Communication

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Catalytic Chemo-, Regio-, and Enantioselective Bromochlorination of Allylic Alcohols

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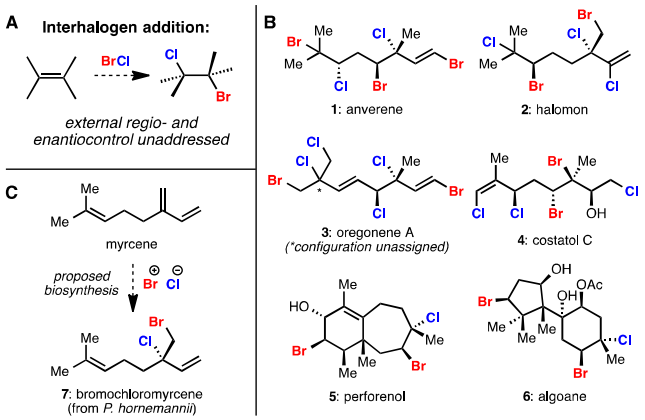
Supporting Information Placeholder

ABSTRACT: Herein we describe a highly chemo-, regio-, and enantioselective bromochlorination reaction of allylic alcohols, employing readily available halogen sources and a simple Schiff base as the chiral catalyst. The application of this interhalogenation reaction to a variety of substrates, the rapid enantioselective synthesis of a bromochlorinated natural product, and preliminary extension of this chemistry to dibromination and dichlorination are reported.

Alkene dihalogenation is a classic *anti*-difunctionalization reaction of carbon–carbon double bonds with few enantioselective variants.[1] Despite impressive recent work in the stereoselective synthesis of vicinal dichlorides and polychlorinated natural products,[2–7] no general methods exist for the enantio- and regioselective addition of two halogen atoms across non-conjugated olefins.[8–10] Additionally, catalyst control over the regioselective addition of two *different* halogens (heterodihalogenation or *interhalogen*ation) to an alkene is unprecedented (Fig. 1A). This lack of a general enantioselective method for alkene dihalogenation represents a significant gap in regio- and stereoselective methodology that remains unsolved, despite the prevalence of chiral bioactive poly- and interhalogenated compounds in nature[11,12] and the widespread use of alkyl halides as intermediates in organic synthesis.

Nearly 2,000 halogenated natural products that contain either a chlorine- or a bromine-bearing stereocenter have been identified from natural sources.[11,12] Many of these natural products demonstrate potent and selective biological activities,[11–17] which have remained underexplored at times explicitly due to a lack of isolable material.[16,17] The enzymatic machinery responsible for dihalogenation is not yet known,[18] but many polyhalogenated secondary metabolites appear to arise from the selective dibromination, dichlorination, or bromochlorination of unsaturated terpenes (**1–6**, Fig. 1B).[19] The cytotoxic[17] secondary metabolite bromochloromyrcene (**7**), for example, is proposed[19,20] to derive biosynthetically from myrcene via electrophilic bromination and Markovnikov delivery of chloride across one of three double bonds (Fig. 1C). This would represent a remarkable example of selectivity that has yet to be achieved in the laboratory. To this end, we report the development of a catalytic chemo-, regio-, and enantioselective bromochlorination reaction of allylic alcohols. This method provides access to a wide range of interhalogenated compounds that were previously inaccessible, even in racemic form. Furthermore, preliminary results suggest that this strategy will be generalizable to enantioselective dichlorination and dibromination.

FIGURE 1. Alkene bromochlorination is an interhalogenation reaction used by nature with no synthetic regio- and/or enantioselective equivalent.

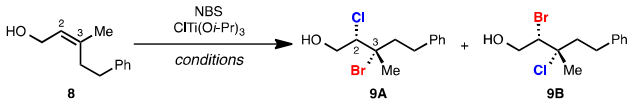


Recently, we reported a titanium-based enantioselective dibromination of allylic alcohols wherein high enantioselectivity was obtained only for substrates in which the regioselectivity of halide delivery was electronically biased (e.g. cinnamyl alcohols).[21] This limitation in substrate scope is attributed to a unique mechanistic challenge inherent to enantioselective

alkene dihalogenation: each enantiomer of the cyclic halonium intermediate can be opened by halide ion to form two possible constitutional isomers.[2,8,21] When the electrophilic and nucleophilic halogen atoms are the same element, the two products of regioisomeric opening are enantiomers. When the electrophilic and nucleophilic halogen atoms are different, four *distinct* products can be formed. Interested in exploring this interplay between regioselectivity and enantioselectivity and cognizant of the fact that catalyst-controlled interhalogenation of carbon–carbon double bonds did not exist, we directed our efforts to designing a system capable of selective bromochlorination of allylic alcohols. It was anticipated that the development of such chemistry would enable access to a broad range of interhalogenated natural product motifs while providing mechanistic insight by allowing independent quantification of enantioselectivity and regioselectivity.

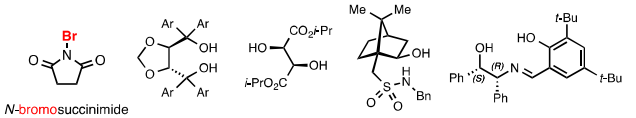
Table 1 summarizes the optimization of this selective bromochlorination reaction. When allylic alcohol **8** was treated with pyridinium chloride and *N*-bromosuccinimide (NBS), a convenient non-disproportionating equivalent to bromine monochloride,[22,23] a constitutional isomer ratio (cr) of 1:4 was obtained for **9A** and **9B**, favoring chloride addition to C3 (Table 1, entry 1). This is consistent with the electronic preference for nucleophiles to add to non-symmetric halonium intermediates in a Markovnikov fashion.[24] With chlorotitanium triisopropoxide and NBS, the inherent sense of regioselectivity was maintained, albeit in a lower ratio (entry 2). Diol **10** exerted a small influence on selectivity (entry 3), but further ligand investigations (**11**–**13**, entries 4–6) identified tridentate Schiff base **13**[25] as being particularly promising. When 50 mol % **13** was added to the reaction mixture, equal amounts of the two constitutional isomers were formed, but significant enantiomeric excess (ee) was observed only for the isomer arising from delivery of chloride to C2 (entry 6). This difference in enantioselectivity between constitutional isomers could have been deconvolved only through studying interhalogenation. A crucial finding was that in nonpolar solvents, such as hexanes, the regioselectivity of this Schiff base-catalyzed bromochlorination favors anti-Markovnikov halide addition to C2, with a concomitant improvement in enantioselectivity (entry 7). Optimal selectivities were observed at lower temperatures (–20 °C), conditions that allow for a reduction in catalyst loading (entries 8 and 9). Here, nearly exclusive formation of anti-Markovnikov product **9A** was observed, demonstrating that this system is capable of overriding inherent substrate bias. Such external regiocontrol over halogenation provides access to compounds for which separation or resolution of isomers would otherwise be non-trivial.

TABLE 1. Development of an enantio- and regioselective bromochlorination of allylic alcohols.



8 **9A** **9B**

entry	*conditions*	yield **9A** + **9B** (%)	**9A** : **9B** (cr)	ee **9A**, ee **9B** (%)
1	Pyr•HCl *instead of* ClTi(O*i*-Pr)$_3$ CH_2Cl_2, r.t.	80	1 : 4	–
2	CH_2Cl_2, r.t.	85	1 : 2	–
3	50 mol % **10**, CH_2Cl_2, r.t.	88	1 : 2	6, 8
4	50 mol % **11**, CH_2Cl_2, r.t.	73	1 : 2	12, 6
5	50 mol % **12**, CH_2Cl_2, r.t.	89	1 : 1	17, 0
6	50 mol % **13**, CH_2Cl_2, r.t.	67	1 : 1	63, 6
7	50 mol % **13**, hexanes, r.t.	70	8 : 1	94, 52
8	50 mol % **13**, hexanes, –20 °C	80	> 20 : 1	98, –
9	10 mol % **13**, hexanes, –20 °C	88	> 20 : 1	94, –

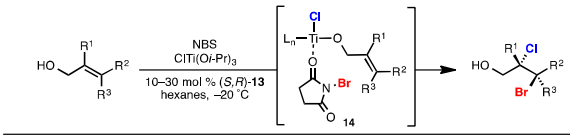


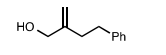
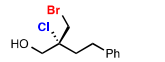
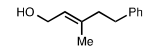
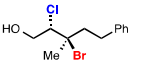
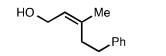
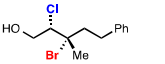
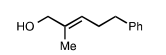
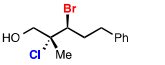
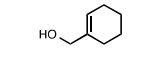
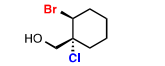
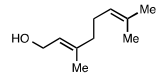
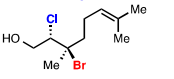
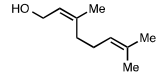
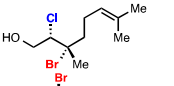
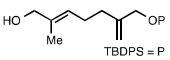
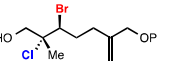
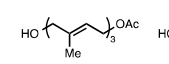
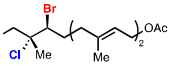
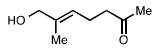
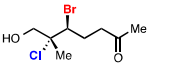
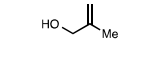
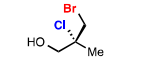
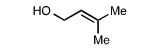
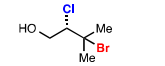
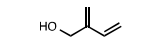
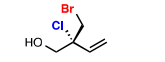
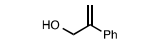
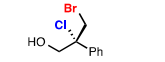
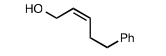
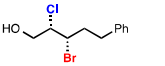
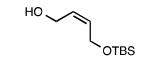
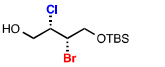
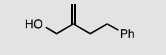
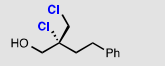
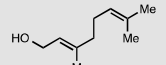
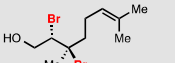
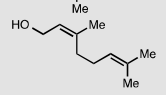
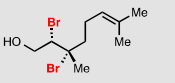
N-bromosuccinimide (NBS) **10**: Ar = 2-Np **11** **12** (*S*,*R*)-**13**

Reactions were conducted on 0.1 mmol scale; constitutional isomers assigned based on observation of ^{13}C-NMR chlorine isotopic shifts; absolute configuration of **9A** assigned by X-ray crystallography; absolute configuration of **9B** not determined.

Under the optimized conditions, five prevalent dihalogenated terpenoid motifs could be produced on preparative scale in high yields and with high levels of selectivity (Table 2, entries 1–5). Substrates with multiple olefins are halogenated with high chemoselectivity at the less nucleophilic allylic alcohol alkene (entries 6–9, and 13). Ester (entry 9), ketone (entry 10), and silyl ether (entries 8 and 16) functionalities are also well tolerated. 1,1-Disubstituted (entries 1, 11, 13, and 14), trisubstituted (entries 2–10, and 12), and *cis*-disubstituted alkene (entries 15 and 16) substrates are bromochlorinated selectively under these conditions. *trans*-Disubstituted alkenes react with poor regioselectivity, and significant enantio- and regioselectivity have not yet been observed for alkenes lacking allylic hydroxyl functionality. Absolute configuration was assigned for several products or derivatives (entries 1, 3, 6, and 10) by X-ray crystallography. A proposed intermediate for this reaction is shown at the top of Table 2 that invokes a ligand- and substrate-bound titanium complex (**14**) wherein the halide is delivered to the nearest olefinic carbon.

TABLE 2. Substrate scope.

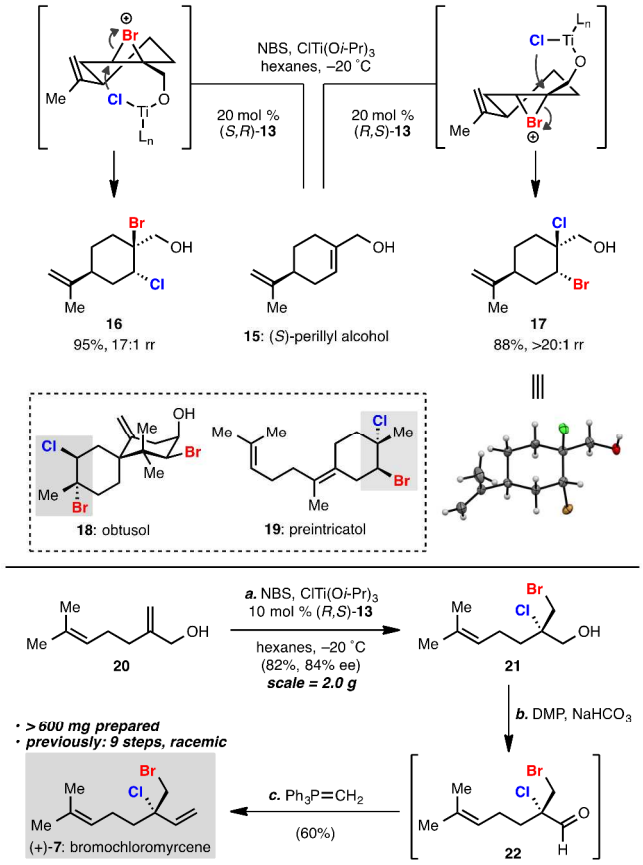


entry	substrate	product	yield (%)	ee (%)	cr	mol % **13**
1			88	89	>20 : 1	20
2			94	89	8 : 1	10
3			89	92	18 : 1	10
4			60	92	>20 : 1	10
5			86	94	6 : 1	20
6			69	96	6 : 1	20
7			73	97	14 : 1	20
8			64	78	>20 : 1	10
9			75	92	>20 : 1	20
10[a]			56	91	>20 : 1	30
11			59	90	>20 : 1	20
12			82	96	7 : 1	10
13			74	88	>20 : 1	10
14			57	82	>20 : 1	20
15			92	91	>20 : 1	20
16			70	91	>20 : 1	10
17[b]			61	90	–	30
18[c]			74	92	–	20
19[c]			78	95	–	20

Conditions unless otherwise noted: ≥ 1 mmol scale, 1.05 equiv NBS, 1.10 equiv ClTi(O*i*-Pr)$_3$, 10–30 mol % (*S,R*)-**13**, hexanes, –20 °C, 4–12 hours; constitutional isomers assigned based on observation of ^{13}C-NMR chlorine isotopic shifts; reported isolated yields are for the sum of constitutional isomers; ***a.*** solvent = 3:1 hexanes/CCl_4; ***b.*** 1.05 equiv *tert*-butyl hypochlorite used in place of NBS; ***c.*** 1.10 equiv BrTi(O*i*-Pr)$_3$ used in place of ClTi(O*i*-Pr)$_3$.

Using *tert*-butyl hypochlorite and chlorotitanium triisopropoxide (entry 17) or NBS and bromotitanium triisopropoxide (entries 18 and 19), enriched dichlorides or dibromides are produced that map directly onto known dihalogenated natural product motifs (**3** and **4**, Figure 1).

Scheme 1. Applications of selective bromochlorination.



Reagents and conditions: ***a.*** NBS (1.05 equiv), ClTi(O*i*-Pr)$_3$ (1.10 equiv), 10 mol % (*R,S*)-**13**, hexanes, –20 °C; ***b.*** Dess–Martin periodinane (DMP) (1.5 equiv), $NaHCO_3$ (10.0 equiv), CH_2Cl_2, r.t.; ***c.*** methyltriphenylphosphonium bromide (1.8 equiv), sodium hexamethyldisilazide (NaHMDS) (1.4 equiv), toluene, –78 °C to 0 °C, 60% over two steps.

Substantial catalyst influence has also been observed with enantioenriched (*S*)-perillyl alcohol (**15**, Scheme 1, top). When **15** was subjected to bromochlorination conditions employing (*S,R*)-**13**, bromochloride **16** was formed as the major product. When enantiomeric (*R,S*)-**13** was used, constitutional isomer **17** was produced almost exclusively. The unusual preference for chloride delivery to the distal olefinic carbon in the former case (**16**) is rationalized as a combination of catalyst facial control of alkene halogenation with the requirement for *trans*-diaxial delivery of halogens to a conformationally restricted cyclohexene.[26] Both isomeric bromochlorocyclohex-

ane motifs in **16** and **17** can be found within several natural products including obtusol[27] (**18**) and preintricatol[28] (**19**).

The utility of the bromochloroalcohol motif is illustrated by a short chemo-, regio-, and enantioselective synthesis of (+)-bromochloromyrcene (**7**). Selective bromochlorination of known alcohol **20** on multigram scale provided **21**, which was readily converted into (+)-(**7**) in two steps via aldehyde **22** (Scheme 1, bottom). This natural product was prepared previously in racemic form in 9 steps.[29] An optical rotation taken at the same concentration (c = 147 mg/mL) as the original isolation[20] suggests that natural bromochloromyrcene is produced in only ca. 35% ee, raising an intriguing question about the level of enantiocontrol in its biosynthesis. The present methodology should facilitate future investigations into the degree of enantiopurity of similar natural products.

External enantio- and regiocontrol in alkene interhalogenation has been demonstrated. The developed method is practical and scalable given the trivial cost of reagents and the ease of preparation of the chiral ligand. Multiple organohalogen building blocks can now be readily accessed in isomerically enriched form. We anticipate that this chemistry will enable enantioselective syntheses of a wide variety of polyhalogenated natural products. Such investigations are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterizations, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, 2009. (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: New York, 1999.

(2) (a) Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134–8137. (b) Monaco, M. R.; Bella, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11044–11046.

(3) (a) Nilewski, C.; Deprez, N. R.; Fessard, T. C.; Li, D. B.; Geisser, R. W.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7940–7943. (b) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature* **2009**, *457*, 573–576. (c) Nilewski, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2012**, *9*, 1685–1698.

(4) (a) Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744–5745. (b) Brucks, A. P.; Treitler, D. S.; Liu, S.-A.; Snyder, S. A. *Synthesis* **2013**, *45*, 1886–1898.

(5) (a) Chung, W.-J.; Carlson, J. S.; Vanderwal, C. D. *J. Org. Chem.* **2014**, *79*, 2226–2241. (b) Chung, W. J.; Vanderwal, C. D. *Acc. Chem. Res.* **2014**, *47*, 718–728.

(6) (a) Yoshimitsu, T.; Fukumoto, N.; Nakatani, R.; Kojima, N.; Tanaka, T. *J. Org. Chem.* **2010**, *75*, 5425–5437. (b) Umezawa, T.; Shibata, M.; Kaneko, K.; Okino, T.; Matsuda, F. *Org. Lett.* **2011**, *13*, 904–907. (c) Yoshimitsu, T.; Nakatani, R.; Kobayashi, A.; Tanaka, T. *Org. Lett.* **2011**, *13*, 908–911. (d) Umezawa, T.; Matsuda, F. *Tetrahedron Lett.* **2014**, 55, 3003–3012.

(7) Recently a catalytic, stereospecific, *syn*-dichlorination of alkenes was reported: Cresswell, A. J.; Eey, S. T.-C.; Denmark, S. E.; *Nature Chem.* **2015**, *7*, 146–152.

(8) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10938–10953.

(9) Chen, J.; Zhou, L. *Synthesis* **2014**, *46*, 586–595.

(10) Cheng, Y. A.; Yu, W. Z.; Yeung, Y.-Y. *Org. Biomol. Chem.* **2014**, *12*, 2333–2343.

(11) Gribble, G. W. Naturally Occurring Organohalogen Compounds – A Comprehensive Survey; Springer-Verlag: Wien, 1996.

(12) Gribble, G. W. Naturally Occurring Organohalogen Compounds – A Comprehensive Update; Springer-Verlag: Wien, 2010.

(13) Fuller, R. W.; Cardellina, J. H., II; Kato, Y.; Brinen, L. S.; Clardy, J.; Snader, K. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 3007–3011.

(14) Andrianasolo, E. H.; France, D.; Cornell-Kennon, S.; Gerwick, W. H. *J. Nat. Prod.* **2006**, *69*, 576–579.

(15) Kladi, M.; Vagias, C.; Roussis, V. *Phytochem. Rev.* **2014**, *3*, 337–366.

(16) Vogel, C. V.; Pietraszkiewicz, H.; Sabry, O. M.; Gerwick, W. H.; Valeriote, F. A.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 12205–12209.

(17) Fuller, R. W.; Cardellina, J. H.; Jurek, J.; Scheuer, P. J.; Alvarado-Lindner, B.; McGuire, M.; Gray, G. N.; Steiner, J. R.; Clardy, J.; Menez, E.; Shoemaker, R. H.; Newman, D. J.; Snader, K. M.; Boyd, M. R. *J. Med. Chem.* **1994**, *37*, 4407–4411.

(18) Vaillancourt, F. H.; Yeh, E.; Vosburg, D. A.; Garneau-Tsodikova, S.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3364–3378.

(19) Burreson, J. B.; Woolard, F. X.; Moore, R. E. *Chem. Lett.* **1975**, *4*, 1111–1114.

(20) Woolard, F. X.; Moore, R. E.; Mahendran, M.; Sivapalan, A. *Phytochemistry* **1976**, *15*, 1069–1070.

(21) Hu, D. X.; Shibuya, G. M.; Burns, N. Z. *J. Am. Chem. Soc.* **2013**, *135*, 12960–12963.

(22) Popov, A. I.; Mannion, J. J. *J. Am. Chem. Soc.* **1952**, *74*, 222–224.

(23) Buckles, R. E.; Long, J. W. *J. Am. Chem. Soc.* **1951**, *73*, 998–1000.

(24) De la Mare, P. D. B. Electrophilic Halogenation; Cambridge Univ. Press: Cambridge, 1976.

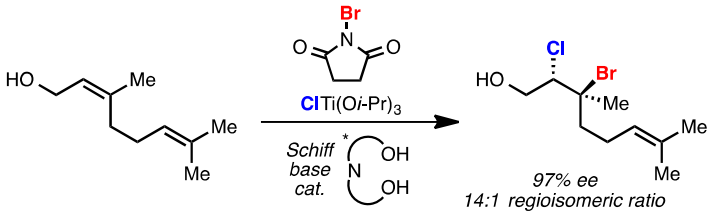
(25) (a) Jiang, Y.; Zhou, X.; Hu, W.; Wu, L.; Mi, A. *Tetrahedron: Asymmetry* **1995**, *6*, 405–408. (b) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611–1613.

(26) (a) Hageman, H. J.; Havinga, E. *Rec. Trav. Chim.* **1966**, *85*, 1141–1150. (b) Fürst, A.; Plattner, P. A. *Helv. Chim. Acta.* **1949**, *32*, 275–283.

(27) Perales, A.; Martínez-Ripoll, M.; Fayos, J. *Acta Cryst. B* **1979**, *35*, 2771–2773.

(28) König, G. M.; Wright, A. D. *J. Nat. Prod.* **1994**, *57*, 477–485.

(29) Jung, M. E.; Parker, M. H. *J. Org. Chem.* **1997**, *62*, 7094–7095.



*catalyst-controlled selective **interhalogenation***