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Chiral Epoxides via Borane Reduction of 2-Haloketones Catalyzed By Spiroborate Ester: Application to the Synthesis of Optically Pure 1,2-Hydroxy Ethers and 1,2-Azido Alcohols

Kun Huang, Haiyang Wang, Viatcheslav Stepanenko, Melvin De Jesús, Carilyn Torruellas, Wildeliz Correa, and Margarita Ortiz-Marciales*

Department of Chemistry, University of Puerto Rico-Humacao, CUH Station, Humacao, Puerto Rico 00791, USA.

Abstract



An enantioselective borane-mediated reduction of a variety of 2-haloketones using 10% of spiroaminoborate ester **1** as catalyst is described. By a simple basic workup of 2-halohydrins, optically active epoxides are obtained in high yield and with excellent enantiopurity (up to 99% ee). Ring opening of oxiranes with phenoxides or sodium azide is investigated under different reaction conditions affording nonracemic 1,2-hydroxy ethers and 1,2-azido alcohols with excellent enantioselectivity (99% ee) and in good to high chemical yield.

Nonracemic epoxides are not only recognized for their biological importance, but also as key intermediates in diverse chemical transformations for the synthesis of chiral auxiliaries, natural products and chiral drugs.^{2,3} Moreover, chiral epoxides have been recently used as catalysts for asymmetric induction in the auto-catalyzed organozinc addition to an aldehyde. ⁴ Consequently, in the last thirty years, a variety of direct epoxidation and resolution methods for the synthesis of enantiopure oxiranes have been successfully developed. 5-8 More convenient and efficient routes to prepare optical pure styrene oxides involve the initial enzymatic⁹ or chemical asymmetric reduction of α-halogenated acetophenones.10⁻12 Asymmetric transfer hydrogenation of 2-chloroacetophenones has been recently applied using Rh, Ru or Ir diamino complexes as chiral catalysts. Environmentally friendly boron reagents have been used for the reduction of a variety of α-haloketones and the halohydrins are easily converted to nonracemic epoxides without racemization.11,12 These methods can be considered, essentially, as a "one pot" procedures valuable for substrates with sensitive groups due to the very mild reaction conditions. Lithium and sodium borohydride reduction of α-haloacetophenones with an stoichiometric amount of (L)-TarB-NO₂, prepared from tartaric acid and *m*-nitrophenylboronic acid, was employed recently to afford styrene oxides in moderate to high enantiopurity. 11a The most recognized chiral catalysts for the enantioselective borane-mediated reduction of unsymmetrical ketones with outstanding and predictable stereoselectivities are 1,3,2-oxazaborolidines (OAB) derived from nonracemic 1,2-amino alcohols. 12 These remarkable reagents were initially discovered by Itsuno and further developed and studied by Corey and others.12 The in situ prepared B-H

margarita.ortiz1@upr.edu.

oxazaborolidine derived from diphenylprolinol was first proposed and used by Corey's group in the borane reduction of α -chloroacetophenone in THF affording the (S)-chlorohydrin in high yield and excellent enantiomeric excess. ^{12b} Nevertheless, the *in situ* prepared B-H oxazaborolidines are known to form side-products diminishing in some cases the effectiveness of the catalyst. ¹³

A series of stable crystalline aminoborate esters, derived from a variety of nonracemic 1,2-amino alcohols, ethylene glycol and inexpensive triisopropyl borate, were previously reported by our group. ^{14,15} The most effective and convenient aminoborate complexes used as catalyst for the borane-mediated reduction of ketones ^{14,}15a–g and benzyl oximes ^{15h} are shown in Fig. 1.

Spiroaminoborate ester 1 derived from diphenylprolinol was highly effective for the reduction of a variety of aryl,15a–d heteroaryl,15e, α -alkoxy15f and aliphatic ^{15g} ketones providing the desired secondary alcohols in excellent yield with excellent enantioselectivity, higher or similar to Corey's OAB (CBS reagent). Presently, we are interested in the synthesis of nonracemic α -aryloxy- and α -amino alcohols as important chiral building blocks for the preparation of neurobiological active molecules. We, herein, describe a simple and convenient procedure for the preparation of optical active epoxides in high yield with excellent enantiopurity and their application to the synthesis of optically pure β -hydroxy ethers and 1,2-azido alcohols.

To develop a suitable procedure for the synthesis of epoxides, the asymmetric reduction of α -chloroacetophenone was initially carried out using 10% catalyst **1** and 0.7 equiv BH₃•DMS in THF at room temperature, followed by treatment of the crude chlorohydrin with 2 N NaOH. The styrene oxide was afforded in good yield and without racemization. To optimize the reaction conditions, α -Cl and α -Br acetophenone were reduced under different catalytic loads and borane sources, and subsequently, the crude halohydrins were cyclized under basic conditions. Since BH₃•DMS provides similar enantioselectivity as BH₃•THF, we consider its use more attractive for a convenient method due to its low price and stability. In addition, the reduction of α -Br acetophenone afforded the corresponding epoxide in higher enantiopurity than the chloro analogue, providing 99% ee, and good chemical yield with 10% of catalyst **1**, 0.7 equiv BH₃•DMS in THF at room temperature for 0.5 h.

Encouraged by the remarkable enantioselectivity obtained in the synthesis of the styrene oxide using spiroaminoborate 1, we explored its scope in the reduction of a variety of aromatic and aliphatic α-halogenated ketones and their halohydrins conversion to enantioenriched oxiranes. As indicated in Table 1, α-haloacetophenones with Me, MeO, Cl, F, CN and NO₂ ring-substituents (entries 1–10) were reduced to the S-2-bromo-1phenylethanols, which were transformed under basic conditions to the S-epoxides in good to excellent yields and outstanding enantioselectivities (97 – 99% ee). The presence of different substituents on the aromatic ring has no significant effect on the ee values (entries 2–10). However, the cyclization of 2-bromo-4-methylphenyl-1-ethanol (entry 9) by treatment with 2 N NaOH afforded the corresponding epoxide in lower yield. However, the use of t-BuOK led us to the expected epoxide in good yield. In addition, the α bromocyclohexyl ethanone and α -bromo adamanty ethanone afforded the epoxides in high yield and excellent enantiomeric excess (entries 11–12). The absolute configuration of the oxiranes was determined by comparing the optical rotation with the literature values. 8,10,11a,15f,16a Racemic β-hydroxy ethers were prepared as standards for HPLC analysis by the sodium borohydride reduction of β -phenoxyketones (8).

Regioselective ring opening of oxiranes with nucleophiles is an important route to obtain a broad range of nonracemic 1,2-substituted alcohols as intermediates for the synthesis of key

pharmaceutical compounds, as well as chiral catalysts.^{3,17–19} Optically active β-hydroxy ethers are valuable synthetic intermediates in a wide variety of potentially bioactive compounds, ^{2g}, 17a Although, asymmetric syntheses of terminal epoxides in high optical purity are well established, 5⁻⁸ efficient methods for the synthesis of nonracemic β-aryloxy alcohols via epoxide ring-opening remains limited. ¹⁸ Moreover, synthesis of 2-aryloxy-1phenylethanols by kinetic resolution of styrene oxide with phenol in the presence of (salen)Co(OAc) in tert-butyl ether resulted in a mixture of regioisomers in a 2:1 ratio, although the products were not identified. 16b Thus, we were interested in studying the regioselective ring-opening of enantiopure epoxides with phenols or phenoxides. Initially, the ring-opening of racemic 2-phenyloxirane was studied using sodium phenoxide in the presence of β-cyclodextrin in water at 60 °C. ^{18c} However, the major product was, 2phenoxy-2-phenylethanol (9a), produced by ring opening at the benzylic position contrary to the reported 2-aryloxy-1-phenylethanol (10a). The compound 9a was identified by ¹H NMR analysis and compared with a standard sample of 10a prepared according to previous reported procedure. ^{15f} Further analyses of the reaction mixture by ¹H NMR showed **9a**, **10a** and diol 11 in 100/8/88 ratio, and in 46%, 6% and 38% isolated yield, respectively. For comparison purposes, other substrates were also reinvestigated. See Supporting Information.

The low regioselectivity and poor yields in the previous methods led us to search an alternative route for the synthesis of the desired (S)-1,2-aryoxy ethanols **10**. After various optimization studies with different bases (K_2CO_3 , NaOH, KOH and NaH) and solvents (CH_3CN , THF and DMF), in addition to various temperatures and reaction times, it was found that the treatment of epoxides **7** with phenol, previously treated with NaH, in anhydrous DMF at 60 °C for 36 h, provided the desired (S)- β -hydroxy ethers **10** in good yield without racemization. As indicated in Table 2, representative aromatic and aliphatic of (S)- β -hydroxy ether were produced under the selected conditions with outstanding enantiopurity (97 to >99% ee) and in moderate to good isolated yields of pure products (entries 1–6).

Optically active 2-azido-2-aryl ethanols are well-known precursor for the synthesis of a broad variety of enantiopure 1,2-amino alcohols, which are essential building blocks in the preparation of neurobiological active compounds.^{3,17} In addition, β -amino alcohols have been extensively used in asymmetric synthesis as chiral ligands,³ organic catalysts^{18e,21} and chiral auxiliaries or transfer agents. ²² Recently, Qu and coworkers ^{20a} reported the preparation of racemic 1,2-diols and 1,2-azido alcohols by the ring-opening of epoxides in hot water. Due to the importance of nonracemic 1,2-amino alcohol, we were interested in studying the ring opening reaction of optically pure epoxides with NaN₃. As indicated in Scheme 1, when styrene epoxide (7a) and sodium azide were heated in water at 60 °C for 3.5 h, 2-azido-2-phenyl ethanol 12a was formed as the main product with only trace amount of regioisomer 13a, as determined by GC-MS and ¹H NMR analyses of the crude product. The ratio of 12a and 13a by GC-MS analysis was 95.4:4.6. After purification by preparative TLC, it was afforded (S)-12a in 91% yield and 99% ee, based on HPLC analysis on a chiral column. Since highly enantiopure (S)-1-phenyl-2-azido ethanol was obtained, and more significantly, with complete inversion of configuration, the reaction was carried out with the p-chlorostyrene oxide 7d to demonstrate the generality of this valuable ring opening reaction. According to the analysis by GC-MS, the ratio of 2-azido-arylethanol 12d to 13d was 93:7. Remarkably, 12d was isolated in excellent yield (88%) and its optical purity was 98% ee. The stereochemistry of these compounds was confirmed by full spectroscopic analysis and optical rotation. Interestingly, this transformation only slightly decreased the enantioselectivities of compounds 12a (99% ee) and 12d (98% ee), obtaining the 2-azido-1arylethanols with inversion of configuration at the stereogenic center. Noteworthy, this highly regioselective and enantioselective conversion of styrene oxides to 1,2-azido alcohols was conducted under mild and environmental favorable conditions using only hot water,

providing a rapid access to important non natural amino alcohols, as well as to biological building blocks that can be used for example in the click chemistry for the formation of chiral triazoles or amides. ²³ Further expansion of the azidolysis reaction of epoxides and reduction of the azido group to obtain a variety of 2-amino-2-heteroaryl ethanols will be addressed in future studies.

In summary, the enantioselective reduction of 2-haloketones using 10% of the spiroaminoborate ester **1** offers a convenient and facile route for the synthesis of a variety of highly enantiopure epoxides. The ring-opening of racemic styrene oxides by aryloxy nucleophiles in hot water in the presence of β -cyclodextrin takes place by a preferential nucleophilic attack to the benzylic position providing 2-aryloxy-2-aryl ethanols as the mayor product. However, the treatment of chiral epoxides, with PhONa in anhydrous DMF at 60 °C for 24–36 h, gives mainly 1-aryl and 1-alkyl β -aryloxy ethanols **10** in outstanding ee and good chemical yield. In addition, remarkable regioselective nucleophilic attack of NaN₃ to (*S*)-epoxides in hot water takes place affording optically pure (*R*)-2-azido-2-aryl ethanols **13** with complete inversion of configuration in outstanding enantiopurity (up to 99% ee) and in high yield.

Experimental Section

General procedure for asymmetric reduction and epoxidation

To a solution of spiroaminoborate ester $\mathbf{1}^{15}$ (64 mg, 0.2 mmol) in dry THF (5 mL) was added BH₃•DMS (0.14 mL, 10 M, 1.4 mmol) at room temperature under N₂ atmosphere, and the solution was stirred for 30 min. A solution of the 2-haloketone (2 mmol) in dry THF (4 mL) was added dropwise for 1 h. After the addition was complete, the reaction mixture was stirred for 30 min, cooled at 0 °C, and quenched with MeOH (5 mL). The solvents were removed under reduced pressure, and the residue was treated with 2 N NaOH (5 mL) in THF (10 mL) for 2 h. After an aqueous work-up the residue was purified by flash column chromatography on silica.

Typical procedure for the preparation of enantiopure β -hydroxy ethers: (S)-(+)-1-(3-Methoxy-phenyl)-2-phenoxyethanol (10j)

A dried three-necked 25 mL round bottom flask charged with NaH (30.3 mg, 1.2 mmol, 1.2 equiv, 95%) in anhydrous DMF (2 mL) was added dropwise PhOH (94.1 mg, 1.0 mmol) in anhydrous DMF (2 mL) at ambient temperature under nitrogen. After the mixture was stirred for 10 min, a solution of epoxide **7j** (150.2 mg, 1.0 mmol) in anhydrous DMF (2 mL) was added dropwise. The mixture was stirred at 60 °C for 24 h and after aqueous work-up the residue was purified by preparative TLC. The desired product was obtained in 82% yield (200 mg) as colorless oil; 98% ee, determined by chiral HPLC analysis.

General procedure for the preparation of 2-azido-2-arylethanols

To a stirred suspension of epoxide (1 mmol) in distilled water (6 mL) in a 25 mL flask with condenser was added sodium azide (2 mmol, 130 mg). The mixture was stirred for 3.5 h at $60\,^{\circ}$ C and then, 20 mL water was added. The product was isolated by preparative TLC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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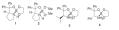


FIGURE 1. Representative Aminoborate Complexes.

No. 1, 90% or 15 year 1, 90% or 10 year 11 M R = Cl. 50% or 16 year 11 M R = Cl. 50% o

SCHEME 1.

Ring-opening of Epoxides with NaN3 in Hot Water

 $\label{eq:TABLE 1} \textbf{Asymmetric Reduction α-Haloketones for the Synthesis of Epoxides}^a$

O		ŌН		_
R^{X}	Cat 1	<u>-</u> Х	NaOH	-,,0
5	BH ₃ ·DMS THE	П 6		R ↑

	5 THF 6	7		
entry	epoxides		yield (%) <i>b</i>	ee (%) ^C
1		7a	90	99
2		7b	90	99
3	F	7c	66	98
	F			
4		7d	89	99
5	CI	7e	95	97
	O ₂ N			

	5 THF 6	7		
entry	epoxides		yield (%) ^b	ee (%)¢
6	NC	7f	78	95
7	Br	7 g	91	99
8	Br	7h	76	99 ^d
9		7i	71 ^e	98 <i>d</i>
10		7 j	72	98 ^f
11		7k	88	97 <i>d</i>
12		71	93	>99d

 $^{^{}a}\mathrm{All}$ the reactions were performed as reported in the experimental procedure.

 $^b\mathrm{Purified}$ by flash chromatography or Kugelrohr distillation.

 $^{^{\}it c}$ Determined by GC on a chiral column.

 $^{^{}d}_{\mbox{\scriptsize Determined}}$ by chiral HPLC on the basis of $\beta\mbox{-hydroxyl}$ ether.

 $^{^{}e}_{t}$ -BuOK was used in the epoxidation reaction.

 $f_{\mbox{Determined by chiral HPLC}}$

 $\label{eq:TABLE 2} \textbf{Preparation of β-Hydroxy Ethers 10 from Epoxides 7}$

$N = \frac{P(0) - P(0) + A(1) + C(0)}{n < \sum_{i} n_i} = \frac{Q^2}{n + C(0)}$				
entry	product		yield (%) ^a	ee (%)b
1	OH OPh	10a	77	>99
2	BrOPh	10h	62	99
3	OH OPh	10i	88	98
4	O OPh	10j	82	98
5	OPh	10k	52	97
6	OPh	101	77 ^c	>99

^aThe products were obtained by preparative TLC.

 $[^]b\mathrm{Determined}$ by HPLC (Chiralcel OD-H).

^cReaction time 36 h.