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

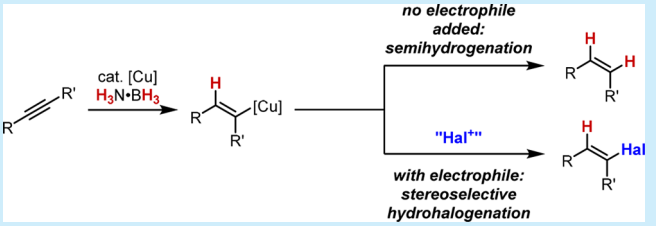
Stereoselective Alkyne Hydrohalogenation by Trapping of Transfer Hydrogenation Intermediates

Manas Das, Trinadh Kaicharla, and Johannes F. Teichert*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 115, 10623 Berlin, Germany

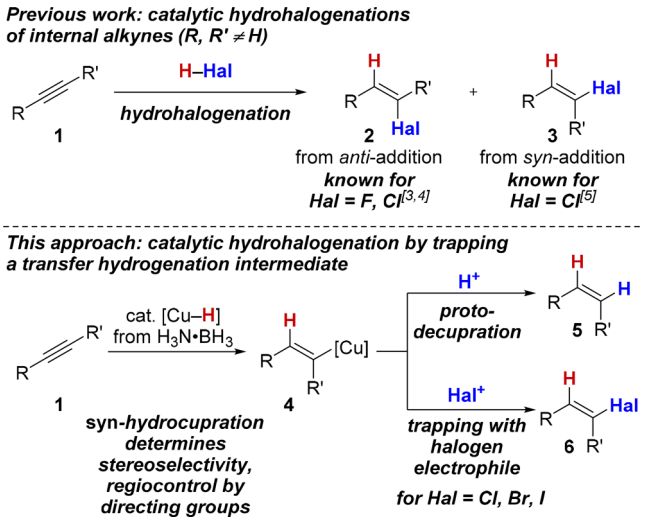
Supporting Information

ABSTRACT: A catalytically generated vinylcopper complex, the reactive intermediate of a copper(I)-catalyzed alkyne transfer hydrogenation, can be trapped by commercially available halogen electrophiles. In this manner, internal alkynes can stereoselectively be hydrohalogenated to the corresponding vinyl chlorides, bromides, and iodides.



The stereoselective hydrohalogenation of internal alkynes **1** provides direct synthetic access to highly substituted vinyl halides (**2** or **3**),[1] which are important reaction partners for cross-coupling reactions (Scheme 1, top).[2] Considering this valuable application, it is noteworthy that relatively few catalytic hydrohalogenations of internal alkynes have been reported: while some studies on hydrofluorination and hydrochlorination of internal alkynes with catalysts based on gold,[3] palladium,[4] and ruthenium[5] have been disclosed, to the best of our knowledge, no catalytic hydrobrominations or hydroiodinations of internal alkynes have been reported.[6−8] This is a crucial limitation, as generally, vinyl bromides and iodides are more reactive in cross-coupling reactions than the corresponding chlorides.[2]

Scheme 1. Hydrohalogenations of Internal Alkynes, Trapping Transfer Hydrogenation Intermediates



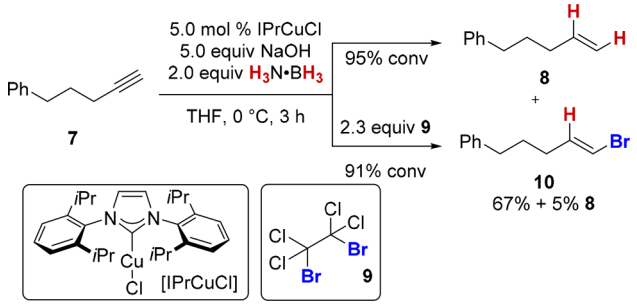
Inspired by a recent report on copper(I)-catalyzed hydrobrominations of terminal alkynes,[9a] and based on our interest in reductive transformations with alkynes employing copper(I) catalysts,[10,11] we turned our attention to a possible hydrohalogenation of internal alkynes. Such a process should ideally enable the stereoselective preparation of vinyl chlorides, bromides, and iodides from internal alkynes via one common catalytic protocol. We envisaged an approach based on an "interrupted" copper(I)-catalyzed transfer hydrogenation of internal alkynes **1** with ammonia borane ($H_3N{\cdot}BH_3$, Scheme 1, bottom).[11,12] As the key reactive intermediate of the transfer hydrogenations, a vinyl copper complex **4**[13,14] has been put forward, and sufficiently fast trapping of **4** with suitable halogen electrophiles should produce the desired vinyl halides **6** preferentially over the alkene **5**. One advantage of this approach would be that vinyl halides **6** would be formed with excellent stereoselectivity, generated in the upstream *syn* hydrocupration step (**1** → **4**).[10,13] This reaction control would offer orthogonal selectivity to the previously reported alkyne hydrohalogenations, which generally take place with an *anti* addition mode.[3,4,15]

Emanating from our previous results in transfer hydrogenation of internal alkynes,[11] we have established a protocol for the transformation of hitherto untolerated terminal alkynes such as **7** using catalytic amounts of commercially available [IPrCuCl][16] and sodium hydroxide as activator.[17] Slow addition of ammonia borane suppressed the rapid release of H_2 (dehydrocoupling), giving the terminal alkene **8** as the sole product (95% conversion, Scheme 2). However, when dibromotetrachloroethane (**9**) as electrophilic bromine source[18] was added simultaneously, formation of vinyl bromide **10** as single stereo- and regioisomer (91% conv, 67% yield) was observed, while the transfer hydrogenation was largely suppressed (5% of **8**). This result demonstrates that trapping of a transfer hydrogenation intermediate is a viable alternative to the use of hydrosilanes as reducing agents for the hydrobromination of terminal alkynes.[9a]

Received: June 30, 2018

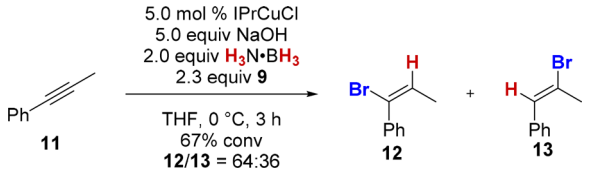
DOI: 10.1021/acs.orglett.8b02055
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Trapping a Transfer Hydrogenation Intermediate; Hydrobromination of a Terminal Alkyne



As the hydrohalogenation of internal alkynes is more challenging and had not been reported as a generally applicable method with copper catalysts, we moved on to internal alkynes as substrates: when phenylpropyne (**11**) was subjected to similar conditions, bromomethyl styrene was obtained as a 64:36 mixture of regioisomers (**12**/**13**, Scheme 3). This result

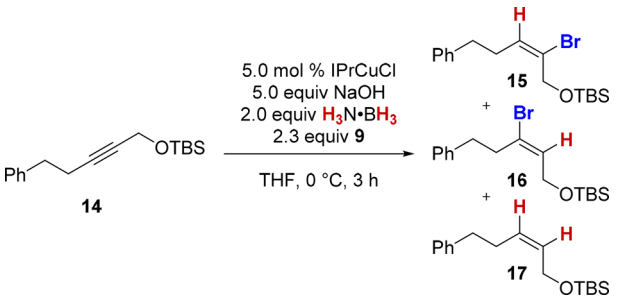
Scheme 3. Copper(I)-Catalyzed Hydrobromination of an Internal Alkyne



indicates a lack of regiocontrol of the hydrocupration step. The regioselectivity of hydrocuprations of internal alkynes can be facilitated by electronic predisposition using polar substituents.[19] Therefore, to control the regioselectivity of the overall hydrohalogenation for nonsymmetric internal alkynes, we employed propargyl silyl ethers such as **14** as a regiodirecting element (Table 1).[19,20]

Indeed, with 5 mol % of [IPrCuCl] as catalyst in THF at 0 °C, alkyne **14** could be hydrobrominated with a high regioselectivity favoring **15** (**15**/**16** = 91:7, Table 1, entry 1). While a negligible amount of transfer hydrogenation product **17** (2%) was detected, excellent *E*-selectivity for **15** and **16** was observed (*E*/*Z* > 95:5, judged by NMR analysis), indicating an efficient initial *syn* hydrocupration step. Raising the temperature to 21 °C led to increased formation of the transfer hydrogenation product **17**, demonstrating that the rate of the protodecupration of the presumed vinylcopper intermediate becomes competitive (Table 1, entry 2). On the other hand, lowering the temperature to −20 °C led to diminished conversion of **14** (67%, Table 1, entry 3). Importantly, in the absence of the electrophilic bromine source **9**, complete conversion to **17** was observed (Table 1, entry 4), indicating that, indeed, a trapping of a viable transfer hydrogenation intermediate takes place in the presence of **9**. Other electrophilic bromine sources such as NBS or CBr_4 led to either no formation of **15** or diminished conversion of **14** (Table 1, entries 5 and 6). The use of sodium *tert*-butoxide, a commonly used activator in copper hydride catalysis,[21] led to only 4% conversion of **14** (Table 1, entry 7). Finally, other copper(I)/NHC complexes such as IMesCuCl and IPr*CuCl[22] gave either lower regioselectivity or lower turnover of **14**, respectively (Table 1, entries 8 and 9).[23]

Table 1. Hydrobromination of Internal Alkynes[a]



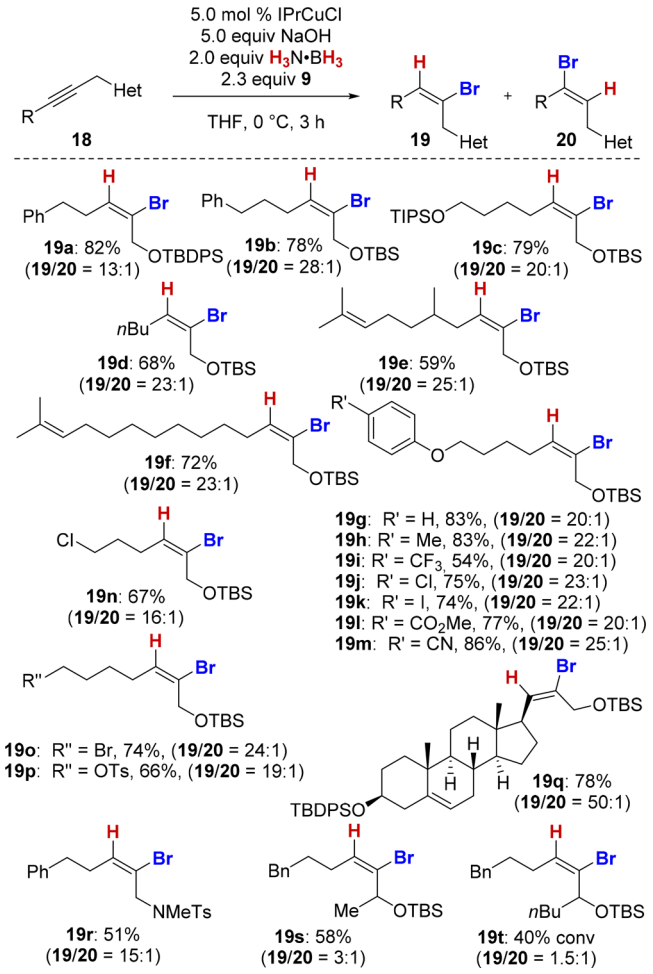
entry	deviation from standard conditions	conv[b] (%)	15/16/17
1	none	100 (72[c])	91:7:2
2	21 °C	100	72:9:19
3	−20 °C	67	94:6:<1
4	no **9**	100	0:0:100
5	NBS instead of **9**	78	0:0:100
6	CBr_4 instead of **9**	59	88:7:5
7	NaO*t*Bu instead of NaOH	4	100:0:0
8	IMesCuCl instead of IPrCuCl	95	76:7:17
9	IPr*CuCl[d] instead of IPrCuCl	61	85:13:2

[a]All reactions were carried out on a 0.2 mmol scale. [b]Determined by GC and ^{1}H NMR analysis. [c]Isolated yield of the corresponding allyl alcohol after TBS deprotection. [d]IPr* = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazo-2-ylidene.

With the optimized conditions in hand, we explored the substrate scope of the hydrobromination of internal alkynes. A variety of propargylic silyl ethers **18** could be hydrobrominated to give vinyl bromides **19** with generally excellent *E*-stereoselectivity (*E*/*Z* > 95:5) and good to excellent regioselectivity throughout (Scheme 4): Unfunctionalized vinyl bromides **19a**–**19f** including a protected alcohol (no deprotection of TIPS ether in **19c** observed) could all be isolated in good to very good yields. Terpenoid **19e** gave similar results in terms of regio- and stereoselectivity. We employed phenol ethers **19g** to **19m** as model compounds to investigate the functional group tolerance of the present protocol: trifluoromethyl, chloro, and iodo substituents (in **19i** to **19k**) as well as functional groups that might be potentially reduced (ester **19l** or nitrile **19m**) were tolerated by the catalytic hydrobromination. The presence of both an aryl iodide/chloride and a vinyl bromide makes compounds such as **19j** and **19k** ideal starting points for divergent cross-coupling reactions in further elaborations. Also, the present protocol tolerates leaving groups such as an alkyl chloride, bromide or a tosylate **19n**–**p**, which are all left untouched to give the desired vinyl bromides with the usual good results in terms of yield and regioselectivity.[24] Pregnenolone derivative **19q** was obtained with good yield (78%) and excellent regioselectivity (50:1).[25] The formation of sulfonyl amide **19r** displays the possible extension to nitrogen-based directing groups with equally good results; the corresponding propargylic thioethers (not shown) did not undergo hydrobromination. Introduction of additional substituents in the propargylic position interfered with the catalytic process: while methyl-substituted **19s** was still formed in 58% yield, lower regioselectivity (**19s**/**20s** = 3:1) was observed. The corresponding sterically more demanding butyl derivative **18t** gave incomplete conversion with loss of regioselectivity (**19t**/**20t** = 1.5:1). These results indicate that through increased steric demand not only regioselectivity of the hydrocupration step is compromised, but also the overall reactivity of the propargylic

DOI: 10.1021/acs.orglett.8b02055
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Hydrobromination of Propargylic Ethers: Scope

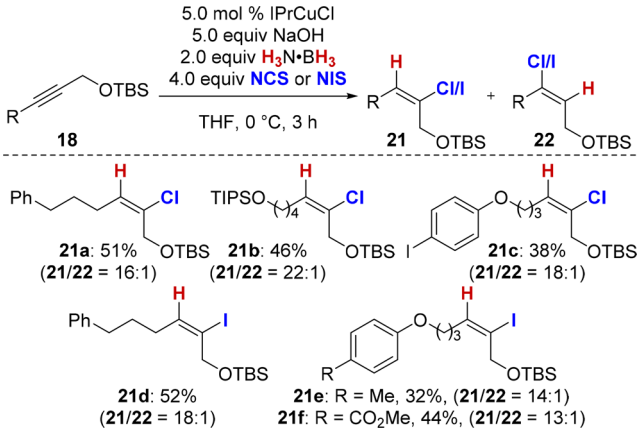


substrated is lowered. Both observations underscore that the electronic predisposition of the alkyne through polarization is the key for the overall catalytic hydrohalogenation. To display the applicability of the present hydrobromination protocol, the synthesis of **19b** was carried out on gram scale with similar results (4 mmol, 76%, **19**/**20** = 24:1).

It should be noted that while trisubstituted vinyl halides can be accessed via olefination protocols employing, e.g., phosphorus-based compounds, generally, the achievement of high *E*/*Z*-stereoselectivity is challenging.[26] The present protocol does not suffer from this shortcoming, as it hinges on a highly stereoselective *syn* hydrocupration step for the construction of the alkene.

One of the main advantages of the present protocol is that in a similar way, also hydrochlorinations and hydroiodinations of internal alkynes **18** (employing NCS or NIS, respectively) can successfully be effected with similarly good stereoselectivities (Scheme 5). This is in contrast to the hydrobrominations (see Scheme 4), where NBS was not effective. We speculate that traces of Br_2 in NBS suppress successful trapping of the reactive vinylcopper(I) intermediate. In this manner, vinyl chlorides and the arguably more synthetically useful vinyl iodides **21** can be accessed. For these transformations, the transfer hydrogenation became competitive, leading to somewhat lower yields (32−52%) (due to tedious separation of the undesired alkene from the hydrohalogenation products **21**). Halogenated allyl silyl ethers **21a**−**f** could be isolated with excellent stereoselectivity

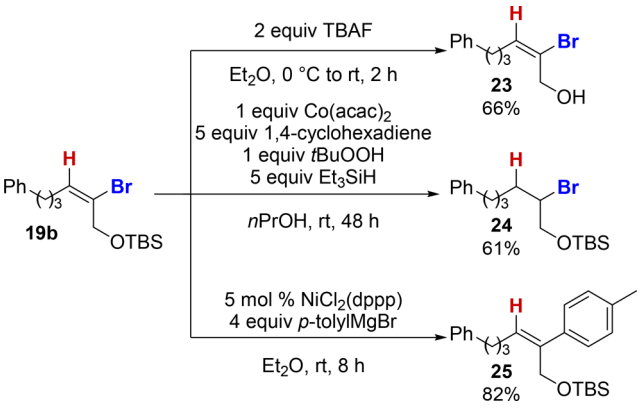
Scheme 5. Hydrochlorination and -iodination of Propargylic Ethers



(*E*/*Z* > 95:5) throughout, and with acceptable to good regioselectivity exceeding 13:1 (**21**/**22**). Therefore, the current approach by trapping the reactive intermediate of alkyne-transfer hydrogenation offers a convenient hydrohalogenation of internal alkynes leading to vinyl chlorides, bromides, and iodides with one common protocol displaying high stereoselectivity.

To demonstrate the applicability of the products of the alkyne hydrohalogenation protocol, we have further derivatized vinyl bromide **19b** (Scheme 6). Liberating the allyl alcohol **23** with

Scheme 6. Diversification of Brominated Allyl Ether 19b



TBAF proved feasible. Furthermore, a selective reduction of the carbon−carbon double bond employing a cobalt-mediated process[27] to give silyl-protected bromo alcohol **24** could be carried out. Finally, the use of vinyl bromide **19b** in a Kumada cross-coupling[28] successfully delivered styrene derivative **25**.

In conclusion, we have developed a catalytic stereoselective hydrohalogenation of internal alkynes which relies on the trapping of a transfer hydrogenation intermediate, namely a vinyl copper complex. As a directing element for regiocontrol, protected propargylic alcohols and amines are employed. By in situ addition of halogen electrophiles to the transfer hydrogenation protocol, the resulting overall hydrohalogenation process allows for the stereoselective preparation of vinyl chlorides, bromides, and iodides from internal alkynes. In particular, the latter two are valuable building blocks for cross-coupling reactions and can for the first time are made available from internal alkynes through the copper(I)-catalyzed transformation.

DOI: 10.1021/acs.orglett.8b02055
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02055.

Detailed starting material synthesis, general procedures, characterization data, and NMR spectra for all compounds(PDF)

Spectra for synthetic intermediates (PDF)

Accession Codes

CCDC 1811522 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: johannes.teichert@chem.tu-berlin.de.

ORCID

Johannes F. Teichert: 0000-0003-1043-8092

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Fonds der Chemischen Industrie (Liebig-Stipendium for J.F.T.), the German Research Council (DFG, Emmy Noether Fellowship to J.F.T.), and the Boehringer Ingelheim Stiftung (Exploration Grant to J.F.T.). We thank Dr. Sebastian Kemper (NMR analysis), Dr. Elisabeth Irran (elucidation of the crystal structure), Sebastian Möhle (initial experiments), and Prof. Dr. Martin Oestreich (all TU Berlin) for generous support.

■ REFERENCES

(1) For reviews on hydrohalogenations, see: (a) Petrone, D. A.; Ye, J.; Lautens, M. *Chem. Rev.* **2016**, *116*, 8003−8104. (b) Zeng, X. *Chem. Rev.* **2013**, *113*, 6864−6900. (c) Urch, C. J. In *Comprehensive organic functional group transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; pp 605−633.

(2) For an overview of cross-coupling reactions, see: de Meijere, A.; Bräse, S.; Oestreich, M. *Metal-catalyzed cross-coupling reactions and more*; Wiley-VCH: Weinheim, 2014.

(3) (a) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1983. (b) Akana, J. A.; Bhattacharyya, K. X.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7736−7737. (c) Gorske, B. C.; Mbofana, C. T.; Miller, S. J. *Org. Lett.* **2009**, *11*, 4318−4321. (d) Ebule, R.; Liang, S.; Hammond, G. B.; Xu, B. *ACS Catal.* **2017**, *7*, 6798−6801.

(4) (a) Derosa, J.; Cantu, A. L.; Boulous, M. N.; O'Duill, M. L.; Turnbull, J. L.; Liu, Z.; de La Torre, D. M.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139*, 5183−5193. For the related hydrochlorination of terminal alkynes using copper and palladium catalysts, see: (b) Dupont, J.; Basso, N. R.; Meneghetti, M. R.; Konrath, R. A.; Burrow, R.; Horner, M. *Organometallics* **1997**, *16*, 2386−2391.

(5) Dérien, S.; Klein, H.; Bruneau, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 12112−12115.

(6) For the related hydrohalogenations of haloalkynes, see: (a) Zhu, G.; Chen, D.; Wang, Y.; Zheng, R. *Chem. Commun.* **2012**, *48*, 5796−5798. (b) Zeng, X.; Liu, S.; Hammond, G. B.; Xu, B. *ACS Catal.* **2018**, *8*, 904−909.

(7) For a recent example of a noncatalytic hydrohalogenation of ynones and ynamides, see: Zeng, X.; Lu, Z.; Liu, S.; Hammond, G. B.; Xu, B. *J. Org. Chem.* **2017**, *82*, 13179−13187.

(8) For a rare example of an Ir-catalyzed hydroiodination of terminal alkynes, see: Ez-Zoubir, M.; Brown, J. A.; Ratovelomanana-Vidal, V.; Michelet, V. *J. Organomet. Chem.* **2011**, *696*, 433−441.

(9) (a) Uehling, M. R.; Rucker, R. P.; Lalic, G. *J. Am. Chem. Soc.* **2014**, *136*, 8799−8803. This report also contains a single example of a hydrobromination of internal alkynes. For a theoretical investigation of this transformation, see: (b) Deng, X.; Dang, Y.; Wang, Z.-X.; Wang, X. *Organometallics* **2016**, *35*, 1923−1930.

(10) For catalytic alkyne semihydrogenations, see, for example: (a) Pape, F.; Thiel, N. O.; Teichert, J. F. *Chem. - Eur. J.* **2015**, *21*, 15934−15938. (b) Thiel, N. O.; Teichert, J. F. *Org. Biomol. Chem.* **2016**, *14*, 10660−10666.

(11) For catalytic alkyne transfer hydrogenations with ammonia borane, see: Korytiaková, E.; Thiel, N. O.; Pape, F.; Teichert, J. F. *Chem. Commun.* **2017**, *53*, 732−735.

(12) For related H_2-mediated reductive couplings, see: (a) Hassan, A.; Krische, M. *Org. Process Res. Dev.* **2011**, *15*, 1236−1242. (b) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34−46.

(13) For characterization of vinylcopper(I)/NHC compounds, see: Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369−3371.

(14) For use of vinylcopper intermediates in catalysis, see, for example: (a) Fujihara, T.; Xu, T.; Semba, K.; Terao, J.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 523−527. (b) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10830−10834. (c) Uehling, M. R.; Suess, A. M.; Lalic, G. *J. Am. Chem. Soc.* **2015**, *137*, 1424−1427. (d) Sidera, M.; Fletcher, S. P. *Chem. Commun.* **2015**, *51*, 5044−5047. (e) Shi, S.-L.; Wong, Z. L.; Buchwald, S. L. *Nature* **2016**, *532*, 353−356.

(15) An exception to this is the *syn* hydrochlorination of internal alkynes given in ref 5.

(16) For a review on copper/NHC catalysts, see: Lazreg, F.; Cazin, C. S. J. In *N-Heterocyclic Carbenes: Effective Tools for Organometallic Synthesis*; Nolan, S. P.. Ed.; Wiley-VCH: Weinheim, 2014; pp 199−242.

(17) Presumably, a copper(I) hydroxide complex is formed in situ: Fortman, G. C.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2010**, *29*, 3966−3972.

(18) For the use of **9** as electrophilic brominating agent, see, for example: (a) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351−352. (b) Söderman, S. C.; Schwan, A. L. *J. Org. Chem.* **2012**, *77*, 10978−10984. (c) Reference 9a.

(19) Propargylic silyl ethers have been employed as directing groups in other copper hydride-based transformations: Mailig, M.; Hazra, A.; Armstrong, M. K.; Lalic, G. *J. Am. Chem. Soc.* **2017**, *139*, 6969−6977.

(20) The triethylsilyl ether also led to conversion. See the Supporting Information for details.

(21) For reviews on catalysis with copper hydride complexes, see: (a) Jordan, A. J.; Lalic, G.; Sadighi, J. P. *Chem. Rev.* **2016**, *116*, 8318−8372. (b) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916. (c) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 498−504.

(22) Berthon-Gelloz, G.; Siegler, M. A.; Spek, A. L.; Tinant, B.; Reek, J. N. H.; Markó, I. E. *Dalton Trans.* **2010**, *39*, 1444−1446.

(23) In the absence of a copper catalyst, no hydrobromination or transfer hydrogenation took place.

(24) CuH-catayzed defunctionalization of alkyl triflates and iodides: Dang, H.; Cox, N.; Lalic, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 752−756.

(25) X-ray diffraction analysis of **19q** clearly displays the *syn* relationship of H and Br atoms on the newly formed carbon−carbon double bond.

(26) For an example and an overview, see: Olpp, T.; Brückner, R. *Synthesis* **2004**, *2004*, 2135.

(27) King, S. M.; Ma, X.; Herzon, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 6884−6887.

(28) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374−4376.

DOI: 10.1021/acs.orglett.8b02055
Org. Lett. XXXX, XXX, XXX−XXX