Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 5282–5285

pubs.acs.org/OrgLett

Synthesis and Reactivity of *N*-Allenyl Cyanamides

James N. Ayres,[†] Matthew T. J. Williams,[†] Graham J. Tizzard,[‡] Simon J. Coles,[‡] Kenneth B. Ling,[§] and Louis C. Morrill*[,†]

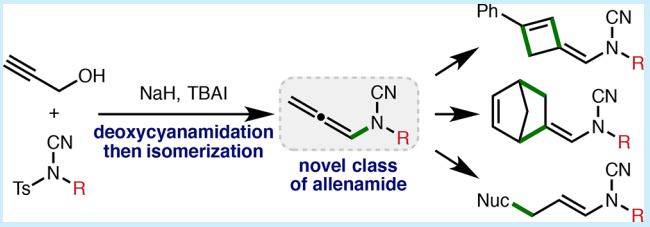
[†]School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, U.K.

[‡]UK National Crystallographic Service, Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, U.K.

[§]Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, U.K.

Supporting Information

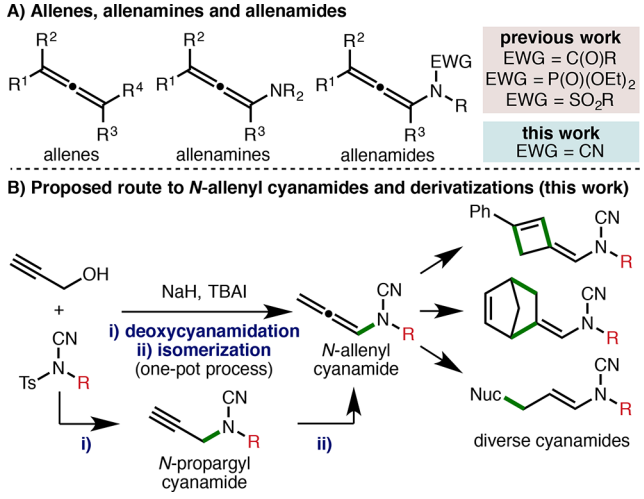
ABSTRACT: *N*-Allenyl cyanamides have been accessed via a one-pot deoxycyanamidation−isomerization approach using propargyl alcohol and *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide. The utility of this novel class of allenamide was explored through derivatization, with hydroarylation, hydroamination, and cycloaddition protocols employed to access an array of cyanamide products that would be challenging to access using existing methods.



Allenamides, also referred to as *N*-allenyl amides,[1] are versatile synthetic building blocks in organic chemistry.[2] In comparison to allenamines,[3] which require careful preparation and handling due to their susceptibility toward hydrolysis and polymerization, allenamides exhibit enhanced stability due to delocalization of the nitrogen lone pair of electrons into the electron-withdrawing carbonyl. In addition to *N*-acyl allenamides,[4] alternative classes have been introduced through variation of the electron-withdrawing *N*-substituents, including *N*-phosphoryl,[5] *N*-sulfonyl,[6] and *N*-heteroaryl[7] allenamides (Scheme 1A).

Taking inspiration from these reports, and as a part of our ongoing investigations into the development of new synthetic routes toward cyanamides,[8] we envisaged accessing *N*-allenyl cyanamides, where the cyano group serves as the stabilizing electron-withdrawing *N*-substituent. A variety of biologically active compounds, including agrochemicals and pharmaceuticals, contain the cyanamide (N−CN) functional group,[9] which is most commonly introduced via electrophilic *N*-cyanation of amines using highly toxic cyanogen bromide.[10] Employing our recently developed deoxycyanamidation method,[8b] we anticipated that the reaction of propargyl alcohol with *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS)[11] would afford an *N*-propargyl cyanamide, which could undergo a base-catalyzed isomerization in situ to access an *N*-allenyl cyanamide (Scheme 1B). Herein, we report the successful implementation of this strategy and describe a one-pot deoxycyanamidation−isomerization protocol for the synthesis of *N*-allenyl cyanamides. Furthermore, the derivatization of the allenyl functional group within this novel class of allenamide has been explored through cycloaddition, hydroarylation, and hydroamination protocols, accessing cyanamide products that would be difficult to access using traditional approaches.

Scheme 1. Proposed Synthesis and Derivatization of *N*-Allenyl Cyanamides

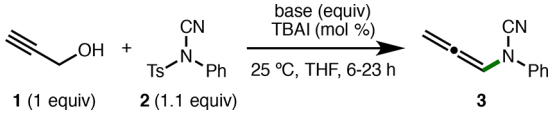


To test our hypothesis, we selected propargyl alcohol **1** and NCTS **2** (1.1 equiv) in THF as a model system (Table 1).[12] Tetrabutylammonium iodide (TBAI) (10 mol %) was employed as an additive from the start of our investigation due to the previous observation that it improved the efficiency of deoxycyanamidation via both cation exchange and in situ conversion of the alkyl tosylate to a more reactive alkyl iodide.[8b] Initially, the base was added to a mixture of propargyl alcohol **1** and TBAI in THF to preform the sodium alkoxide prior to addition of NCTS **2**. We were encouraged to observe 76% conversion to *N*-allenyl cyanamide **3** using sodium hydride (2 equiv) as a base at rt after 6 h (Table 1, entry 1).

Received: July 17, 2018
Published: August 14, 2018

DOI: 10.1021/acs.orglett.8b02225
Org. Lett. 2018, 20, 5282–5285

Table 1. Optimization of *N*-Allenyl Cyanamide Synthesis[a]



1 (1 equiv) 2 (1.1 equiv) 3

entry	base (equiv)	TBAI (mol %)	yield (6 h, 23 h)[b] (%)
1	NaH (2)	10	76, 56
2	DBN (2)	10	0, 0
3	DBU (2)	10	0, 5
4	LHMDS (2)	10	0, 0
5	KO*t*-Bu (2)	10	18, 19
6	NaO*t*-Am (2)	10	61, 58
7	NaH (2)	0	36, 40
8[c]	**NaH (2)**	**10**	**73, 76 (57)**
9[c]	NaH (1.5)	10	52, 56

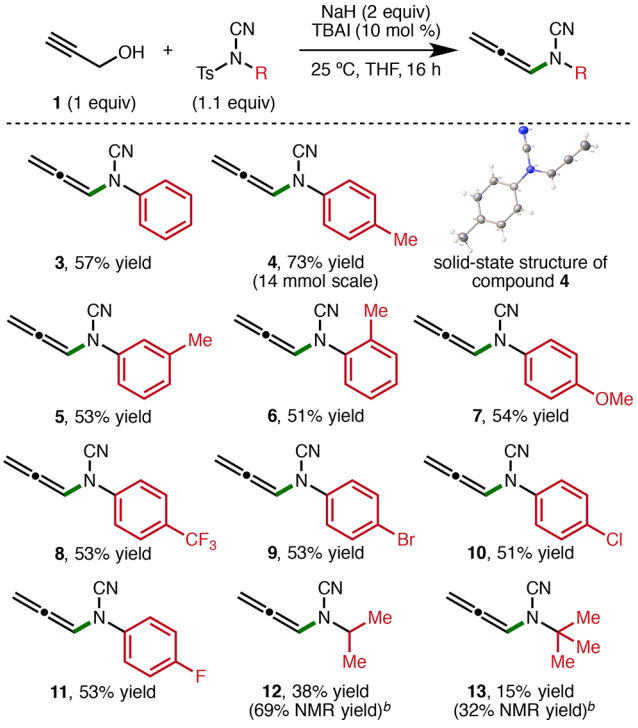
[a]Reactions performed using 1 mmol of alcohol **1**. [**1**] = 0.2 M. Bases (2 equiv) added to **1** in THF prior to the addition of **2**. [b]Determined by ^{1}H NMR analysis of crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parenteses. [c]NaH (2 equiv) added last to the reaction mixture.

However, the NMR yield decreased to 56% after 23 h, indicating that the *N*-allenyl cyanamide was decomposing slowly under the reaction conditions. A selection of alternative bases were examined, but lower conversion to **3** was observed in each case (Table 1, entries 2−6). As anticipated, removing TBAI also resulted in diminished NMR yield (Table 1, entry 7). It was found that simply adding NaH last to the reaction mixture suppressed decomposition of the *N*-allenyl cyanamide product after 23 h (Table 1, entry 8), allowing **3** to be obtained in a synthetically useful 57% isolated yield.[13] Reducing the quantity of NaH to 1.5 equiv resulted in only 56% conversion to **3** after 23 h (Table 1, entry 9), confirming the requirement for 2 equiv of base to be used.

For the purpose of assessing the scope of this protocol, the reaction time was set to 16 h to ensure full conversion across a range of substrates (Scheme 2). Under the optimized reaction conditions (Table 1, entry 8) with propargyl alcohol **1**, it was found that a range of *N*-aryl substituents within the sulfonamide could be incorporated, giving aryl/allenyl cyanamides in good yields (products **3**−**11**, 51−73% yields). Aryl substitution at the 4-, 3-, and 2-position was tolerated in addition to electron-donating (4-OMe) and electron-withdrawing (4-CF_3) substituents. Unambiguous structural confirmation was obtained via X-ray crystal structure analysis of *N*-allenyl cyanamide **4**. The reaction performs well upon scale-up, with the formation of **4** successfully carried out on a 14 mmol scale in 73% yield to provide 1.69 g of product. The use of *N*-4-chlorophenyl- and *N*-4-bromophenyl-substituted sulfonamides was successful, incorporating an additional functional handle into the products for subsequent elaboration via cross-coupling methods.[14] *N*-Isopropyl and *N*-butyl sulfonamides were used to afford alkyl/allenyl cyanamides **12** and **13** in 38% and 15% isolated yields, respectively. The low isolated yields observed for **12** and **13** were attributed to volatility (higher NMR yields) and poor product stability, both under the reaction conditions and when subjected to silica gel chromatographic purification.

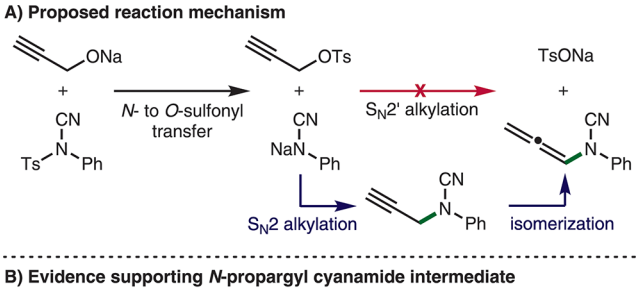
With respect to the mechanism of this process, in accordance with our previous studies,[8b] we proposed an initial *N*- to *O*-sulfonyl transfer between NCTS and sodium alkoxide (generated in situ from propargyl alcohol and NaH), to give propargyl tosylate (Scheme 3A). Subsequent S_N2-type alkylation of the cyanamide anion with propargyl tosylate affords *N*-propargyl cyanamide, which undergoes base-

Scheme 2. Substrate Scope[a]



[a]Reactions performed using 1 mmol of alcohol starting material. All yields are isolated yields after chromatographic purification. [b]Determined by ^{1}H NMR analysis of crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

Scheme 3. Mechanistic Studies[a]



NaH (equiv)	propargyl tosylate[a] (%)	*N*-propargyl cyanamide[a] (%)	*N*-allenyl cyanamide[a] (%)
0.5	51	49	0
1	27	30	31
1.5	25	19	46
2	**<5**	**<5**	**90**

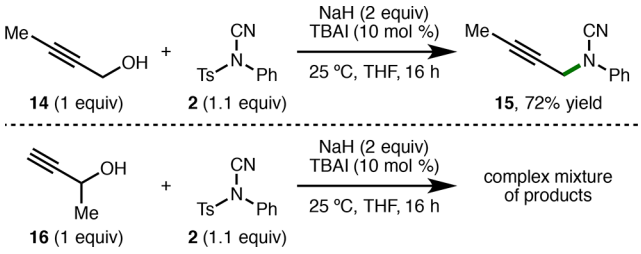
[a]Determined by ^{1}H NMR analysis of crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

DOI: 10.1021/acs.orglett.8b02225
Org. Lett. 2018, 20, 5282−5285

catalyzed isomerization[4] to give *N*-allenyl cyanamide. The validity of *N*-propargyl cyanamide as an intermediate was probed via treatment with NaH (2 equiv) at 25 °C in THF, giving >95% conversion to the expected *N*-allenyl cyanamide after 23 h (Scheme 3B). An S_N2-type alkylation was favored over an alternative S_N2'-type alkylation due to studies involving the reaction of propargyl tosylate with phenyl cyanamide (Scheme 3C). Under the standard reaction conditions, employing NaH (0.5 equiv) as base, 49% conversion to *N*-propargyl cyanamide was observed, with no *N*-allenyl cyanamide formed. Upon increasing the quantity of NaH employed to 1, 1.5, and 2 equiv, increasing conversion to *N*-allenyl cyanamide was observed, providing evidence for an initial S_N2-type alkylation followed by isomerization. In light of the three-step reaction process (*N*- to *O*-sulfonyl transfer, cyanamide alkylation, isomerization), we believe that this one-pot access to *N*-allenyl cyanamide is synthetically attractive.

With an understanding of the reaction mechanism in place and having successfully demonstrated the formation of *N*-allenyl cyanamide from propargyl alcohol, we next investigated the use of substituted propargyl alcohols (Scheme 4). Using

Scheme 4. Use of Substituted Propargyl Alcohols

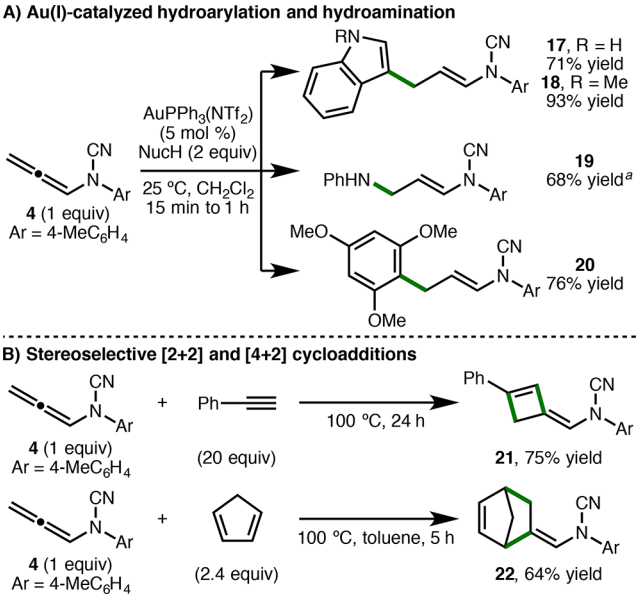


the optimized reaction conditions (Table 1, entry 8), reaction of 2-butyn-1-ol **14** with NCTS **2** gave exclusively *N*-propargyl cyanamide **15** in 72% isolated yield. Treatment of purified **15** with NaH (2 equiv) at 25 °C in THF gave no observable conversion to the corresponding *N*-allenyl cyanamide after 23 h, indicating that the isomerization is not favored in **15**. Alternatively, employing 3-butyn-2-ol **16** as the alcohol resulted in the formation of a complex mixture of inseparable products. From analysis of the reaction mixture before and after silica gel chromatographic purification, it appeared that multiple allene- and alkyne-containing products are formed, which may be attributed toward competing *β*-elimination, S_N2 and S_N2'-type cyanamide *N*-alkylation processes involving a secondary alkyl tosylate intermediate (cf. Scheme 3).

Considering that *N*-allenyl cyanamides are a novel structural motif, we next explored their derivatization with a view toward generating a variety of cyanamides that would be challenging to access using existing methods. To this end, employing the method developed by Kimber and co-workers,[15] a variety of *N*-alkenyl cyanamides[16] **17**–**20** were accessed from *N*-allenyl cyanamide **4** in high yields (68–93%) via intermolecular Au(I)-catalyzed hydroarylation and hydroamination protocols (Scheme 5A). Furthermore, **4** participates in stereoselective [2 + 2] and [4 + 2] cycloadditions with phenylacetylene[17] and cyclopentadiene,[18] giving cycloadducts **21** and **22** in 75% and 64% yield, respectively (Scheme 5B). In both cases, the structure of the major stereoisomer formed was determined using NOESY experiments.[12]

In conclusion, we have introduced a new class of allenamide, namely *N*-allenyl cyanamides. The operationally simple one-

Scheme 5. Derivatization of *N*-Allenyl Cyanamides[a]



[a]Aniline (1.05 equiv) employed as nucleophile.

pot deoxycyanamidation–isomerization protocol developed proceeds via an initial *N*- to *O*-sulfonyl transfer, followed by cyanamide *N*-alkylation and isomerization, giving a selection of *N*-allenyl cyanamides in good yields. The utility of these products was explored through derivatization, with hydroarylation, hydroamination, and cycloaddition protocols employed to access an array of cyanamide products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02225.

Optimization data, experimental procedures, characterization of new compounds, and spectral data (PDF)

Accession Codes

CCDC 1844708 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: morrilllc@cardiff.ac.uk.

ORCID

Simon J. Coles: 0000-0001-8414-9272

Louis C. Morrill: 0000-0002-6453-7531

Notes

The authors declare no competing financial interest.

Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/10.17035/d.2018.0055747356 (accessed Aug 14, 2018).

DOI: 10.1021/acs.orglett.8b02225
Org. Lett. 2018, 20, 5282–5285

■ ACKNOWLEDGMENTS

We gratefully acknowledge the School of Chemistry, Cardiff University, for generous support, the EPSRC Doctoral Training Grant for a part-funded Ph.D. studentship (J.N.A., EP/M50631X/1) and the EPSRC UK National Mass Spectrometry Facility at Swansea University.

■ REFERENCES

(1) For selected reviews on allenes, see: (a) Schuster, H. E.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley and Sons: New York, 1984. (b) Sainsbury, M. *Rodd's Chemistry of Carbon Compounds*; Elsevier: Oxford, 1991; pp 115−155. (c) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. (d) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH Verlag: Weinheim, 2004; Vols. *1 and 2*. (e) Ma, S. *Chem. Rev.* **2005**, *105*, 2829−2872.

(2) For selected reviews on allenamides, see: (a) Wei, L.-I.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773−782. (b) Standen, P. E.; Kimber, M. C. *Curr. Opin. Drug Discovery Devel.* **2010**, *13*, 645−657. (c) Lu, T.; Lu, Z.; Ma, Z.-X.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2013**, *113*, 4862−4904. (d) Manoni, E.; Bandini, M. *Eur. J. Org. Chem.* **2016**, *2016*, 3135−3142.

(3) Saalfrank, R. W.; Lurz, C. J. In *Methoden Der Organischen Chemie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; pp 3093−3102.

(4) Dickinson, W. B.; Lang, P. C. *Tetrahedron Lett.* **1967**, *8*, 3035−3040.

(5) (a) Corbel, B.; Paugam, J.-P.; Dreux, M.; Savignac, P. *Tetrahedron Lett.* **1976**, *17*, 835−838. (b) Danowitz, A. M.; Taylor, C. E.; Shrikian, T. M.; Mapp, A. K. *Org. Lett.* **2010**, *12*, 2574−2577. (c) Yin, G.; Zhu, Y.; Zhang, L.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 940−943.

(6) (a) van Boxtel, L. J.; Körbe, S.; Noltemeyer, M.; de Meijere, A. *Eur. J. Org. Chem.* **2001**, *2001*, 2283−2292. (b) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499−1502. (c) Persson, A. K. Å.; Johnston, E. V.; Bäckvall, J.-E. *Org. Lett.* **2009**, *11*, 3814−3817. (d) Zhu, Y.; Yin, G.; Hong, D.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 1024−1027.

(7) (a) Balasubramanian, K. K.; Venugopalan, B. *Tetrahedron Lett.* **1974**, *15*, 2643−2644. (b) Galons, H.; Bergerat, I.; Combet-Farnoux, C.; Miocque, M.; Decodts, G.; Bram, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1730−1731.

(8) (a) Ayres, J. N.; Ling, K. B.; Morrill, L. C. *Org. Lett.* **2016**, *18*, 5528−5531. (b) Ayres, J. N.; Ashford, M. W.; Stöckl, Y.; Prudhomme, V.; Ling, K. B.; Platts, J. A.; Morrill, L. C. *Org. Lett.* **2017**, *19*, 3835−3838.

(9) For selected reviews that detail the biological relevance, synthesis, and reactivity of cyanamides, see: (a) Larraufie, M.-H.; Maestri, G.; Malacria, M.; Ollivier, C.; Fensterbank, L.; Lacôte, E. *Synthesis* **2012**, *44*, 1279−1292. (b) Prabhath, M. R. R.; Williams, L.; Bhat, S. V.; Sharma, P. *Molecules* **2017**, *22*, 615−642.

(10) For pioneering studies, see: (a) Wallach, O. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 1872−1875. (b) Braun, J. v. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 1438−1452. (c) Scholl, R.; Nörr, W. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 1555 For selected recent applications in synthesis, see:. (d) Goldberg, K.; Clarke, D. S.; Scott, J. S. *Tetrahedron Lett.* **2014**, *55*, 4433−4436. (e) Hashimoto, T.; Ishii, S.; Yano, R.; Miura, H.; Sakata, K.; Takeuchi, R. *Adv. Synth. Catal.* **2015**, *357*, 3901−3916.

(11) For pioneering early examples, see: (a) Kurzer, F. *J. Chem. Soc.* **1949**, 1034−1038. (b) Kurzer, F. *J. Chem. Soc.* **1949**, 3029−3033. (c) Anbarasan, P.; Neumann, H.; Beller, M. *Chem. - Eur. J.* **2011**, *17*, 4217−4222. (d) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 519−522. (e) Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 5608−5611 For selected recent reviews, see:. (f) Ping, Y.; Ding, Q.; Peng, Y. *ACS Catal.* **2016**, *6*, 5989−6005. (g) Cui, J.; Song, J.; Liu, Q.; Liu, H.; Dong, Y. *Chem. - Asian J.* **2018**, *13*, 482−495.

(12) See the Supporting Information for full experimental details.

(13) A similar NMR yield (75% after 23 h) was observed using NaO-*t*-Am (2 equiv) as base in 1,2-dimethoxyethane as solvent. However, this procedure exhibited poor reproducibility when compared to the optimized reaction conditions (Table 1, entry 8).

(14) (a) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085. (b) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564−12649. (c) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. *ACS Catal.* **2016**, *6*, 1540−1552.

(15) (a) Kimber, M. C. *Org. Lett.* **2010**, *12*, 1128−1131. (b) Hill, A. W.; Elsegood, M. R. J.; Kimber, M. C. *J. Org. Chem.* **2010**, *75*, 5406−5409.

(16) (a) Luo, K.; Meng, L.; Zhang, Y.; Zhang, X.; Wang, L. *Adv. Synth. Catal.* **2013**, *355*, 765−780. (b) Nitelet, A.; Wouters, J.; Dewez, D. F.; Evano, G. *Org. Lett.* **2017**, *19*, 6276−6279.

(17) (a) Kimura, M.; Horino, Y.; Wakamiya, Y.; Okajima, T.; Tamaru, Y. *J. Am. Chem. Soc.* **1997**, *119*, 10869−10870. (b) Horino, Y.; Kimura, M.; Tanaka, S.; Okajima, T.; Tamaru, Y. *Chem. - Eur. J.* **2003**, *9*, 2419−2438.

(18) (a) Banert, K.; Groth, S.; Hüchstädt, H.; Lehmann, J.; Schlott, J.; Vrobel, K. *Synthesis* **2002**, 1423−1433. (b) Bacci, J. P.; Greenman, K. L.; Van Vranken, D. L. *J. Org. Chem.* **2003**, *68*, 4955−4958. (c) Reference 5b.

DOI: 10.1021/acs.orglett.8b02225
Org. Lett. 2018, 20, 5282−5285