.; Ishii, M.; Itoh, K. *J. Org. Chem.* **1989**, *54*, 4497.

(20) Nagashima, H.; Seki, K.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985.

(21) (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317. (b) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

DOI: 10.1021/acs.orglett.7b03135
Org. Lett. XXXX, XXX, XXX−XXX