Tetrahedron Letters 57 (2016) 4477–4479

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The practical stereocontrolled synthesis of vicinal halohydrins and haloamines from vinyl epoxides and vinyl aziridines

Łukasz J. Weseliński [a], Michael J. Grillo [a,b], Marina Tanasova [a,*]

[a] Department of Chemistry, Michigan Technological University, 1400 Townsend Drive, Houghton, MI 49931, USA
[b] Department of Medicinal Chemistry, University of Minnesota, 308 Harvard Street SE, Minneapolis, MN 55455, USA

ARTICLE INFO

Article history:
Received 20 July 2016
Revised 19 August 2016
Accepted 20 August 2016
Available online 22 August 2016

Keywords:
α,β-Unsaturated-γ,δ-epoxyesters
Vinylepoxides
Vinylaziridines
Vicinal chloroamines

ABSTRACT

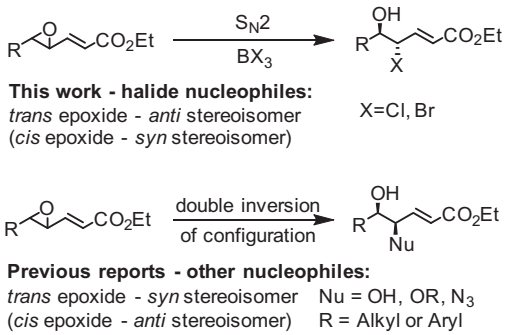
A new metal-free method is reported for the stereocontrolled opening of vinyl epoxides using boron trichloride or tribromide to yield the corresponding vicinal chlorohydrins and bromohydrins with high regioselectivities and exclusive diastereoselectivity. Synthesis of vicinal haloamines from vinyl aziridines was also demonstrated under the same conditions.

Vicinal halohydrins are useful synthetic intermediates in the synthesis of marine natural products,[1] including stereochemically complex chlorosulfolipids.[1b,d,e] Therefore, their stereoselective synthesis remains an attractive synthetic target. A variety of stereoselective substitution reaction of epoxides and vinyl epoxides by the S_N2 mechanism have been reported. However, there is still a room to improve the efficiency and the simplicity of the reaction.[2] Furthermore, the processes including double inversion of configuration (retention) are mostly limited to boronic/boric acids,[3a,3b] azides,[3c] and alkoxy or phenoxy[3d] nucleophiles, reacting with unsaturated epoxides in the presence of suitable boron reagents and palladium catalyst. Broadening the scope of such transformations would be very useful for organic synthesis, providing the access to both stereochemical products from the same precursor (Scheme 1). To the best of our knowledge, no such process has been demonstrated with halide nucleophiles.[2,4] Here, we report the results of our investigations that led to the development of the mild method for the practical stereocontrolled synthesis of vicinal halohydrins and haloamines from unsaturated three-member ring heterocycles, that proceeds through the S_N2 displacement.

Vinyl epoxides, possessing strong electron withdrawing group at the double bond, allow for higher regioselectivity control of the epoxide opening, due to their increased reactivity for a nucleophilic attack of halides at the allylic position.[2] Therefore, it seemed interesting to investigate the reaction of vinyl esters with the boron halides. We speculated that the palladium-catalyzed reaction of boron trihalide reagents with α,β-unsaturated-γ,δ-epoxyesters would involve the formation of π-allyl palladium intermediates, which might undergo an intramolecular nucleophilic attack by halides at the γ-position with a double inversion of the configuration, yielding syn-opening of the epoxide.[3] Alternatively, an S_N2 displacement would lead the anti-opening of the epoxide (Scheme 1). All of the epoxide substrates tested in this study were obtained in racemic form by the sequence consisting of epoxidation of allylic alcohols by mCPBA, Parikh-Doering oxidation of hydroxyl group and Wittig or Horner–Wadsworth–Emmons olefination. For the initial studies, we selected (*E*)-ethyl 6-benzyloxy-*cis*-4,5-epoxy-2-hexenoate[3a] (**1a**, Table 1, entry 1) as a model substrate and tested its reactions with 3 equiv of commercial solution of boron trichloride in dichloromethane (1 M) in the presence of palladium catalyst ($Pd(PPh_3)_4$, 10 mol%). A screen of solvents revealed that ethereal (such as tetrahydrofuran, 2-methyltetrahydrofuran, dioxane, diethyl ether, isopropyl ether, methyl tert-butyl ether) or non-polar solvents (like dichloromethane or toluene) were not suitable, leading to either mixture of products or decomposition of the starting material. The reaction performed best in neat ethanol or methanol. In the latter case, a high level of transesterification of the ethyl esters was observed, and the products were isolated mostly as the methyl esters (entry 1, footnote b); higher order alcohols (2-propanol, 2-methyl-2-butanol) were less successful in terms of yields and purities. The products were obtained as a

* Corresponding author. Tel.: +1 906 487 1163; fax: +1 906 487 2061.
E-mail address: mtanasov@mtu.edu (M. Tanasova).

http://dx.doi.org/10.1016/j.tetlet.2016.08.070
0040-4039/



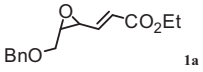
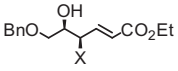
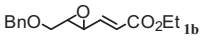
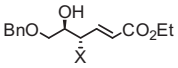
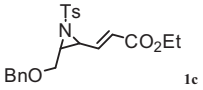
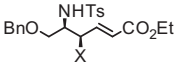
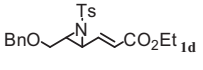
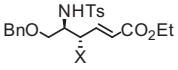
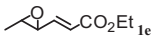
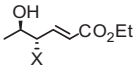
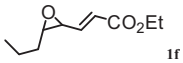
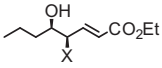
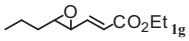
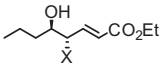
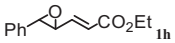
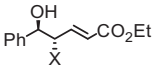
Scheme 1. Alternative stereochemistry of the epoxide opening reactions.

single diastereomer in good yields with high regiocontrol (>95:5), after the concentration of the reaction mixture in vacuo and its chromatographic purification on a short silica pad. However, we found that under these conditions reactions proceeded quickly also in the absence of palladium catalyst.[5] In both cases the stereochemical result was the same; as shown in Table 1, the reactions of *cis*-epoxide **1a** led to *syn*-chlorohydrin **2a** (entry 1), resulting from the inversion of configuration. The stereochemistry of the model product was confirmed by the independent synthesis of *anti*-chlorohydrin **2c** (entry 3) from *trans*-epoxide **1b** by the trimethylsilyl chloride/charcoal method[6b] and the comparison of its proton NMR spectra. Additives like pinacol[3d] or varying the ratio of boron halide to the substrate has not changed the stereochemical outcome of the reaction. The reaction was successful also with substoichiometric amounts of BCl_3 (0.7 equiv), indicating the efficiency of halide transfer. Replacing boron trichloride with boron tribromide (commercial 1 M solution in dichloromethane) afforded the corresponding bromohydrin **2b** (entry 2) in high yields and high selectivities.

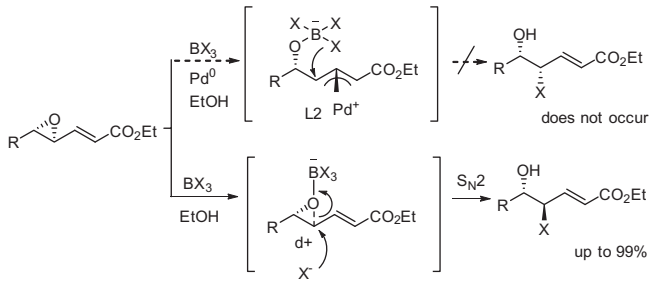
Under all the tested conditions, an intramolecular attack of the halide that would lead to a double inversion of configuration does not occur, even if the reaction conditions allow the formation of the putative π-allyl palladium intermediates. These results suggest that the halide ion is not delivered from the epoxide-coordinated boron halide[3] but is present in the reaction solution. The presence of the free halide suggests a rapid hydrolysis of BX_3 to $B(OR)_3$ in the presence of ROH. Also, unlike other nucleophiles tested for the processes involving a double inversion of configuration, reaction with halides does not require additional activation of the allylic position of the α,β-unsaturated-γ,δ-epoxyester substrate for a nucleophilic attack. A plausible reaction mechanism would imply the activation of the C-heteroatom bond of the heterocycle by a coordination of the BX_3 (or BOR_3) and the subsequent attack of the halide ion at the γ-position (allylic) proceeding through the S_N2 type substitution (Scheme 2).[2]

The protocol seems synthetically attractive, affording highly pure S_N2 type products under simple conditions in short times and without the need for additional work-up steps, such as the deprotection of silyl ethers for the methods involving the use of TMSCl as a reagent.[6] Taking advantage of simplicity and practicability of our method, we tested several other substrates (Table 1) under these conditions. We obtained products **2c–d** with high yields and regiocontrol (entries 3–4). The obtained compounds

Table 1
Substrate scope for the reaction of vinyl epoxides and azidiridines with boron trihalides

Entry	Substrate	BX_3	Product		Time (h)	Yield (%)	Footnotes
1	 **1a**	BCl_3		**2a** X = Cl	3	88	a, b
2		BBr_3		**2b** X = Br	3.5	85	a
3	 **1b**	BCl_3		**2c** X = Cl	21	86	a
4		BBr_3		**2d** X = Br	4	90	a
5	 **1c**	BCl_3		**2e** X = Cl	4	99	a
6		BBr_3		**2f** X = Br	3	99	a
7	 **1d**	BCl_3		**2g** X = Cl	6.5	96	a
8		BBr_3		**2h** X = Br	5.5	74	a
9	 **1e**	BCl_3		**2i** X = Cl	5	93	a, c
10		BBr_3		**2j** X = Br	3	97	a, d
11	 **1f**	BCl_3		**2k** X = Cl	5	93	a, e
12		BBr_3		**2l** X = Br	5	92	a, f
13	 **1g**	BCl_3		**2m** X = Cl	4	99	a
14		BBr_3		**2n** X = Br	4	97	a
15	 **1h**	BCl_3		**2o** X = Cl	3.5	83	g
16		BBr_3		**2p** X = Br	3	-	g, h

[a] EtOH as a solvent.
[b] In MeOH >85% of transesterification with similar yields of the product (see Supplementary Material).
[c] Regioisomeric ratio of >90:10 determined by ^{1}H NMR by integration of methyl group signals (doublets at 1.24 and 1.46 ppm, respectively).
[d] Regioisomeric ratio of >95:5 determined by ^{1}H NMR by integration of methyl group signals (doublets at 1.27 and 1.65 ppm, respectively).[9b]
[e] Regioisomeric ratio of ca 4:1 determined by ^{1}H NMR by integration of methine group signals (multiplets at 3.74 and 3.98 ppm, respectively).
[f] Regioisomeric ratio of ca 5:1 determined by ^{1}H NMR by integration of α-carbon proton signals (doublets of doublets at 7.05 and 6.91 ppm, respectively).
[g] Et_2O as a solvent.
[h] A mixture of polymeric products.



Scheme 2. Plausible mechanisms of the epoxide opening reactions mediated by boron trihalides.

are stable under the reaction conditions, with similar yields obtained for the reaction times between 3 and 21 hrs (entries 1 and 3). Next, to probe the scope of the heterocycle component, we tested the reactions of novel vinyl *N*-tosyl azidirines **1c** and **1d** to obtain haloamines **2e–h** (entries 5–8) with excellent yields as well as high levels of regioselectivity. The aziridines **1c** and **1d** were prepared in good yields and with excellent *E*-selectivities by Horner–Wadsworth–Emmons olefination[7] of the aziridine 2-carboxaldehydes developed by the Borhan group (see Supplementary Material for details).[8]

Using ^{1}H NMR, we were not able to detect the presence of any significant amounts of regioisomeric products (>5%) for the reactions of substrates **1a–d** bearing a benzyloxymethyl group on the epoxide ring (entries 1–8). For the reaction of smaller (*E*)-ethyl *trans*-4,5-epoxy-2-hexenoate (**1e**) with the adjacent methyl substituent, a similar regioisomeric ratio of >95:5 for the obtained bromohydrin **2j** was readily determined by integration of methyl group signals in ^{1}H NMR spectra (entry 10, see footnote d).[9b] The minor regioisomer results from the attack of the halide at the homoallylic position. By analogy, we determined the regioisomeric ratio of >90:10 for the corresponding chlorohydrin **2i** (entry 9, see footnote c). The significantly lower regioselectivities (ca. 4:1–5:1) were obtained only for the reactions of propyl substituted *cis*-epoxide **1f**[10] (entries 11–12, and footnotes e and f, respectively), while its *trans*-isomer **1g**[10] afforded products **2m–n** with much higher selectivities (<5% of regioisomers, entries 13–14). These results show that the combination of both steric and electronic effects can be responsible for the control of regiochemistry. Notably, all products in Table 1 were obtained with exclusive diastereoselectivity, favoring the formation of the anti stereoisomers for the *trans* configuration of the starting materials, supporting the S_N2 mechanism.

The more challenging electron-deficient cinnamyl derivative **1h**[9] possessing an additional activated benzylic position, reacted successfully with boron trichloride to produce *anti*-chlorohydrin **2o** (entry 15) as a major regioisomer, after changing the solvent to diethyl ether. This compound could not be obtained by the TMSCl/charcoal protocol[6b] or other methods.[9a] However, we were not able to isolate the corresponding bromohydrin **2p** (entry 16, reported as a 2:1 mixture of regioisomers[9b]) in pure form; a mixture of polymeric products was detected in the ^{1}H NMR and ESI-MS spectra. It is noteworthy that under our standard conditions (i.e. MeOH or EtOH as solvent), we observed competitive epoxide opening and this side-product could not be separated.

In summary, we developed a practical method for the stereocontrolled synthesis of vicinal halohydrins from α,β-unsaturated-γ,δ-epoxyesters, that utilizes boron halides as a source of halide. A variety of chloro- and bromohydrins were obtained with high yields and selectivities, including cinnamyl derivative. We also demonstrated the examples of vicinal haloamines, obtained from the same reaction of the corresponding vinyl *N*-tosylaziridines.

Acknowledgment

We gratefully acknowledge financial support from Michigan Technological University (Start-up funds, Prof. Tanasova).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08.070.

References and notes

1. (a) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1983; Vol. V, pp 131–257; (b) Elovson, J.; Vagelos, P. R. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957–963; (c) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49; (d) Nilewski, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2012**, 1685–1698; (e) Chung, W.-J.; Vanderwal, C. D. *Acc. Chem. Res.* **2014**, *47*, 718–728.
2. (a) Olofsson, B.; Somfai, P. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; pp 315–443; (b) Pineschi, M.; Bertolini, F.; Di Bussolo, V.; Crotti, P. In *Advances in Organic Synthesis*; Atta-ur-Rahman, Ed.; Bentham Science: Sharjah, United Arab Emirates, 2013; Vol. 5, pp 101–184; (c) Pineschi, M.; Bertolini, F.; Di Bussolo, V.; Crotti, P. *Curr. Org. Synth.* **2009**, *6*, 290–324; (d) He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, 8037–8128.
3. (a) Hirai, A.; Yu, X.-Q.; Tonooka, T.; Miyashita, M. *Chem. Commun.* **2003**, 2482–2483; (b) Yu, X.-Q.; Hirai, A.; Miyashita, M. *Chem. Lett.* **2004**, *33*, 764–765; (c) Miyashita, M.; Mizutani, T.; Tadano, G.; Iwata, Y.; Miyazawa, M.; Tanino, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5094–5097; (d) Yu, X.-Q.; Yoshimura, F.; Ito, F.; Sasaki, M.; Hirai, A.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 750–754.
4. For palladium-catalyzed nucleophilic openings of epoxides, see: Muzart, J. *Eur. J. Org. Chem.* **2011**, 4717–4741 and references cited therein.
5. *General procedure:* To a solution of substrate (0.35–0.5 mmol) in the corresponding solvent (2–3 ml) at 0 °C under Ar were added 3 equiv of boron trihalide (1 M in CH_2Cl_2), and the mixture was stirred for 3–24 h allowing to warm up. It was concentrated under vacuum and the products were purified by chromatography on a short pad of silica eluting with 30–40% ethyl acetate in hexane.
6. (a) Murakami, T.; Shimizu, T.; Taguchi, K. *Tetrahedron* **2000**, *56*, 533–545; (b) Yoshimura, F.; Matsui, A.; Hirai, A.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2009**, *50*, 5126–5129; (c) Nilewski, C.; Geisser, R. W.; Ebert, M.-O.; Carreira, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 15866–15876.
7. Righi, G.; Bovicelli, P.; Tirotta, I. *Synthesis* **2012**, *44*, 3202–3208.
8. Kulshrestha, A.; Schomaker, J. M.; Holmes, D.; Staples, R. J.; Jackson, J. E.; Borhan, B. *Chem.-Eur. J.* **2011**, *17*, 12326–12339.
9. (a) Díaz, D.; Martín, T.; Martín, V. S. *J. Org. Chem.* **2001**, *66*, 7231–7233; (b) Ha, J. D.; Kim, S. Y.; Lee, S. J.; Kang, S. K.; Ahn, J. H.; Kim, S. S.; Choi, J.-K. *Tetrahedron Lett.* **2004**, *45*, 5969–5972; (c) Righi, G.; Salvati Manni, L.; Bovicelli, P.; Pelagalli, R. *Tetrahedron Lett.* **2011**, *52*, 3895–3896.
10. (a) Righi, G.; Mandic', E.; Naponiello, G. C. M.; Bovicelli, P.; Tirotta, I. *Tetrahedron* **2012**, *68*, 2984–2986; (b) Righi, G.; Bovicelli, P.; Barontini, M.; Tirotta, I. *Green Chem.* **2012**, *14*, 495–502; (c) Righi, G.; Bovicelli, P.; Tirotta, I. *Tetrahedron Lett.* **2013**, *54*, 6439–6442.