ORGANIC LETTERS

2013
Vol. 15, No. 15
3860–3863

Rh(III)-Catalyzed Halogenation of Vinylic C—H Bonds: Rapid and General Access to *Z*-Halo Acrylamides

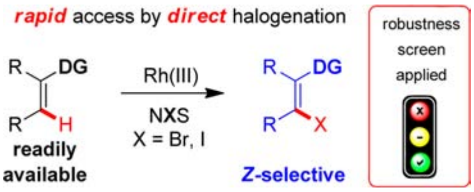
Nadine Kuhl,[†] Nils Schröder,[†] and Frank Glorius*

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster, Germany

glorius@uni-muenster.de

Received June 5, 2013

ABSTRACT



Herein, the regio- and stereoselective iodination, along with some examples for the bromination, of readily available acrylamides to access a variety of differently substituted *Z*-haloacrylic acid derivatives is reported. The reaction proceeds under mild conditions via a Rh(III)-catalyzed C—H-activation/halogenation mechanism and represents a rare example of a direct halogenation of electron-poor acrylic acid derivatives.

C—H bond activation is arguably one of the most promising strategic tools in organic synthesis for simplifying the preparation of functionalized building blocks and intermediates.[1] Its combination with other reliable and well established transformations allows the synthesis of natural products and biologically active compounds to be further streamlined. In this regard, applying the C—H bond activation approach to the preparation of halogenated compounds, which can be further utilized in well-established cross-coupling reactions,[2] would be valuable. *Z*-Haloacrylic acid derivatives represent attractive building blocks for the selective construction of the ubiquitous *Z*-configured olefin motif.[3] Known syntheses of *Z*-haloacrylic acid derivatives, including carbohalogenations,[4,5] hydrohalogenations,[6] or Morita—Baylis—Hilman-type[7] transformations, utilize alkynes as starting materials and therefore are

---

[†] The authors contributed equally.

(1) Recent reviews on C—H bond activation: (a) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (c) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (d) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (e) Kuhl, N.; Hopkinson, M. N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (f) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (g) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (h) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (i) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (j) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (k) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (l) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (m) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (n) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (o) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (p) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874.

(2) (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Eds.; John Wiley & Sons: Hoboken, NJ, 2002. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

(3) Examples for *Z*-halo compounds as intermediates in synthesis: (a) Français, A.; Leyva-Pérez, A.; Etxebarria-Jardi, G.; Peña, J.; Ley, S. V. *Chem.—Eur. J.* **2011**, *17*, 329. (b) Skepper, C. K.; Quach, T.; Molinski, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 10286. (c) Bian, M.; Yao, W.; Ding, H.; Ma, C. *J. Org. Chem.* **2010**, *75*, 269. (d) Tang, S.; Erickson, K. L. *J. Nat. Prod.* **2008**, *71*, 898. (e) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936. (f) Negishi, E.-i.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. (g) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

(4) Examples on transition-metal catalyzed carbohalogenation: (a) Huang, L.; Wang, Q.; Liu, X.; Jiang, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5696. (b) Wen, Y.; Huang, L.; Jiang, H.; Chen, H. *J. Org. Chem.* **2012**, *77*, 2029. (c) Friest, J. A.; Broussy, S.; Chung, W. J.; Berkowitz, D. B. *Angew. Chem., Int. Ed.* **2011**, *50*, 8895. (d) Huang, J.-M.; Dong, Y.; Wang, X.-X.; Luo, H.-C. *Chem. Commun.* **2010**, *46*, 1035. (e) Li, J.-H.; Tang, S.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 477. (f) Hua, R.; Shimada, S.; Tanaka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12365.

(5) Examples for carbohalogenation using organometallic reagents: (a) Abarbri, M.; Parrain, J.-L.; Duchêne, A.; Thibonnet, J. *Synthesis* **2006**, *17*, 2951 and references therein. (b) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1.

(6) Examples on Hydrohalogenation: (a) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709. (b) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643. (c) Tanigushi, M.; Kobayashi, S.; Nakagawa, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4763.

10.1021/ol4015915

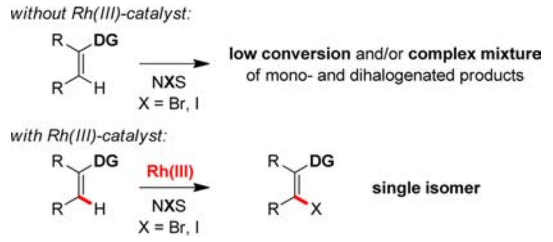


Figure 1. Effect of the Rh(III)-catalyst on the direct halogenation of acrylic acids.

often limited with regard to the accessible substitution patterns.[8] Consequently, the application of C−H bond activation in the direct halogenation of electron-deficient olefins is desirable, as it would provide a more general route to these halogenated motifs due to the ready availability of diversely substituted acrylic acid derivatives.

In the past decade, a variety of methods for the palladium-catalyzed *ortho*-directed halogenation of aromatic sp^2 C−H bonds have been developed by Sanford,[9] Yu,[10] Shi,[11] and others[12] which allow the functionalization of benzoic acid, aniline, or phenol derivatives. In addition, our group recently demonstrated that also a Rh(III)-catalyst is competent for the *ortho*-halogenation of different benzene derivatives.[13,14] However, it seems that the direct halogenation of vinylic C−H bonds is still unprecedented. Olefins are quite challenging substrates to functionalize in C−H bond activation reactions due to their lability and increased reactivity relative to arenes.[15,16] This challenge is predominant in the case of C−H bond halogenation of olefins using *N*-halosuccinimides, as competing radical or cationic background reactions will have to be circumvented in order to provide a chemo- and regioselective outcome (Figure 1). Using the rather mild Rh(III)-catalyzed halogenation methodology developed in our group,[14] we anticipated that these challenges could be met to provide a stereoselective synthesis of the *Z*-haloacrylic acid motif.

Herein, we describe the first transition-metal catalyzed iodination and bromination of vinylic C−H bonds which provides a simple and selective access to a variety of *Z*-haloacrylic acid derivatives starting directly from the alkene-oxidation state. Additionally, a broad overview on the functional group tolerance and the application to different amide directing groups are presented to facilitate potential applications of the methodology described.

We began our study on vinylic C−H bond halogenations with the iodination of methacrylamide **2**. When applying similar reaction conditions as used for the halogenation of arenes[14] (Scheme 1), **2** was smoothly converted to the desired iodinated product **2-I** in 76% yield as determined by GC analysis. Control experiments demonstrated that a cationic RhCp*-species and the pivalic acid are essential to obtain satisfying conversion to **2-I**. Notably, no conversion of the starting material was detected when the reaction was conducted without $[\text{RhCp*Cl}_2]_2$ and AgSbF_6, whereas if only the Rh(III)-catalyst was omitted significant side reactions were observed, highlighting the efficiency of the Rh(III)-catalyzed pathway.[17]

With the optimized conditions in hand, we continued to study the influence of different substituents on the efficiency of the iodination and the corresponding bromination reaction (Scheme 1). In the case of the unsubstituted vinylamide **1** the iodination reaction led to the desired product **1-I**. The bromination was dominated by a background reaction yielding a dibrominated amide as the major product.[17]

In contrast, α-substituted vinylamides **2** and **3** were successfully halogenated under these reaction conditions in excellent yields. Nevertheless, conducting the halogenations of vinylamide **3** in the absence of the Rh(III)-catalyst gave the same yields and selectivities for the *Z*-halogenated products.[18] Interestingly, for the *β*-substituted vinylamides **4** and **5**, halogenation with NIS

---

(7) Examples on Morita−Baylis−Hilman-type reactions: (a) Senapati, B. K.; Hwang, G.-S.; Lee, S.; Ryu, D. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 4398. (b) Lee, S. I.; Hwang, G.-S.; Ryu, D. H. *Synlett* **2007**, *1*, 59. (c) Wei, H.-X.; Hu, J.; Purkiss, D. W.; Paré, P. W. *Tetrahedron Lett.* **2003**, *44*, 949. (d) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4767.

(8) For an aminohalogenation of α,*β*-unsaturated carbonyl compounds, see: Sun, H.; Zhang, G.; Zhi, S.; Han, J.; Li, G.; Pan, Y. *Org. Biomol. Chem.* **2010**, *8*, 4236.

(9) (a) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523. (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.

(10) (a) Mei, T. S.; Wang, D.-H.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 3140. (b) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215. (c) Giri, R.; Chen, X.; Yu, Y.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112.

(11) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416.

(12) Selected examples on the halogenation of arenes via C−H-bond activation: (a) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4440. (b) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5524. (c) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466. (d) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009**, *131*, 11310.

(13) Recent reviews on Rh(III)-catalyzed C−H bond activation: (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (b) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. (c) Satoh, T.; Miura, T. *Chem.—Eur. J.* **2010**, *16*, 11212.

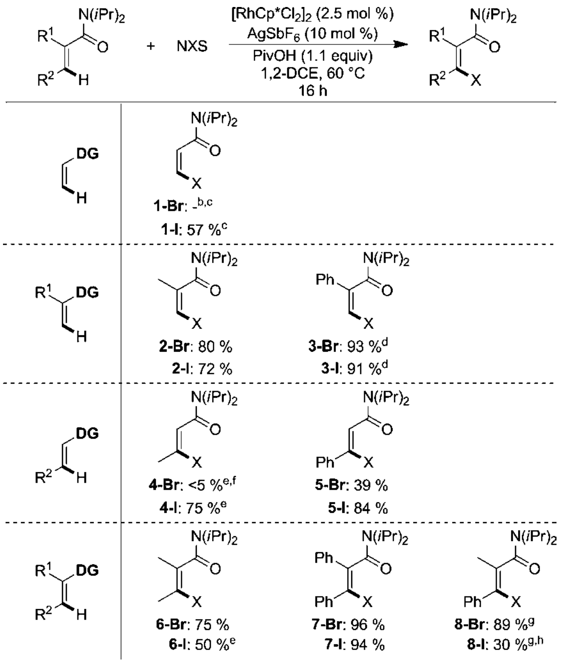
(14) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298.

(15) Selected examples for transition-metal catalyzed vinylic C−H bond activation: (a) Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176. (b) Duttwyler, S.; Chen, S.; Takase, M. K.; Wiberg, K. B.; Bergman, R. G.; Ellman, J. A. *Science* **2013**, *339*, 678. (c) Yu, H.; Jin, W.; Sun, C.; Chen, J.; Du, W.; He, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2009**, *49*, 5792. (d) Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372. (e) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (f) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623. (g) Sato, T.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett.* **1998**, 893. For a recent review on this topic, see: (h) Shang, X.; Liu, Z.-Q. *Chem. Soc. Rev.* **2013**, *42*, 3253.

(16) Selected articles on Rh(III)-catalyzed vinylic C−H bond activation: (a) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 629. (b) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 66. (c) Zhang, J.; Loh, T.-P. *Chem. Commun.* **2012**, *48*, 11232. (d) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Chem.—Asian J.* **2012**, *7*, 1208. (e) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7167. (f) Hyster, T. K.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1606. (g) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 3024. (h) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 9548. (i) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5462. (j) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6295.

(17) For further details see SI.

Scheme 1. Halogenation of Differently Substituted Vinylamides[a]



[a] 0.4 mmol scale using 1.1 equiv of NXS; isolated yields are given. Undesired *E*-isomers were not detected. [b] 39% of a dibrominated product were isolated, [c] 2 × 0.8 equiv of NXS, 24 h. [d] Similar yields were obtained without [RhCp*Cl$_2$]$_2$. [e] 2 × 0.7 equiv of NXS, 120 °C, 24 h. [f] Determined by GC-MS. [g] 5 mol % [RhCp*Cl$_2$]$_2$, 20 mol % AgSbF$_6$ were used. [h] Determined by ^{1}H NMR. Inseparable mixture of **8** and **8-I**.

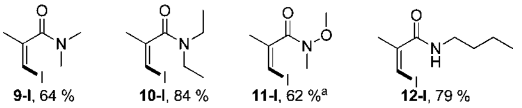


Figure 2. 0.4 mmol scale using 1.1 equiv of NIS; isolated yields. [a] 1 mmol scale.

proved more facile. However, in the case of crotylamide **4** a higher reaction temperature and two successive additions of NIS were necessary to avoid noncatalyzed side reactions. In contrast, α,*β*-disubstituted vinylamides **6**–**8** smoothly underwent bromination with NBS whereas the iodination only proceeded in the case of the α-phenyl cinnamic amide **6** with good efficacy. For the α,*β*-disubstituted vinylamides, in particular, it was noted that unselective bromination takes place when [RhCp*Cl$_2$]$_2$ is omitted.[17] Exemplary rate measurements based on the conversion of **6** with and without the Rh(III)-catalyst revealed markedly different reaction profiles in which the catalyzed reaction exhibits a much higher initial rate.[19] This further underlines the ability of the Rh(III)-catalyzed process to suppress unwanted side reactions.

Noting that the iodination reaction was more robust toward changes in the substitution pattern of the substrate, further studies were preferentially undertaken using NIS as the halogen source. A short screen of different amide groups on the standard methacrylate framework revealed that the iodination reaction is not dependent on the steric character of the tertiary amide directing group (Figure 2). Besides the bulky *N*,*N*-diisopropylamide, the smaller amides **9** and **10** efficiently directed the iodination yielding the desired *Z*-configured products **9-I** and **10-I** exclusively in 64% and 84% isolated yield, respectively. Gratifyingly, the synthetically versatile Weinreb amide **11** and the secondary butyl amide **12** also gave the corresponding iodinated products in moderate to good yields.

In order to study the influence of functionality directly connected to the reactive center, the iodination of various vinylamide derivatives leading to densely functionalized *Z*-haloacrylic amides was investigated (Scheme 2). Gratifyingly, the α- and *β*-brominated substrates **13** and **17** smoothly reacted under standard reaction conditions. The corresponding dihalogenated products **13-I** and **17-I** were obtained in excellent yields and represent attractive intermediates for further sequential functionalization.[20] Interestingly, an ester functionality installed in close proximity to the reactive center was well tolerated under the reaction conditions. The corresponding product **16-I** was obtained in excellent yield. In comparison the reaction of alcohol **14** led to decomposition of the starting material and benzyl protection was required to obtain the iodinated motif **15-I**. Investigation of cinnamic acid derivatives **18**–**20** further disclosed a significant impact of the aryl substituent on the efficacy of the iodination reaction. Whereas the *p*-methoxy cinnamic amide **18** led to a complex reaction mixture, the iodination of the less electron-rich substrate **20** yielded the desired product **20-I** in excellent 88% isolated yield.

To facilitate the application of this methodology, we applied a robustness screen recently developed in our group[21] to access both the functional group tolerance of the vinylic C–H bond halogenation reaction and the tolerance of specific motifs to the reaction conditions. Therefore, the standard iodination reaction of **2** was performed in the presence of a given functional group or common motif ("additive"), and the conversion of the starting material (sm), yield of **2-I**, and stability of the additive were determined by GC analysis. A selection of the data obtained is summarized in Table 1 using simple labeling to facilitate a quick assessment of the results (for the full screening, see Supporting Information (SI)).[17]

To our delight, a variety of versatile and synthetically useful functional groups such as an aromatic ester, aromatic and aliphatic ketones, nitriles, aliphatic alcohols, aryl and alkyl halides, and notably, the relatively sensitive aldehyde functionality proved to be stable under the standard halogenations conditions. In contrast, alkynes, alkenes,

---

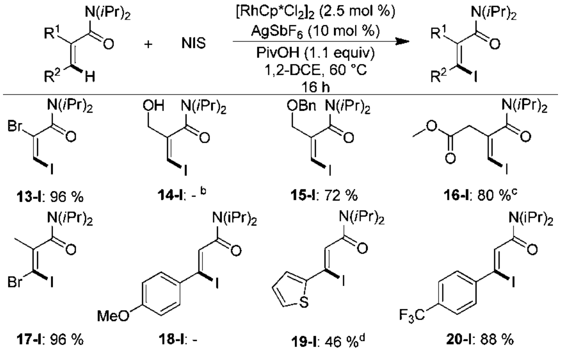
(18) For all substrate classes the bromination and iodination reactions were also tested without the Rh(III)-catalyst and/or the silver salt. For more details, see SI.

(19) For the bromination of **6** without the Rh(III)-catalyst full conversion to a mixture of ***(E)*-6-Br**, ***(Z)*-6-Br**, and allylic-bromination products was observed. For further details see SI.

(20) A method for the sequential functionalization of compounds related to **16-I** has already been described: Vu, V. A.; Marek, I.; Knochel, P. *Synthesis* **2003**, 1797.

(21) (a) Collins, K.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597. (b) Collins, K.; Glorius, F. *Tetrahedron* **2013**, *69*, 7817.

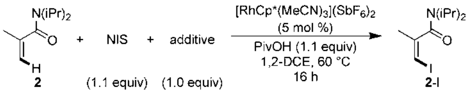
Scheme 2. Exploring Functional Group Tolerance[a]

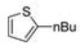
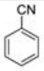
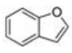
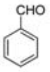
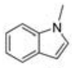
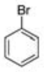
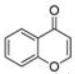
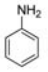
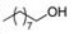
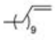
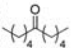


13-I: 96 %
14-I: - [b]
15-I: 72 %
16-I: 80 %[c]
17-I: 96 %
18-I: -
19-I: 46 %[d]
20-I: 88 %

[a] 0.4 mmol scale using 1.1 equiv of NIS; isolated yields are given. If not stated otherwise no *E*-isomers were detected. [b] Decomposition of **14**. [c] Reaction conducted on a 1 mmol scale. *Z*/*E* = 95:5 from the isolated compound. [d] 80 °C reaction temperature.

Table 1. Selected Examples of the Robustness Screen[a]

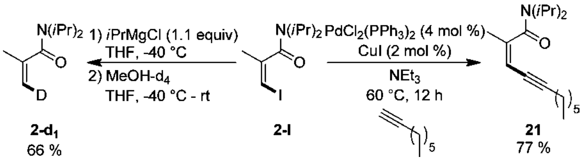


additive	yields [%]			additive	yields [%]		
	product	additive	sm		product	additive	sm
	56 -	54 -	36		52 -	100 ✓	11
	80 ✓	83 ✓	9		79 ✓	90 ✓	8
	0 ✗	36 -	100		74 ✓	91 ✓	<5
	73 ✓	100 ✓	<5		0 ✗	25 ✗	100
	14 ✗	55 -	60		68 ✓	86[b] -	
	5 ✗	62 ✓	80		79 ✓	100 ✓	<5

[a] 0.125 mmol scale. GC-yields using mesitylene as the internal standard. $[RhCp^*(MeCN)_3](SbF_6)_2$ was used for simplification. [b] Combined yield of recovered sm and additive. sm = starting material.

as well as activated benzene derivatives, such as aniline, were not well tolerated and also significantly hampered the iodination reaction itself. In addition to functional groups, the standard reaction of methacrylamide **2** was also performed in the presence of different heterocycles. Unfortunately, N-containing or electron-rich heterocycles typically led to complete inhibition of the halogenation reaction. However, satisfying results could be obtained in the presence of the more electron-deficient *n*-butyl thiophene, benzofuran, and the 2-chloroquinoline heterocycles suggesting that these motifs could be indeed applied in the vinylic C–H halogenation of more complex structures.

Scheme 3. Representative Applications



2-d1
66 %
2-I
21
77 %

Finally, some additional experiments to further examine characteristics of our methodology showed that our standard reaction still proceeds with similar efficacy when conducted at rt or 60 °C with only 1 mol % Rh(III)-dimer (and 4 mol % of the silver salt) leading to a 73% and 68% isolated yield of **2-I**, respectively. Notably, the reaction can be easily scaled up to a 6 mmol scale without loss in reactivity (80% isolated yield of **2-I** with 1 mol % $[RhCp^*Cl_2]_2$, 4 mol % $AgSbF_6$, 0.5 equiv of PivOH, and otherwise identical conditions).[17] Initial rate measurements of **2-d₀** and **2-d₁** (easily prepared from **2-I**, Scheme 3) revealed a KIE of 2.3 showing that the halogenation mechanism includes a C–H activation event which is rate determining.[17]

Additionally, a Sonogashira coupling of **2-I** with 1-octyne yielding enyne **21** in 77% isolated yield was performed to demonstrate that such valuable motifs can be easily accessed in two steps by applying this C–H halogenation approach.

In summary, we have developed an efficient method to selectively access *Z*-haloacrylic acid derivatives via a direct route from readily available α,β-unsaturated carbonyl compounds using Rh(III) C–H bond activation.

The reaction offers a general approach to differently substituted haloacrylic acid derivatives. Moreover, it proceeds under fairly mild conditions allowing the tolerance of a variety of synthetically useful functional groups and moieties. We expect this method to be complementary to already existing methods for the synthesis of these highly useful compounds.

Acknowledgment. This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction. We thank C. Weitkamp and C. Benndorf for experimental support and K. Collins for helpful discussions (all WWU Münster). Generous support by the DFG (IRTG Münster-Nagoya and Leibniz award 2013), the Fonds der Chemischen Industrie (N.K.), and the European Research Council under the European Community's Seventh Framework Program (FP7 2007-2013)/ERC Grant Agreement No. 25936 is gratefully acknowledged.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.