ChemPubSoc Europe

DOI: 10.1002/chem.201804504

CHEMISTRY
A European Journal
Communication

C–H Halogenation

Multiple Halogenation of Aliphatic C–H Bonds within the Hofmann–Löffler Manifold

Estefanía Del Castillo[+],[a] Mario D. Martínez[+],[a] Alexandra E. Bosnidou,[a] Thomas Duhamel,[a, b] Calvin Q. O'Broin,[a] Hongwei Zhang,[a] Eduardo C. Escudero-Adán,[a] Marta Martínez-Belmonte,[a] and Kilian Muñiz*[a, c]

Abstract: An innovative approach to position-selective polyhalogenation of aliphatic hydrocarbon bonds is presented. The reaction proceeded within the Hofmann-Löffler manifold with amidyl radicals as the sole mediators to induce selective 1,5- and 1,6-hydrogen-atom transfer followed by halogenation. Multiple halogenation events of up to four innate C–H bond functionalizations were accomplished. The broad applicability of this new entry into polyhalogenation and the resulting synthetic possibilities were demonstrated for a total of 27 different examples including mixed halogenations.

Polyhalogenated aliphatic compounds represent fascinating molecules with important properties that have triggered significant interest from various fields of the chemical sciences. Nature has made use of this particular motif to a large extent with the family of polyhalogenated natural products, which have emerged as an important class of natural marine toxins.[1] As a result, recent synthetic efforts were elaborated on the polyhalogenation theme. Apart from conventional functional group transformation, commonly employed elegant approaches to this class of compounds rely on allylic and olefinic halogenation strategies.[2,3] An attractive alternative would consist of direct halogenation of ubiquitous aliphatic C–H bonds. Although attempts toward such challenging endeavors have been undertaken for monohalogenation,[4] the synthetic concept of predictable multiple C–H halogenation has remained notably unaddressed so far. A possible synthetic realization may derive from the application of suitable functional groups to direct the C–H halogenation event. In this regard, radical processes appear particularly promising.[5] Amidyl radicals[6] are known to promote such C–H halogenation as the key step in photochemically initiated Hofmann–Löffler reactions.[7] Recent improvements by several groups have provided mild reaction conditions based on the stoichiometric use of electrophilic halide sources.[7,8] Our recent efforts to develop new protocols for the Hofmann–Löffler reaction identified manifolds that are catalytic in halogen.[9] Their most important feature is the accelerated final C–N bond formation to regenerate the halide catalyst. To accomplish multiple halogenation, the NH group must remain intact to re-engage in the C–H halogenation. Unlike monofunctionalization, the anticipated multiple C–H functionalization needs to address several challenges (Figure 1). At the outset, the required N-halogenation of the substrate proceeds with an external halogenating agent [N]X. The photochemically generated amidyl radical provides the required selectivity through intramolecular selection of accessible C–H bonds, guided by 1,5-[8] or 1,6-hydrogen-atom transfer (HAT).[10] In Hofmann–Löffler reactions, the initial C–H halogen-

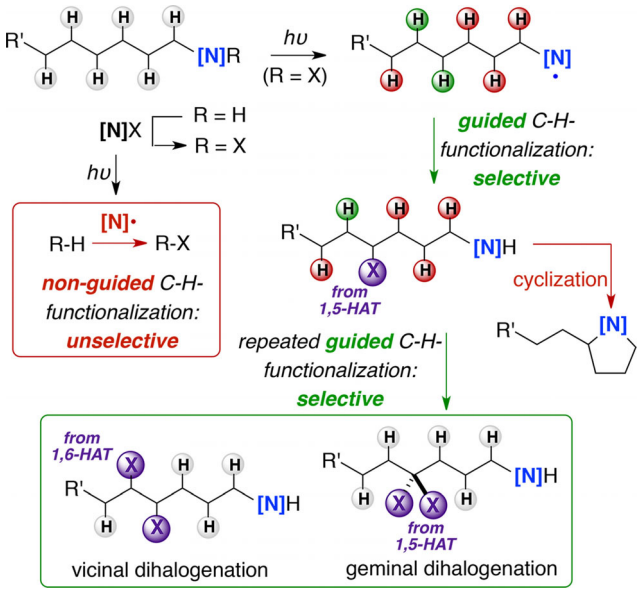


Figure 1. Strategy for multiple carbon–halogen bond formation through consecutive Hofmann–Löffler reaction. [N]X = halogenating agent. Representative hydrogens are depicted for each methylene group.

[a] E. Del Castillo,[+] Dr. M. D. Martínez,[+] A. E. Bosnidou, T. Duhamel, C. Q. O'Broin, Dr. H. Zhang, Dr. E. C. Escudero-Adán, Dr. M. Martínez-Belmonte, Prof. Dr. K. Muñiz
Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology
Av. Països Catalans 16, 43007 Tarragona (Spain)
E-mail: kmuniz@iciq.es

[b] T. Duhamel
Facultad de Química, Universidad de Oviedo
C/Julián Clavería, 33006 Oviedo (Spain)

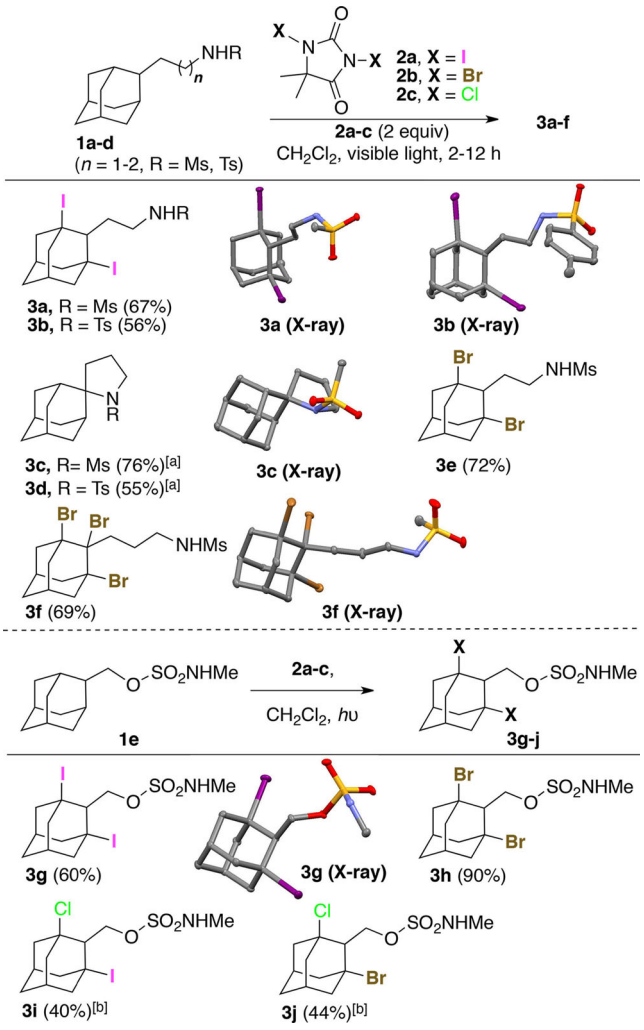
[c] Prof. Dr. K. Muñiz
Catalan Institution for Research and Advanced Studies (ICREA)
Pg. Lluís Companys 23, 08010 Barcelona (Spain)

[+] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.201804504.

ation is usually followed by nucleophilic amination to the heterocyclic product, which is commonly a pyrrolidine. Provided that another N–H halogenation would kinetically outperform the nucleophilic amination, multiple aliphatic C–H bond decoration, including the depicted vicinal (from sequential 1,5- and 1,6-HAT) and geminal (from two 1,5- or 1,6-HATs) dihalogenation becomes available. Additional structural motifs arise from branched or cyclic hydrocarbon substrates. As an additional challenge, a potential background reaction arising from competing amidyl radicals from the halogenating agent itself must be avoided because the resulting non-guided C–H functionalization process would result in unselective halogenation.

As a result, multiple C–H halogenation events appear challenging at the outset, because only pertinent kinetic dominance of the guided pathway shown in Figure 1 would ensure the required selectivity. Based on these considerations, we screened possible conditions for multiple halogenation reactions and chose the 2-adamantane derivatives **1a–e** as substrates targeting tertiary C–H bonds (Scheme 1). Halogenated hydantoins **2a–c** were chosen as halogenating agents.[4a,b,11,12]



Scheme 1. Multiple directed halogenation at the adamantane core: reaction scope. [a] With **2a** as reagent. [b] i) **2c**, CH_2Cl_2, ii) C_6H_6, black LEDs, iii) **2a,b**, CH_2Cl_2, visible light. Yields refer to the overall three-step process.

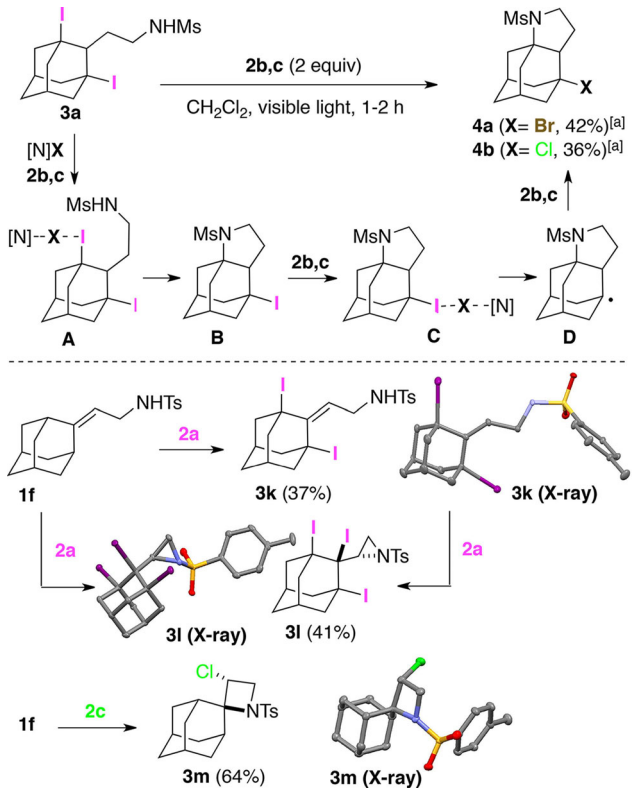
Under photochemical initiation, in situ-formed N-halogenated derivatives engaged cleanly in the expected C–H halogenation reactions for X = I, Br.

The reaction outcome depends on the length of the alkyl chain spacer. For ethylenylamides clean diiodination products **3a,b** were observed.[13] The position-selective C–H halogenation drew its origin from a spontaneous 1,5-HAT via N-centered radicals of the Hofmann–Löffler pathway. In contrast, the homologous propylenylamides provided a sufficiently fast cyclization after the initial iodination leading to selective formation of the pyrrolidine products **3c,d**. Such a cyclization should be disfavored for the less reactive bromination products. Indeed, the corresponding mesylamides generated the expected brominated products, which were isolated as dibromides **3e** and tribromide **3f**. The former compound was generated through the common 1,5-HAT, whereas the latter was formed through sequential 1,5- and 1,6-HAT. The potentially competing non-guided halogenation of the remaining tertiary C–H bonds by direct free-radical functionalization with reagents **2a,b** was never observed, indicating the exclusive involvement of innate Hofmann–Löffler pathways.[14] These reactions provide the selectivity proof of principle for the kinetic dominance of an essentially amidyl-radical-guided multiple C–H halogenation.

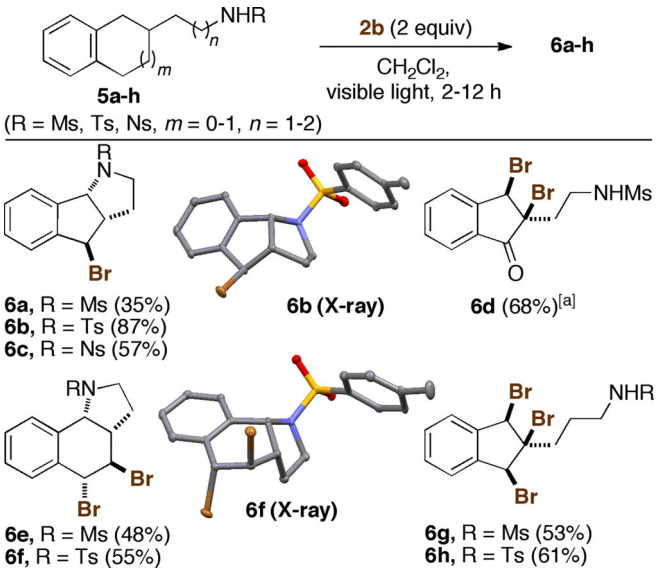
In a related manner, recently introduced N-alkyl sulfamate groups[10] could be employed for this purpose (Scheme 1). Although halogenation with N-alkyl sulfamates has been reported,[10] their use in polyhalogenation is again entirely without precedence. These groups promote the expected preferential 1,6-HAT with visible light as the only initiator and, consequently, substrate **1e** provided the selectively diiodinated and dibrominated products **3g** and **3h**, respectively. Applying sequential halogenation reactions with (i) **2c** and (ii) **2a** or **2b** allowed for the introduction of two different halide groups, as demonstrated for **3i** and **3j**. To the best of our knowledge, these are the first examples of defined mixed dihalogenation from Hofmann–Löffler reaction conditions.

Attempts to generate such compounds through alternative halogen-exchange reactions did not succeed. For example, treatment of crude **3a** with hydantoins **2b,c** led to exclusive formation of the chlorinated and brominated pyrrolidines **4a,b** (Scheme 2). A control experiment with the N-methylated derivative of **3a** also provided halogen exchange, indicating that the potential involvement of a sulfonamide amidyl radical did not take place.[15] Instead, iodine oxidation[16] to iodine(III) **A** should be involved in these transformations. This would generate an iodine leaving group for pyrrolidine formation affording **B**, as previously demonstrated[9a] and corroborated with a control experiment using $PhICl_2$.[15] Oxidation of the remaining iodine with liberated IX[17] would initiate iodide extrusion to cationic **C** and, thus, subsequent nucleophilic halogenation[16a,b,18] would provide the halogenated pyrrolidines **4a,b** within a unique oxidatively induced transformation of the diiodide.

Interestingly, the corresponding unsaturated substrate **1f** underwent unprecedented diiodination with **2a** to give the corresponding product **3k**. With respect to the mechanism, an unprecedented sequence of two Hofmann–Löffler reactions



Scheme 2. Additional halogenation at the adamantane core. [a] Yields refer to the overall two-step process from **1a**.

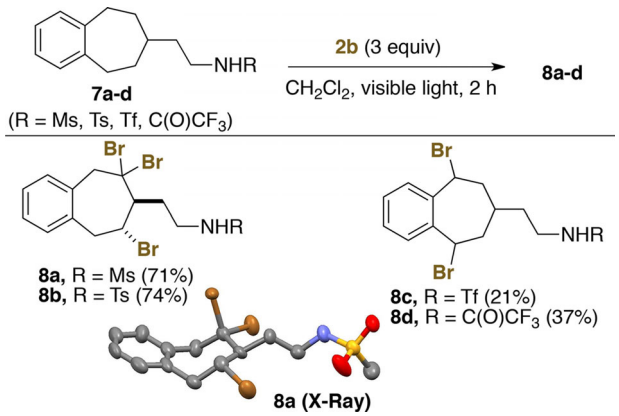


Scheme 3. Multiple halogenation of cyclic aliphatic C–H bonds. [a] With 5 equiv of **2b**.

may be involved. After the initial iodination, non-bonded interactions should initiate the known double-bond isomerization[19] under the present reaction conditions followed by a second Hofmann–Löffler iodination.[15] Alternative allylic functionalization events appear less plausible due to the lack of stabilization of the putative allylic radical because the rigid adamantyl core would induce orthogonality between the radical and the alkene π-system. With an excess of hydantoin, double-bond oxidation took place leading to the formation of the triiodinated aziridine **3l**. The selective aziridine formation over the azetidine is believed to originate from steric preferences. In fact, chlorination of **1f** led to clean four-membered ring formation.

Given the observed higher stability in the cases of the brominated adamantyl derivatives and the general interest in brominated organic compounds as important synthons,[20] polybromination was investigated further for additional alicyclic substrates (Scheme 3). For indane-derived substrates **5a–c**, the 2-ethylenylamides induced selective 1,5-HAT at the benzylic positions, demonstrating that dual halogenation is also possible involving methylene groups. Concomitant cyclization took place to provide the annelated pyrrolidines **6a–c** as single diastereoisomers. The same occurred for the related tetrahydronaphthalene substrates, which displayed additional selective C–H bromination from 1,5- and 1,6-HAT, affording products **6e,f**, which are also formed in a completely diastereoselective manner. In case of a higher excess of hydantoin **2b**, dibrominated ketone **6d** was obtained as a single diastereomer, in which the carbonyl group was formed from hydrolysis of the geminal dibromination product.[8d,21] Use of a longer propyl spacer provided the tribrominated products **6g,h** without cyclization. Control experiments indicated again that free non-guided radical bromination[22c–e] was not competitive with the Hofmann-Löffler reactions in the cases for **6a–h**.[15] Although all products **6a–h** form in high yields, their tendency for decomposition reduced the isolated yields.

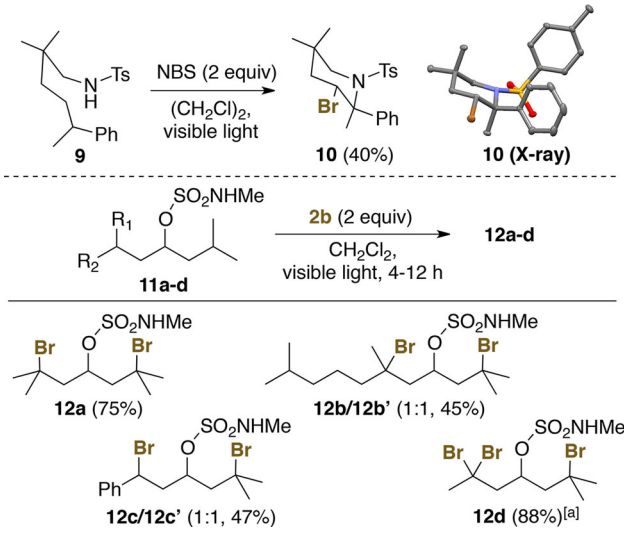
In view of the interesting formation of **6d**, we next sought to stabilize the geminal dibromination motif and, to this end, decided to choose a more flexible cycloheptane ring system (Scheme 4). For mesylated and tosylated derivatives **7a,b**, the expected selective tribromination at the homobenzylic position was obtained. This outcome corresponds to three independent 1,5-HAT processes and exemplifies the potential of sequential Hofmann–Löffler reactions. For the first time, this process has thus been employed for the formation of a geminal dihalogenation motif.[23] In contrast, less stabilized triflamide and trifluoroacetamide amidyl radicals[6b] did not promote halogena-



Scheme 4. Selectivity in multiple C–H amination. Hofmann-Löffler vs. free radical pathways.

tion through the amidyl pathway and only low yields were obtained for products **8c**,**d** due to free-radical benzylic bromination. The outcome in the case of **8a**,**b** suggests that loss of rigidity in the substrate favors multiple halogenation.

To further explore this context, acyclic substrates were investigated. In contrast to cyclic aliphatic substrates, their acyclic counterparts performed less efficiently for sulfonamides. An exception was encountered for acyclic sulfonamide **9**, which under reported conditions[23] underwent dihalogenation followed by amination at the more activated benzylic position and formed diastereomerically pure piperidine **10** (Scheme 5).



Scheme 5. Multiple halogenation of acyclic aliphatic C–H bonds. [a] With 4 equiv of **2b**.

Importantly, N-methyl sulfamates **11a–d** could be applied for amidyl-radical-promoted sequential di- and tribromination within a Hofmann–Löffler pathway. These reactions again occurred through their common 1,6-HAT,[10] and provided selective dibromination affording the symmetric **11a** and the terpene derivative **11b**. For the latter compound, the remote tertiary C–H bond remained intact due to the absence of any free-radical pathway. The reaction is not restricted to tertiary C–H bonds, and provided exclusive double bromination at the benzylic and tertiary positions of **11c**, respectively. Furthermore, in the presence of an excess of hydantoin **2b**, multiple bromination of **11d** allowed access tribrominated **12d** with a geminal dibromination motif.

In summary, we have pioneered conditions that allow for multiple position-selective C–H halogenation reactions within the Hofmann–Löffler manifold. These reactions provide access to various new structures, which derive from unprecedented mixed dihalogenation and polyhalogenation of up to four selective C–H oxidation events and geminal dihalogenation. These results render amidyl radicals important tools for sequential innate C–H halogenation and overall streamline C–H halogenation strategy.

Acknowledgements

Financial support was provided by the Spanish Ministry for Economy and Competitiveness and FEDER (CTQ2017-88496R grant to K.M., and Severo Ochoa Excellence Accreditation 2014–2018 to ICIQ, SEV-2013-0319). H.Z. thanks ICIQ-COFUND Program for a postdoctoral fellowship. The authors are grateful to the CERCA Program of the Government of Catalonia and to COST Action CA15106 "C–H Activation in Organic Synthesis (CHAOS)".

Conflict of interest

The authors declare no conflict of interest.

Keywords: bromine · C–H functionalization · Hofmann–Löffler reaction · iodine · polyhalogenation

[1] a) W.-j. Chung, C. D. Vanderwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 4396; *Angew. Chem.* **2016**, *128*, 4470; b) W.-j. Chung, C. D. Vanderwal, *Acc. Chem. Res.* **2014**, *47*, 718; c) C. Nilewski, E. N. Carreira, *Eur. J. Org. Chem.* **2012**, 1685; d) T. Umezawa, F. Matsuda, *Tetrahedron Lett.* **2014**, *55*, 3003.

[2] a) A. J. Cresswell, S. T.-C. Eey, S. E. Denmark, *Angew. Chem. Int. Ed.* **2015**, *54*, 15642; *Angew. Chem.* **2015**, *127*, 15866; b) A. M. Arnold, A. Ulmer, T. Gulder, *Chem. Eur. J.* **2016**, *22*, 8728; c) U. Hennecke, *Chem. Asian J.* **2012**, *7*, 456.

[3] a) Y. Tan, S. Luo, D. Li, N. Zhang, S. Jia, Y. Liu, W. Qin, C. E. Song, H. Yan, *J. Am. Chem. Soc.* **2017**, *139*, 6431; b) K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch, J. S. Chen, *J. Am. Chem. Soc.* **2011**, *133*, 8134; c) A. J. Cresswell, S. T.-C. Eey, S. E. Denmark, *Nat. Chem.* **2015**, *7*, 146.

[4] a) R. K. Quinn, Z. A. Konst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal, E. J. Alexanian, *J. Am. Chem. Soc.* **2016**, *138*, 696; b) A. Artaryan, A. Mardyukov, K. Kulbitski, I. Avigdori, G. A. Nisnevich, P. R. Schreiner, M. Gandelman, *J. Org. Chem.* **2017**, *82*, 7093; c) S. H. Combe, A. Hosseini, L. Song, H. Hausmann, P. R. Schreiner, *Org. Lett.* **2017**, *19*, 6156; d) J. Ozawa, M. Kanai, *Org. Lett.* **2017**, *19*, 1430; e) R. Y. Zhu, T. G. Saint-Denis, Y. Shao, J. He, J. D. Sieber, C. H. Senanayake, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 5724; f) T. Liu, M. C. Myers, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 306; *Angew. Chem.* **2017**, *129*, 312.

[5] A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58; *Angew. Chem.* **2016**, *128*, 58.

[6] a) M. D. Kärkäs, *ACS Catal.* **2017**, *7*, 4999; b) D. Šakić, H. Zipse, *Adv. Synth. Catal.* **2016**, *358*, 3983.

[7] a) M. E. Wolff, *Chem. Rev.* **1963**, *63*, 55; b) R. S. Neale, *Synthesis* **1971**, 1.

[8] Recent examples: a) J. Long, X. Cao, L. Zhu, R. Qiu, C.-T. Au, S.-F. Yin, T. Iwasaki, N. Kambe, *Org. Lett.* **2017**, *19*, 2793; b) E. A. Wappes, K. M. Nakafuku, D. A. Nagib, *J. Am. Chem. Soc.* **2017**, *139*, 10204; c) N. R. Paz, D. Rodríguez-Sosa, H. Valdés, R. Marticorena, D. Melián, M. B. Copano, C. C. González, A. Herrera, *Org. Lett.* **2015**, *17*, 2370; d) C. Q. O'Broin, P. Fernández, C. Martínez, K. Muñiz, *Org. Lett.* **2016**, *18*, 436.

[9] a) C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287; *Angew. Chem.* **2015**, *127*, 8405; b) P. Becker, T. Duhamel, C. J. Stein, M. Reiher, K. Muñiz, *Angew. Chem. Int. Ed.* **2017**, *56*, 8004; *Angew. Chem.* **2017**, *129*, 8117; c) P. Becker, T. Duhamel, C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2018**, *57*, 5166; *Angew. Chem.* **2018**, *130*, 5262.

[10] Recent examples: a) M. A. Short, J. M. Blackburn, J. L. Roizen, *Angew. Chem.* **2018**, *130*, 302; *Angew. Chem. Int. Ed.* **2018**, *57*, 296; b) S. Sathyamoorthi, S. Banerjee, J. Du Bois, N. Z. Burns, R. N. Zare, *Chem. Sci.* **2018**, *9*, 100.

[11] Ref. [4c].

[12] For alternative approaches to amidyl-mediated C–H halogenation: a) E. M. Dauncey, S. P. Morcillo, J. J. Douglas, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2018**, *57*, 744; b) V. A. Schmidt, R. K. Quinn, A. T. Brusoe, E. J. Alexanian, *J. Am. Chem. Soc.* **2014**, *136*, 14389.

[13] CCDC 1838889 (**3a**), 1838890 (**3b**), 1838891 (**3c**), 1838892 (**3f**), 1838893 (**3g**), 1838894 (**3l**), 183889 (**3m**), 1838896 (**6b**), 1838897 (**6f**), 1838898 (**3k**), 1838899 (**10**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
[14] In contrast, 1-adamantyl derivatives generate product mixtures; see Ref. [15]
[15] Please see Supporting Information for further details.
[16] a) J. Thiele, W. Peter, *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2842; b) J. Thiele, J.; W. Peter, *Justus Liebigs Ann. Chem.* **1909**, *369*, 149; W. Peter, *Justus Liebigs Ann. Chem.* **1909**, *369*, 149; c) F. M. Beringer, H. S. Schultz, *J. Am. Chem. Soc.* **1955**, *77*, 5533.
[17] A. G. Yurchenco, N. I. Kulik, V. P. Kuchar, V. M. Djakovkaja, V. F. Baklan, *Tetrahedron Lett.* **1986**, *27*, 1399.
[18] a) E. J. Corey, W. J. Wechter, *J. Am. Chem. Soc.* **1954**, *76*, 6040; b) K. B. Wiberg, W. E. Pratt, M. G. Matturo, *J. Org. Chem.* **1982**, *47*, 2720.
[19] Y. Ohga, K. Takeuchi, *J. Phys. Org. Chem.* **1993**, *6*, 293.
[20] I. Saikia, A. J. Borah, P. Phukan, *Chem. Rev.* **2016**, *116*, 6837.
[21] M. Katohgi, H. Togo, K. Yamaguchi, Y. Masataka, *Tetrahedron* **1999**, *55*, 14885.
[22] a) C. Djerassi, *Chem. Rev.* **1948**, *43*, 271; b) P. S. Skell, J. C. Day, *Acc. Chem. Res.* **1978**, *11*, 381; c) K. Shibatomi, Y. Zhang, H. Yamamoto, *Chem. Asian J.* **2008**, *3*, 1581; d) M. Movassaghi, M. A. Schmidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 3725; *Angew. Chem.* **2007**, *119*, 3799; e) D. Dominguez, R. J. Ardecky, M. P. Cava, *J. Am. Chem. Soc.* **1983**, *105*, 1608.
[23] During review, a complimentary dihalogenation process was reported: E. A. Wappes, A. Vanitcha, D. A. Nagib, *Chem. Sci.* **2018**, *9*, 4500.
[24] H. Zhang, K. Muñiz, *ACS Catal.* **2017**, *7*, 4122.

Manuscript received: September 4, 2018
Accepted manuscript online: September 6, 2018
Version of record online: ■■ ■■, 0000

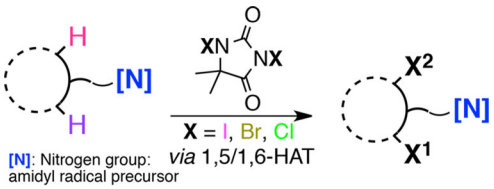
COMMUNICATION

C–H Halogenation

*E. Del Castillo, M. D. Martínez, A. E. Bosnidou, T. Duhamel, C. Q. O'Broin, H. Zhang, E. C. Escudero-Adán, M. Martínez-Belmonte, K. Muñiz**

■■ – ■■

Multiple Halogenation of Aliphatic C–H Bonds within the Hofmann–Löffler Manifold



Scope for cyclic and linear C-H bonds
Site-selective multiple halogenation
Mixed halogenation

More than one at a time! Multiple site-selective C–H halogenation events can be accomplished as an innovative variant of the classic Hofmann–Löffler reaction by using halogenated hydantoins as oxidant and halide source. The reaction scope includes cyclic and linear hydrocarbons, as well as vicinal and geminal halogenation.