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A Simple and Efficient Method for Regioselective and Stereoselective Synthesis of Vicinal Bromohydrins and Alkoxybromides from an Olefin

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A very rapid and efficient method has been developed for the synthesis of vicinal bromohydrins and alkoxybromides directly from an olefin without any catalyst. The reaction was performed in CH_3CN−water (4:1) or alcohol using *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$) as the brominating agent. Excellent yields and regio- and stereoselectivities have been obtained. Bromohydrins are formed instantaneously, whereas formation of alkoxybromides takes 30−60 min.

Introduction

The vicinal fictionalization of an olefin is a powerful synthetic tool for organic chemists, especially when the reaction is carried out in regio- and stereoselective fashion. In particular, selective introduction of two different functional groups, such as hydroxy or alkoxy and halogen, has attracted sustained attention in organic synthesis.[1] The resulting halohydrins and alkoxyhalides are important building blocks in organic, medicinal, as well as industrial chemistry.[2] Halohydrins are usually synthesized by ring opening of epoxides[3] or cyclic sulfate[4] by hydrogen halides or metal halides. However, these procedures are associated with the formation of *vic*-dihalides and 1,2-diols as byproducts.[3a,b] Second, these procedures require prior synthesis of epoxide or cyclic sulfate. There are two general approaches for heterolytic additions of water and halogen to an olefinic bond. One involves the use of molecular halogen or *N*-halosuccinimide for halogenation,[5] and the other uses metal halide along with an oxidizing agent.[6] *N*-Halosuccinimide is a better choice over hazardous molecular halogens for such transformations, but this method suffers the drawback of low yield and longer reaction time. Moreover, this protocol does not work well with electron-deficient alkenes. Recently, Yadav et al. reported a modified

* To whom correspondence should be addressed. Tel: +91-361-2570535 (O). Fax: +91-361-2700311.

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(5) (a) *Comprehensive Organic Transformation*: *A Guide to Functional Group Preparation*, 2nd ed.; Larock, R. C., Ed.; Wiley-VCH: New York, 1999; pp 629−640. (b) Damin, B.; Garapon, J.; Silion, B. *Synthesis* **1981**, 362−363. (c) Rolston, J. H.; Yates, K. *J. Am. Chem. Soc.* **1969**, *91*, 1469−1476. (d) Dalton, D. R.; Dutta, V. P.; Jones, D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5498−5501. (e) Langman, A. W.; Dalton, D. R. *Org. Synth.* **1979**, *59*, 16−19. (f) Chamberlin, A. R.; Dezube, M.; Dussalt P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (g) Barluenga, J.; Marco-Arias, M.; Gonzalez-Bobes, F.; Ballesteros, A.; Gonzalez, J. M. *Chem.*−*Eur. J.* **2004**, *10*, 1677−1682. (h) Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyam, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5050−5055. (i) Yadav, J. S.; Reddy, B. V. S.; Baishya, G.; Harshavardhan, S. J. *Tetrahedron Lett.* **2005**, *46*, 3569−3572. (j) Hanzlik, R. P. *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. 6, pp 560−564. (k) Vishwakarma, L. C.; Walia, J. S. *J. Ind. Chem. Soc.* **1976**, *53*, 156−162.

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SCHEME 1. Synthesis of Bromohydrins and -ethers

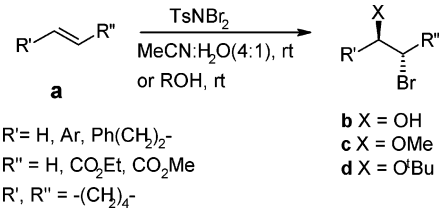
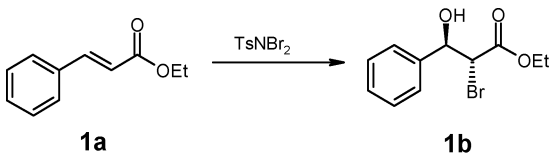


TABLE 1. Bromination of Ethylcinnamate[a]

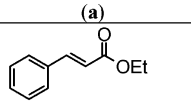
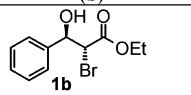
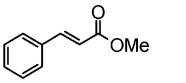
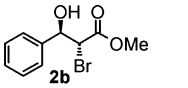
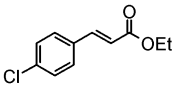
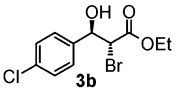
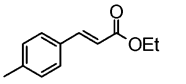
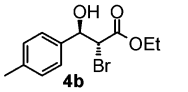
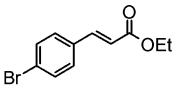
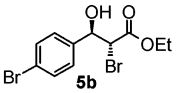
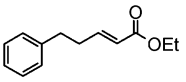
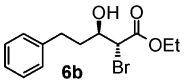
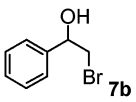
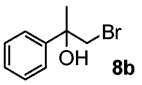
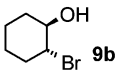
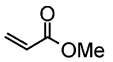
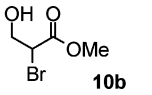


entry	solvent	brominating agent	time	yield[b]
1	MeCN−H_2O (4:2)	$TsNBr_2$	7 min	90
2	MeCN−H_2O (4:1)	$TsNBr_2$	instantaneous	92
3	$CHCl_3$− H_2O (4:1)	$TsNBr_2$	25 min	82
4	CH_2Cl_2− H_2O (4:1)	$TsNBr_2$	25 min	85
5	MeCN−H_2O (4:1)	NBS	6 h	56

[a] Reaction conditions: olefin (1.1 mmol), solvent (5 mL), $TsNBr_2$ (1.2 mmol), rt. [b] Isolated yield after chromatographic purification.

procedure for hydrobromination of olefins using NBS in ionic liquid.[5i] The disadvantage of this method is that ionic liquids are expensive, and in some cases, bromohydrin formation takes longer time. The oxidative halogenation methods[6] require a metal salt as the halogen source, an oxidizing agent, and a catalyst to carry out the transformation. Sudalai et al.[6d] reported a method for such transformation using metal salts, such as LiX (X = Cl, Br) and NaX, as a halogenating agent in the presence of $NaIO_4$ as catalyst. The major drawback of this method is the use of a high amount (25%) of the catalyst and a stoichiometric amount of 30% H_2SO_4 along with the metal halide (1.2 equiv). Oxidative hydrohalogenation with hypohalous acid or bromates suffers the drawback of longer reaction time and low yield.[7] In recent years, haloperoxidases have also been studied extensively for oxidative halogenations, to understand the biosynthesis of many halogenated marine natural products.[8] We wish to report herein a very simple and efficient method for direct synthesis of bromohydrins and alkoxybromides from an olefin using *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$) as the bromine source under mild conditions (Scheme 1).

TABLE 2. Synthesis of Bromohydrin from Various Olefins

entry	olefin (a)	product (b)	yield[a]
1		 **1b**	92[b]
2		 **2b**	91[b]
3		 **3b**	94
4		 **4b**	90
5		 **5b**	90
6		 **6b**	86
7		 **7b**	93[c]
8		 **8b**	91[c]
9		 **9b**	86
10		 **10b**	84

[a] Isolated yield after chromatographic purification. Products are characterized by IR, ^1H NMR, ^{13}C NMR, mass and elemental analysis. [b] From refs 7b and 12. [c] From ref 6d.

N,*N*-Dibromo-*p*-toluenesulfonamide was used first by Kharasch for the synthesis of 1-phenyl-2-(*p*-toluenesulfonamido)-1-bromoethane.[9] The same reagent was also used by Paul et al. for the synthesis of 3,5-dihydroxy-1-substituted piperidines from 1,4-pentadiene.[10] The yield of the intermediate methoxy bromide synthesized for this purpose was found to be very low. In both the cases, the reagent was not studied expeditiously. *N*,*N*-Dihalosulfonamides were also used for the preparation of haloamines and azidins.[11] In the recent past, several procedures have appeared in the literature for the synthesis of bromohydrins.[3−7,12] Understanding the importance of this subject, we have carried out a study to generalize the utility of $TsNBr_2$ as a bromine source for the synthesis of bromohydrins and alkoxybromides.

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TABLE 3. Values of Coupling Constants for Protons of R−C(OH)H^1−CH^{2}BrX

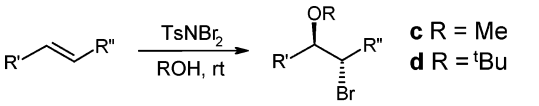
compound	R	X	($\delta_H{}^1$) $J_H{}^1$ (Hz)	reported $J_H{}^1$ (Hz)	($\delta_H{}^2$) $J_H{}^2$ (Hz)	reported $J_H{}^2$ (Hz)	ref
1b	Ph−	−COOEt	(5.07, dd) 8.1, 3.3	(5.08, d) 8.1	(4.36, d) 8.1	(4.36, d) 8.1	7b
2b	Ph−	−COOMe	(5.05, d) 8.4	(5.07, d)/(5.08, d) 8.2/8.3	(4.35, d) 8.4	(4.38, d) 8.2/8.3	7b/12
3b	(4-Cl)−Ph−	−COOEt	(5.05, d) 7.8	-	(4.29, d) 8.1		
4b	(4-Me)−Ph−	−COOEt	(5.03, d) 8.3	-	(4.34, d) 8.4		
5b	(4-Br)−Ph−	−COOEt	(5.04, d) 8.2	-	(4.28, d) 8.2		
7b	Ph−	−H	(4.91, dd) 8.7, 3.3	(4.95, dd) 8.1, 4.0	(3.48−3.67, m) -	(3.55−3.70, m)	6d
10b	H−	−COOMe	(4.05, dd) 7.2, 12.0	-	(4.36, dd) 5.4, 7.5		

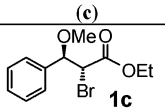
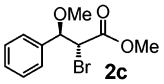
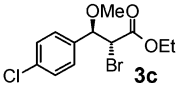
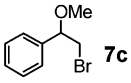
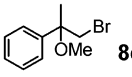
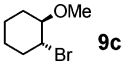
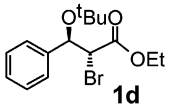
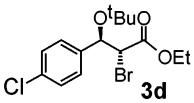
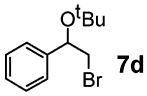
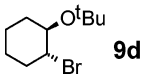
Results and Discussion

The brominating agent $TsNBr_2$ employed for this purpose was prepared from Chloramine-T by the following literature procedure.[13] Initially, a systematic study for the synthesis of bromohydrin was carried out using ethylcinnamate as substrate. The reaction was carried out by adding $TsNBr_2$ (1.1 equiv) to a solution of the organic substrate in acetonitrile−water at room temperature. Use of a stoichiometric amount of the reagent resulted in slightly lower yield. Various solvents, such as MeCN, CH_2Cl_2, and $CHCl_3$, in combination with water were studied (Table 1). A mixture of acetonitrile and water in a 4:1 ratio was found to be the best solvent for halohydrin formation. The reaction takes a relatively longer time for lower acetonitrile−water ratio, which is due to poor solubility of the substrate. We observed that, after addition, the yellow color of $TsNBr_2$ disappears instantaneously along with the olefin. Disappearance of yellow color is indicative of the completion of the reaction, which was further confirmed by monitoring the reaction by TLC. The reaction mixture was stirred for another 10 min. After the usual workup, the corresponding hydrobromide was obtained in excellent yield. The reagent is much faster than NBS for the bromination reaction. For example, when bromination of ethyl cinnamate was carried out with NBS under the same conditions, the respective bromo alcohol was formed in 56% yield in 6 h (Table 1, entry 5). We are pleased to find that both regioselectivity and stereoselectivity were controlled very well in this reaction. Only the *erythro*-*β*-hydroxy-α-bromo isomer was observed as evident by the analysis of ^{1}H NMR data. The mass spectra showed prominent peaks corresponding to $[ArCHOH]^+$ and $[BrCHCOOEt]^+$ ion fragments. The *anti* configuration was further confirmed by structural analysis of X-ray crystallography data of the compound **1b**.

After optimizing the reaction conditions, we have extended the process to a variety of olefins, which are summarized in Table 2. The present method works well for all kinds of olefins, such as cinnamates, styrenes, cyclohexene, and methyl acrylate, to produce bromohydrins in excellent yield. In all cases, the rate of the reaction is very fast, and the reaction occurs instantaneously; *anti*-selectivity of the products was determined by analysis of the coupling constant data of protons attached to the carbons bearing −OH and −Br groups of the bromo alcohol. A comparative result of the coupling constants with the reported value is presented in Table 3.

TABLE 4. Synthesis of Alkoxybromides



entry	ROH	product (**c**)	time (min)	yield[a] (%)
1	MeOH	 **1c**	45	82
2	MeOH	 **2c**	45	79[b]
3	MeOH	 **3c**	30	86
4	MeOH	 **7c**	35	88[b]
5	MeOH	 **8c**	30	88[b]
6	MeOH	 **9c**	60	74
7	*t*-BuOH	 **1d**	45	71
8	*t*-BuOH	 **3d**	45	69
9	*t*-BuOH	 **7d**	35	69
10	*t*-BuOH	 **9d**	70	59

[a] Isolated yield after chromatographic purification. Products are characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis. [b] From ref 6d.

Encouraged by these results, we applied the procedure for the synthesis of different alkoxybromides. Initially, when ethyl cinnamate was subjected to bromination in methanol, corresponding methoxy bromide was obtained in 45 min in excellent

(11) (a) Daniher, F. A.; Butler, P. E. *J. Org. Chem.* **1968**, *33*, 4336−4340. (b) Terauchi, H.; Kowata, K.; Minematsu, T.; Takemura, S. *Chem. Pharm. Bull.* **1977**, *25*, 556−562. (c) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444−2451. (d) Li, G.; Wei, H.-X.; Kim, S. H.; Neighbors, M. *Org. Lett.* **1999**, *1*, 395. (e) Li, G.; Wei, H.-X.; Kim, S. H. *Org. Lett.* **2000**, *2*, 2249. (f) Wei, H.-X.; Kim, S. H.; Li, G. *Tetrahedron* **2001**, *57*, 3869. (g) Wei, H.-X.; Kim, S. H.; Li, G. *Tetrahedron* **2001**, *57*, 8407. (h) Xu, X.; Kotti, S. R. S. S.; Liu, J.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 4881−4884.

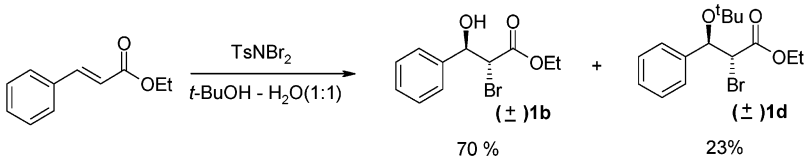
(12) Urankar, D.; Rutar, I.; Modec, B.; Dolenc, D. *Eur. J. Org. Chem.* **2005**, 2349−2353.

(13) Nair, C. G. R.; Indrasen, P. *Talanta* **1976**, *23*, 239.

TABLE 5. Values of Coupling Constants for Protons R−C(OMe)H^1−CH^{2}BrX

compound	R	X	($\delta_H{}^1$) $J_H{}^1$ (Hz)	reported $J_H{}^1$ (Hz)	($\delta_H{}^2$) $J_H{}^2$ (Hz)	reported $J_H{}^2$ (Hz)	ref
1c	Ph−	−COOEt	(4.53, d) 10.0		(4.20, d) 11.6		
2c	Ph−	−COOMe	(4.54, d) 10.0		(4.22, d) 10.0		
3c	(4-Cl)−Ph−	−COOEt	(4.50, d) 10.0		(4.12, d) 10.0		
7c	Ph−	−H	(4.37, dd) 4.0, 8.4	(4.38, dd) 3.0, 9.0	(3.52, dd) 2.4, 10.8	(3.43−3.56, m)	6d

SCHEME 2. Competitive Reaction between *tert*-BuOH and H_2O

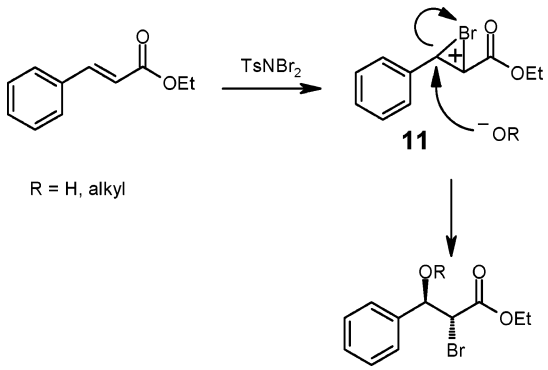


yield. Thereafter, we extended the procedure for various kinds of olefins that are summarized in Table 4.

After a successful attempt at the synthesis of *vic*-methoxybromides, we sought to apply this method to more hindered alcohols, such as *tert*-butyl alcohol. It is remarkable that all kinds of olefins could be easily converted to corresponding vicinal *tert*-butoxybromides in high yield (Table 4). Coupling constants of a proton attached to the carbons bearing −OR and −Br groups of the alkoxybromides are presented in Tables 5 and 6.

We have also carried out a study on the competitive nucleophilicity of *tert*-butyl alcohol and water. It is interesting to observe that when the reaction was carried out in a mixture of *tert*-butyl alcohol and water (1:1 volume ratio) a mixture of bromohydrin (**1b**) and *tert*-butoxybromide (**1d**) was obtained in a 3:1 ratio (Scheme 2).

SCHEME 3. Probable Mechanism of Bromination



A probable mechanistic pathway to explain the regio- and stereoselectivity of the bromohydrins and bromoethers is depicted in Scheme 3. A three-membered cyclic bromonium ion intermediate **11** is formed at the initial stage of the reaction due to electrophilic addition of the Br^+ ion (generated from $TsNBr_2$) onto the olefin.[14] The intermediate **11** undergoes ring opening by the nucleophile via the S_N2 pathway. The S_N2 opening is responsible for high *anti*-stereoselectivity of the bromo product. The regioselectivity can be explained by considering the fact that the β-position is more positive than the α-position due the presence of the aromatic ring. Nucleophilic opening of the cyclic bromonium intermediate is most likely from the more positive β-position. Since analysis of the product **1b** using X-ray crystallography confirms the *trans* addition, we assume that *trans* addition has occurred in all the rest of the reactions because this is also consistent with our assumed mechanistic pathway. This assumption can be realized from the coupling constants of protons attached to the carbon having OR and Br groups in the NMR spectra of the products which match the reported values.

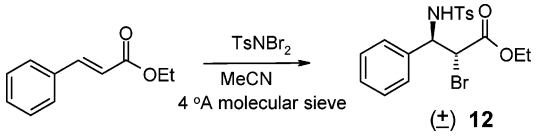
(14) Rodebaugh, R.; Fraser-Reid, B. *Tetrahedron* **1996**, *52*, 7663−7678.

TABLE 6. Values of Coupling Constants for Protons R−C(O-*tert*-Bu)H^1−CH^{2}BrX

compound	R	X	($\delta_H{}^1$) $J_H{}^1$ (Hz)	($\delta_H{}^2$) $J_H{}^2$ (Hz)
1d	Ph−	−COOEt	(4.82, d) 9.9	(4.05, d) 9.9
3d	(4-Cl)−Ph−	-COOEt	(4.85, d) 9.6	(4.04, d) 9.6
7d	Ph−	−H	(4.66, d) 8.0	3.32−3.44, m) -

When the same reagent was used by Kharasch[9] for the synthesis of bromoamines, the attacking nucleophile is a sulfonamide. In this reaction, water or alcohol is present in excess, and they are better nucleophiles than sulfonamide. So, formation of bromohydrin or alkoxybromide was predominant over that of amino bromides. We have carried out the reaction in the absence of water or alcohol as a test case, taking ethyl cinnamate as substrate. When ethyl cinnamate was subjected to reaction with *N*,*N*-dibromo-*p*-toluenesulfonamide in dry acetonitrile under inert atmosphere, corresponding bromoamine **12** was obtained in good yield (Scheme 4).

SCHEME 4. Synthesis of Bromoamine



In conclusion, a regio- and stereoselective method for hydrobromination and alkoxybromination of olefins has been established by using *N*,*N*-dibromo-4-toluenesulfonamide as a bromine source. The procedure is rapid, easy to perform at room temperature, and applicable to different kinds of olefins, such as cinnamates, styrenes, cyclohexene, and methyl acrylate, to give corresponding brominated product in excellent yield.

Experimental Section

General Procedure for the Synthesis of Bromohydrins: To a solution of olefin (1.1 mmol) in acetonitrile−water (4:1) (5 mL) was added $TsNBr_2$ (1.2 mmol). The color of $TsNBr_2$ as well as the olefin disappears immediately. After stirring for another 10 min, sodium thiosulfate (200 mg approximately) was added and the reaction mixture was stirred for 20 min. The reaction mixture was taken up in ether, washed with brine, dried (Na_2SO_4), and

concentrated. Purification of the crude product by flash chromatography on silica gel (230−400 mesh) with petroleum ether−EtOAc (5%) as eluent gave the pure product.

Ethyl-(2*R,3*R**)-2-bromo-3-(4-chlorophenyl)-3-hydroxypropanoate (3b):** IR (neat, cm^{-1}) ν 3460, 2979, 2920, 1731, 1646, 1599, 1492, 1292, 1272, 1014, 537; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, $J = 6.9$ Hz, 3H), 4.2−4.5 (m, 2H), 4.29 (d, $J = 8.1$ Hz, 1H), 5.05 (d, $J = 7.8$ Hz, 1H), 7.28−7.42 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.80, 47.46, 62.47, 128.36, 128.65, 134.48, 137.47, 169.25. Anal. Calcd for $C_{11}H_{12}BrClO_3$: C 42.96%, H 3.93%. Found: C 42.58%, H 4.31%.

Ethyl-(2*R,3*R**)-2-bromo-3-hydroxy-3-(4-methylphenyl)propanoate (4b):** IR (neat, cm^{-1}) ν 3479, 2969, 2920, 1732, 1616, 1459, 1278, 1023, 817, 534; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, $J = 6.8$ Hz), 2.35 (s, 3H), 2.25 (q, $J = 1.8$ Hz, 2H), 4.34 (d, $J = 8.4$ Hz, 1H), 5.03 (d, $J = 8.3$ Hz, 1 H), 7.18 (d, $J = 7.9$ Hz, 2H), 7.27 (d, $J = 6.24$ Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.2, 47.8, 62.4, 75.1, 126.9, 129.2, 129.3, 136.1, 138.8, 169.5.

Ethyl-(2*R,3*R**)-2-bromo-3-(4-bromophenyl)-3-hydroxypropanoate (5b):** IR (neat, cm^{-1}) ν 3450, 2970, 2920, 1739, 1594, 1264, 739, 538; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 ($J = 7.1$ Hz, 3H), 3.29 (br s, 1H), 4.25 (q, $J = 2.6$ Hz, 2H), 4.28 (d, $J = 8.2$ Hz, 1H), 5.04 (d, $J = 8.2$ Hz, 1H), 7.27 (d, $J = 6.7$ Hz), 7.50 (d, $J = 6.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 23.7, 28.9, 47.4, 62.5, 74.6, 122.8, 128.7, 131.7, 138.0, 169.3.

Ethyl-(2*R,3*R**)-2-bromo-3-hydroxy-5-phenylpentanoate (6b):** IR (neat, cm^{-1}) ν 3481, 2976, 2926, 1742, 1601, 1451, 1261, 1154, 1029, 562; ^1H NMR (300 MHz, $CDCl_3$) δ 3.25 (t, $J = 3$ Hz, 3H), 2.0−2.3 (m, 1H), 2.5−2.67 (m, 1H), 2.67−2.75 (m, 1H), 2.75−3.05 (m, 1H), 4.1−4.55 (m, 4H), 7.1−7.6 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 32.5, 36.9, 47.9, 51.9, 62.4, 126.3, 128.3, 128.4, 128.5, 128.6, 140.0, 67.7. Anal. Calcd for $C_{13}H_{17}BrO_3$: C 51.84%, H 5.69%. Found: C 52.02%, H 5.87%.

General Procedure for the Synthesis of Alkoxybromides. To a solution of olefin (1.1 mmol) in alcohol (5 mL) was added $TsNBr_2$ (1.21 mmol). The color of $TsNBr_2$ as well as the olefin disappears slowly. After the reaction was complete, sodium thiosulfate (200 mg approximately) was added, and the reaction mixture was stirred for 20 min. After evaporation of the solvent, the reaction mixture was extracted with ether, washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by flash chromatography on silica gel (230−400 mesh) with petroleum ether−EtOAc (3−5%) as eluent gave the pure product.

Ethyl-(2*R,3*R**)-2-bromo-3-methoxy-3-phenylpropanoate (1c):** IR (neat, cm^{-1}) ν 2978, 2929, 1743, 1454, 1269, 1097, 602; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, $J = 7.6$ Hz, 3H), 3.21 (s, 3H), 4.20 (d, $J = 11.6$ Hz, 1H), 4.23−4.32 (m, 2H), 4.53 (d, $J = 10$ Hz, 1H), 7.30−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 47.4, 57.5, 61.9, 84.1, 127.6, 127.9, 128.2, 128.4, 128.7, 136.7, 168.5. Anal. Calcd for $C_{12}H_{15}BrO_3$: C 50.19%, H 5.27%. Found: C 50.01%, H 5.52%.

Ethyl-(2*R,3*R**)-2-bromo-3-(4-chlorophenyl)-3-methoxypropanoate (3c):** IR (neat, cm^{-1}) ν 2978, 2929, 1745, 1593, 1270, 1096, 556; ^1H NMR (400 MHz, $CDCl_3$) δ 1.3 (t, $J = 7.2$ Hz, 3H), 3.19 (s, 3H), 4.12 (d, $J = 10$ Hz, 1H), 4.19−4.32 (m, 2H), 4.50 (d, $J = 10$ Hz, 1H), 7.22−7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 47.2, 57.6, 62.1, 83.4, 128.4, 129.2, 134.5, 135.4, 168.3. Anal. Calcd for $C_{12}H_{14}BrClO_3$: C 44.82%, H 4.39%. Found: C 44.97% and H 4.04%.

***trans*-1-Bromo-2-methoxycyclohexane (9c):** IR (neat, cm^{-1}) ν 2939, 2861, 1452, 1189, 1097, 648; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19−1.41 (m, 3H), 1.62−1.88 (m, 3H), 2.10−2.24 (m, 1H), 2.24−2.39 (m, 1H), 3.18−3.28 (m, 1H), 3.42 (s, 3H), 3.92−4.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 25.5, 30.1, 35.5, 55.3, 57.1, 83.1.

Ethyl-(2*R,3*R**)-2-bromo-3-(*tert*-butoxy)-3-phenylpropanoate (1d):** IR (neat, cm^{-1}) ν 2977, 2929, 1744, 1267, 1054, 700, 603; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (s, 9H), 1.28 (t, $J = 7.5$ Hz, 3H), 4.05 (d, $J = 9.9$ Hz, 1H), 4.02−4.34 (m, 2H), 4.82 (d, $J = 9.9$ Hz), 7.21−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 28.6, 49.61, 61.8, 75.8, 76.2, 127.8, 128.0, 128.1, 141.0, 169.1. HRMS: calcd mass (M + Na) 351.0572; found 351.0598.

Ethyl-(2*R,3*R**)-2-bromo-3-(*tert*-butoxy)-3-(4-chlorophenyl)-propanoate (3d):** IR (neat, cm^{-1}) ν 2978, 2930, 1743, 1597, 1256, 737, 579; ^1H NMR (400 MHz, $CDCl_3$) δ 1.0 (s, 9H), 1.28−1.42 (m, 3H), 4.04 (d, $J = 9.6$ Hz, 1H), 4.25−4.4 (m, 2H), 4.85 (d, $J = 9.6$ Hz, 1H), 7.22−7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 28.7, 47.5, 49.7, 62.8, 76.5, 128.2, 129.1, 129.3, 130.6, 168.7. Anal. Calcd for $C_{15}H_{20}BrClO_3$: C 49.54%, H 5.54%. Found: C 49.25%, H 5.79%.

(±)-1-[2-Bromo-1-(*tert*-butoxy)ethyl]benzene (7d): IR (neat, cm^{-1}) ν 3057, 2977, 1631, 1266; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 3.32−3.44 (m, 2H), 4.66 (d, $J = 8.0$ Hz, 1H), 7.21−7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 38.1, 74.6, 75.0, 126.3, 127.6, 128.2, 128.7. Anal. Calcd for $C_{12}H_{17}BrO$: C 56.05%, H 6.66%. Found: C 56.36%, H 6.37%.

***trans*-1-Bromo-2-(*tert*-butoxy)cyclohexane (9d):** IR (neat, cm^{-1}) ν 3048, 2924, 1638, 1265, 740, 527; ^1H NMR (400 MHz, $CDCl_3$) δ 1.0−1.4 (m, 13H), 1.66−1.75 (m, 2H), 1.75−1.90 (m, 1H), 1.98−2.15 (m, 1H), 2.25−2.4 (m, 1H), 3.50−3.63 (m, 1H), 3.90−4.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 24.0, 28.8, 29.3, 33.9, 56.7, 72.6, 74.1.

General Procedure for the Synthesis of Bromoamine. A two-necked dry round-bottom flask fitted with a nitrogen inlet was charged with ethyl cinnamate (1.1 mmol), dry acetonitrile (5 mL), and freshly activated 4 Å molecular sieves (200 mg). The flask was flashed with nitrogen, and $TsNBr_2$ (1.21 mmol) was added under a slow stream of nitrogen. The reaction mixture was allowed to stir under nitrogen atmosphere for 2 h at room temperature. Sodium thiosulfate (200 mg approximately) was added, and the reaction mixture was stirred for 20 min. The reaction mixture was filtered, solvent evaporated, and ether (50 mL) was added. The ethereal layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by flash chromatography on silica gel (230−400 mesh) with petroleum ether−EtOAc (15%) as eluent gave the bromoamine **12**: yield 68%; mp 174−176 °C; IR (Nujol, cm^{-1}) ν 3450, 1743, 1669, 1527, 1343, 1164, 1090, 559; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, $J = 7.2$ Hz, 3H), 2.35 (s, 3H), 4.03−4.125 (m, 2H), 4.43 (d, $J = 5.4$ Hz, 1H), 4.87 (dd, $J = 9.3$, 5.4 Hz, 1H), 6.20 (d, $J = 9$ Hz, 1H), 7.10−7.24 (m, 7H), 7.58 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 21.4, 46.6, 60.0, 62.5, 126.9, 127.0, 128.2, 128.5, 129.2, 136.3, 137.3, 143.1, 168.2. HRMS: calcd mass (M + Na) 448.0194; found 448.0209.

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Supporting Information Available: Analytical data, ^1H and ^{13}C NMR spectra, and crystal structure of the compound **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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