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Regio- and stereoselective ring opening of vinyl epoxides with $MgBr_2$

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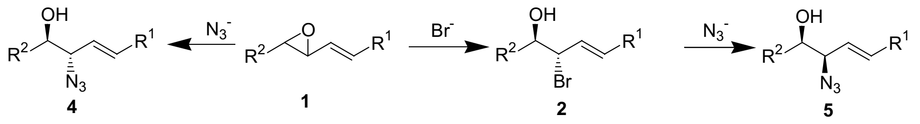
Abstract—The regio- and stereoselective ring opening of vinyl epoxides has been achieved by the use of Lewis acid, $MgBr_2$, affording bromohydrins in excellent yield, which are readily transformed to azidoalcohol, a key intermediate of several classes of pyrrolizidine and indolizidine alkaloids. The scope and limitations of the reaction are discussed.

Epoxides are versatile intermediates that serve as prominent building blocks in organic synthesis.[1] Epoxides can be opened by a variety of heteroatom nucleophiles, such as halides, alcohols, amines, and thiols, to the corresponding halohydrins,[2] alkoxyalcohols,[3] aminoalcohols,[4] and thioalcohols,[5] respectively. Among them, halohydrins are frequently found in many natural products[6] and, if a direct ring opening of epoxides with various nucleophiles does not give a suitable stereochemical outcome, can also be subjected for the further substitution reaction. We have recently reported the regioselective ring opening of vinyl epoxides.[7] As an extension of these studies (Scheme 1), we were interested in the preparation of azidoalcohols or their reduced systems, aminoalcohols, which could be suitable precursors of several classes of pyrrolizidine and indolizidine alkaloids.[8] Both *syn* and *anti* azidoalcohols are readily obtained from the same vinyl epoxides **1** through a direct ring opening by azide or two step sequences, bromination and azide substitution. In order to produce bromohydrins in a regioselective manner, introduction of π-orbital adjacent to the epoxide has been generally used. For example, Corey reported the regioselective ring opening of vinyl epoxide with HBr to give bromohydrin in good yield.[2b]

Also, Righi and Martin recently reported the regioselective and stereospecific ring opening of various vinyl epoxides, using LiBr/Amberlyst 15[2c] and PPh_3Br_2,[2d] respectively, to give bromohydrins in high yields. However, when we subjected our various vinyl epoxides to both Righi and Martin's conditions, two regioisomers were obtained in various ratios. It was found that ring opening of electron deficient vinyl epoxides bearing the ester group (i.e., $R^1 = CO_2Et$) at the vinyl terminus suffered from a little lower regioselectivity than that of simple vinyl epoxides (i.e., $R^1 = H$ or alkyl). These results prompted us to study an alternative method for similar transformations. Herein we wish to report a more simple, and efficient method to obtain bromohydrins from various vinyl epoxides bearing ester group with high regioselectivity.



Scheme 1.

Keywords: Vinyl epoxide; Ring opening; Bromohydrin; $MgBr_2$.

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Our initial studies focused on finding active halogen nucleophiles. The vinyl epoxide **1** was treated with several Lewis acids in some solvent systems under conditions as shown in Table 1. Both ZnBr$_2$ and CuBr$_2$ were ineffective, giving very little amount of product.

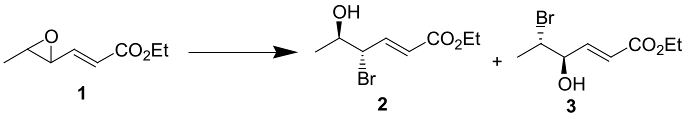
The use of MgBr$_2$ in Et$_2$O (entry 3) was effective to produce the bromohydrins in 92% isolated yield, although with just 4:1 regioselectivity. Although MgBr$_2$ has been utilized frequently for ring opening of epoxides, such as phenyloxiranes[9] or α,β-epoxy esters,[10] there has been no application of MgBr$_2$ to this type of vinyl epoxide. The different solvent system resulted in different levels of regioselectivity. As shown in entry 7, the best result was obtained with CH$_3$CN as solvent at 0 °C to produce bromohydrins **2** and **3** as a 15:1 mixture in nearly quantitative yield. On the other hand, the ring opening of **1** under Righi and Martin's conditions (entries 9 and 10) afforded the bromohydrins in rather lower regioselectivity (8:1 and 11:1, respectively) compared to MgBr$_2$ system. The ratio of regioisomers was readily determined by spectroscopic analysis of the mixtures. In ^{1}H NMR spectra, methyl groups of **2** and **3** apparently appeared as doublet at 1.38 and 1.67 ppm, respectively.

To explore the scope of the ring opening of vinyl epoxides by MgBr$_2$, a variety of vinyl epoxides were prepared by following the literature procedures.[7] As shown in Table 2, vinyl epoxides were subjected to the ring opening conditions as described in Table 1. In a typical experimental procedure, vinyl epoxide **5** in CH$_3$CN was treated with MgBr$_2$ (2 equiv) for 5 h at −10 °C to give the corresponding α-bromohydrin **6**, along with its regioisomer (β-bromohydrin) in a ratio of 15:1 in nearly quantitative yield. Sterically hindered vinyl epoxide **7** gave bromohydrin **8** with slightly better regioselectivity (20:1) and good yield. In the presence of possible nucleophiles, such as NHCbz and hydroxyl groups at the vinyl epoxide terminus (entry 3 and 6, respectively), we were concerned about the likelihood that the known Lewis acid promoted intramolecular cyclization[7a,11] would take place more favorably than the desired ring opening by MgBr$_2$. However, this concern was fortunately unfounded. Both reactions worked well with no deleterious effect by internal nucleophiles to give bromohydrins **10** and **16**[14] in excellent yields (96% and 97%, respectively) and high regioselectivity (16:1 and 19:1, respectively). No trace of cyclized systems, such as piperidine or tetrahydropyran derivatives, was found in reaction mixtures.

One the other hand, in the reaction of *cis*-vinyl epoxide **11** (entry 4), regioselectivity (7:1) was somewhat decreased. Ring opening of vinyl epoxide **13** bearing OTBS substituent gave the best result: isolated yield was excellent (97%) and the regioselectivity (25:1) was slightly higher than those obtained in other examples. Phenyloxirane **17** (entry 7) was poorly regioselective to give only a 2:1 mixture. Sterically very hindered vinyl epoxide **19**, which was prepared from epoxidation of β-ionone,[12] was proved to be ineffective even after prolonged reaction time and increased reaction temperature.

With these results, we tried to transform vinyl epoxide and bromohydrin into the corresponding *anti* and *syn* azidoalcohols by following the procedure previously described in Scheme 1. As illustrated in Scheme 2, direct ring opening of vinyl epoxide **15**, under conditions described by Wipf and Fritch[13] (3.0 equiv of NaN$_3$, 3.0 equiv of NH$_4$Cl, EtOH) for 1 h at 50 °C, gave the corresponding *anti*-azidoalcohol **21** in 89% yield, along with less than 3% of its diastereomer at azide position as determined by ^{1}H NMR analysis of the crude reaction mixtures. For the synthesis of *syn*-azidoalcohol, bromohydrin **16** (19:1 regioisomeric mixture) was treated with sodium azide in DMF, affording *syn*-azidoalcohol **22**[14] in 93% yield, showing no detectable contamination by its diastereomer or no interference by the hydroxyl group as an internal nucleophile.

Table 1. Ring opening of vinyl epoxides by Lewis acids



Entry	Lewis acids	Solvent	Time (h)[a]	Yield (%)[d]	Ratio (**2**/**3**)
1	ZnBr$_2$	CH$_3$CN	48	<10	
2	CuBr$_2$	CH$_3$CN	48	<5	
3	MgBr$_2$	Et$_2$O	3	92	4/1
4	MgBr$_2$	CH$_2$Cl$_2$	6	91	6/1
5	MgBr$_2$	Acetone	24	89	8/1
6	MgBr$_2$	CH$_3$CN	0.5	96	13/1
7	MgBr$_2$	CH$_3$CN	2.5[b]	97	15/1
8	MgBr$_2$	CH$_3$CN	5[c]	97	15/1
9	Amberlyst 15/LiBr	Acetone	2	93	8/1
10	PPh$_3$Br$_2$	CH$_2$Cl$_2$	0.5[b]	81	11/1

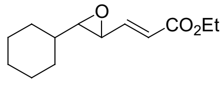
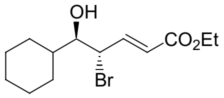
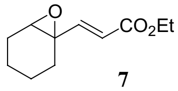
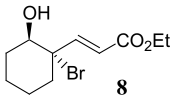
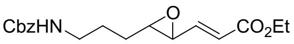
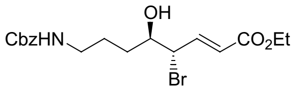
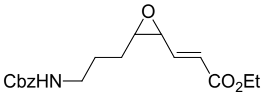
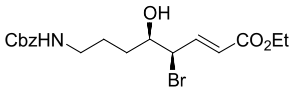
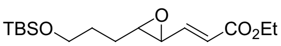
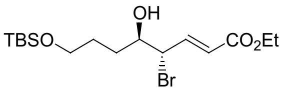
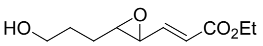
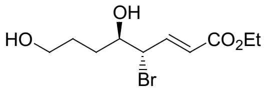
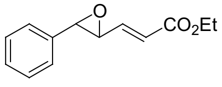
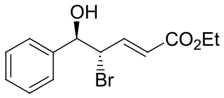
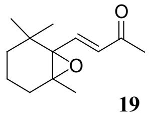
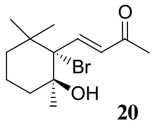
[a] Performed at 25 °C.

[b] At 0 °C.

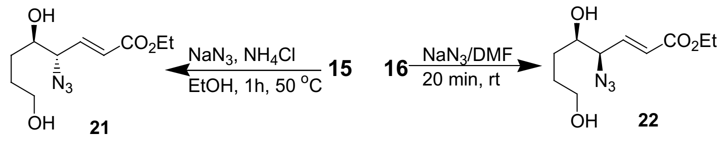
[c] At −20 °C.

[d] Isolated yield.

Table 2. $MgBr_2$ promoted ring opening of vinyl epoxides

Entry	Vinyl epoxides	Time (h)/ Temp (°C)	Products	Yield (%)[a]	Ratio (α-Br/β-Br)
1	 **5**	5/−10	 **6**	96	15/1
2	 **7**	9/0	 **8**	91	20/1
3	 **9**	3/−10	 **10**	96	16/1
4	 **11**	2.5/−10	 **12**	95	7/1
5	 **13**	5/−10	 **14**	97	25/1
6	 **15**	6/−10	 **16**	95	19/1
7	 **17**	6/−10	 **18**	96	2/1
8	 **19**	24/25	 **20**	NR	

[a] Isolated yield.



Scheme 2.

In summary, we described the exploitation of the regio- and stereoselective ring opening of vinyl epoxides with $MgBr_2$ leading to bromohydrin systems. Since optically pure form of the corresponding vinyl epoxides can be readily prepared from the functionalized allylic alcohols in three step sequences (Sharpless asymmetric epoxidation, oxidation, and olefination), these results can be utilized for the synthesis of enantiopure azidoalcohol derivatives, which possess useful functional groups for further elaboration toward several major classes of alkaloids.

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14. Selected spectroscopic data for **16**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.04 (dd, $J = 15.5$, 9.9 Hz, 1H), 6.02 (d, $J = 15.5$ Hz, 1H), 4.59 (dd, $J = 9.8$, 4.1 Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 1.79–1.72 (m, 4H), 1.59–1.56 (m, 1H), 1.30 (t, $J = 7.1$ Hz, 3H); For **21**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.89 (dd, $J = 15.6$, 6.9 Hz, 1H), 6.10 (d, $J = 15.6$ Hz, 1H), 4.22 (q, $J = 6.9$ Hz, 2H), 4.10 (m, 1H), 3.77–3.65 (m, 3H), 1.74–1.65 (m, 3H), 1.53 (m, 1H), 1.31 (t, $J = 6.9$ Hz, 3H); For **22**: ^{1} H NMR (300 MHz, CDCl$_3$) 6.85 (dd, $J = 15.9$, 7.2 Hz, 1H), 6.10 (d, $J = 15.9$ Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 4.02 (dd, $J = 7.2$, 6.3 Hz, 1H), 3.75–3.63 (m, 3H), 1.75–1.68 (m, 3H) 1.55 (m, 1H), 1.31 (t, $J = 7.2$ Hz, 3H).