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ORIGINAL PAPER

# Asymmetric synthesis of α-bromohydrins by carrot root as biocatalyst and conversion to enantiopure β-hydroxytriazoles and styrene oxides using click chemistry and $S_N2$ ring-closure

**Rahman Hosseinzadeh**[1] · **Maryam Mohadjerani**[2] · **Sakineh Mesgar**[1]

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**Abstract**
In this study we have combined the bioreduction of α-bromoketones using carrot root as biocatalyst and click chemistry for the preparation of enantiopure β-hydroxytriazoles in excellent enantiomeric excesses and yields. Moreover, we have utilized chiral α-halohydrins for the synthesis of enantiopure styrene oxides in very good yields and enantiomeric excesses. Structural assignments of the products were based on their $^{1}H$ and $^{13}C$ NMR data and their optical rotations. The enantiomeric excess of the chiral products was obtained by HPLC analysis.

**Keywords** Bioreduction · Biocatalyst · Carrot root · Chiral α-halohydrins · Chiral β-hydroxytriazoles · Chiral styrene oxides

## Introduction

β-Hydroxy 1,2,3-triazoles are particularly interesting, not only due to possessing 1,2,3-triazole structural scaffold which has proven to exhibit interesting biological properties such as antibacterial, antiviral, antiepileptic, and anti-allergic activities [1–5] but also as β-adrenergic receptor blocker analogues [6] and as HIV-1 protease inhibitors [7, 8]. Recently, a few procedures have been reported for the synthesis of chiral β-hydroxytriazoles by the reaction of sodium azide with chiral epoxides [9, 10] or α-haloketones [11, 12] followed by click reaction with terminal alkynes.

Enantiomerically pure styrene oxides are important chiral building blocks for pharmaceutically important compounds such as the antidepressant Sertraline, the adrenergic blockers Nifenalol and Salmeterol, antiviral agents, and some kinase inhibitors [13–15]. Among the approaches developed for the preparation of chiral styrene oxides, we can mention sharpless asymmetric dihyroxylation of styrenes [16, 17], Jacobsens direct epoxidation of styrenes using (salen) Mn complexes [18, 19] and enzymatic kinetic resolution of racemic epoxides [20–23]. The catalytic asymmetric reduction of α-haloketones to the corresponding halohydrins via chiral organo catalysts [24, 25] or biocatalysts [26–32] followed by base catalyzed $S_N2$ ring-closure can be an effective approach to achieve the chiral epoxides.

The use of plant as a whole living cell system in organic biotransformation, especially for asymmetric reduction has been continuously increasing over the past decade [33]. Compared to isolated enzymes involved in reduction (alcohol-dehydrogenases ADHs), these systems do not require cofactors and cofactor regeneration systems since they already have these requirements. In addition, plants are easily obtainable from markets and easily manipulated by organic chemists in a laboratory without special equipment. Besides, they may be edible and be therefore more suitable for being used in food or pharmaceuticals industry [34, 35]. Carrot (*Daucus carota*) roots has been shown to reduce acetophenones [36, 37] and other ketones [38, 39] with excellent selectivity. We have recently studied the bioreduction of carbonyl compounds by carrot [40–42]. In continuation of our studies on developing an efficient method for the preparation of several chiral compounds, we set out now to probe the bioreduction of α-bromoketones to enantiopure α-bromohydrins using carrot root as biocatalyst. The desired

✉ Rahman Hosseinzadeh
r.hosseinzadeh@umz.ac.ir

[1] Department of Organic Chemistry, Faculty of Chemistry, University of Mazandaran, Babolsar, Iran

[2] Department of Molecular and Cell Biology, Faculty of Basic Science, University of Mazandaran, Babolsar, Iran

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products were utilized in the synthesis of chiral styrene oxides and chiral $\beta$-hydroxytriazoles.

## Materials and methods

All reagents and chemicals were purchased from commercial sources and were used without further purification. The starting phenacyl bromides were prepared from the corresponding acetophenones by bromination method [43]. Fresh carrot roots were purchased from a local market. The external layer of roots was removed and the rest was carefully cut into small thin pieces (approximately 5 mm × 5 mm × 2 mm). All melting points were measured on a Thermo scientific model 9100. The $^{1}H$ and $^{13}C$ NMR spectra were registered in $CDCl_3$ with a Bruker Avance III 400 MHz spectrometer using TMS as internal standard. Optical rotations were measured with a Kruess, P3001 polarimeter. The enantiomeric excess of the chiral products was obtained by HPLC with chiral column Chiralpak AS-H (25 cm × 4.6 mm) and mobile phase, *n*-hexane/isopropanol (80:20) with flow rate 0.5 mL/min at a wavelength of 241 nm.

### General method for the asymmetric bioreduction of *α*-bromoketones 1–6 using *Daucus carota*

$\alpha$-Bromoketones (1.0 mmol) were added to a suspension of freshly cut *D. carota* roots (17 g) in 100 mL of distilled water and the reaction mixtures were incubated in an orbital shaker (150 rpm) at 30 °C. The progress of the reaction was monitored by TLC or by GC. After completion of the reaction, the suspensions were filtered off and the carrot root was washed successively with water. Filtrates were extracted with ethyl acetate (3 × 30 mL), dried on anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel using ethyl acetate/*n*-hexane gradient to give the desired products in high purity.

#### (R)-2-Bromo-1-phenylethanol (1a)

$^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta = 8.00$ (dt, $J = 8.2$, 2.0 Hz, 2H, Ar H), 7.63 (tt, $J = 7.2$, 2.0 Hz, 1H, Ar H), 7.56–7.48 (m, 2H, Ar H), 4.73 (dd, $J = 9.6$, 3.6 Hz, 1H, CH), 3.88 (dd, $J = 13.6$, 9.6 Hz, 1H, $CH_2$), 3.77 (dd, $J = 13.6$, 3.6 Hz, 1H, $CH_2$), 2.60 (br s, 1H, OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 140.10$ ($C_q$), 134.02 (Ar C), 128.96 (Ar C), 128.90 (Ar C), 81.71 (CH), 36.62 ($CH_2$). $[\alpha]_D^{25} = -38.2°$ (*c* 1.00 in $CHCl_3$) [lit. +39.80°, *c* 1.2 in $CHCl_3$ for *S* isomer] [44], colorless oil, retention times (min): 11.60 (*S*), 13.21 (*R*).

#### (R)-2-Bromo-1-(4′-bromophenyl) ethanol (2a)

$^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.86$ (dt, $J = 8.8$, 2.0 Hz, 2H, Ar H), 7.66 (dt, $J = 8.8$, 2.0 Hz, 2H, Ar H), 4.70 (dd, $J = 8.0$, 2.8 Hz, 1H, CH), 3.88 (dd, $J = 14.0$, 8.0 Hz, 1H, $CH_2$), 3.82 (dd, $J = 14.0$, 2.8 Hz, 1H, $CH_2$), 2.58 (br s, 1H, OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 139.27$ ($C_q$), 132.50 (Ar C), 128.45 (Ar C), 122.37 ($C_q$), 80.66 (CH), 36.38 ($CH_2$). $[\alpha]_D^{25} = -34.9$ (*c* 1.00 in $CHCl_3$) [lit. −42.7°, *c* 0.5102 in $CHCl_3$] [45], mp: 73 °C [46], retention times (min): 12.95 (*S*), 16.78 (*R*).

#### (R)-2-Bromo-1-(3′-chlorophenyl) ethanol (3a)

$^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.14$ (d, $J = 8.4$ Hz, 1H, Ar H), 7.13–7.09 (m, 2H, Ar H), 6.99–6.97 (m, 1H, Ar H), 4.62 (dd, $J = 3.6$, 3.2 Hz, 1H, CH), 3.78 (dd, $J = 14.1$, 3.6 Hz, 1H, $CH_2$), 3.63 (dd, $J = 14.1$, 3.2 Hz, 1H, $CH_2$), 2.49 (br s, 1H, OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 140.47$ ($C_q$), 134.53 (Ar C), 129.60 (Ar C), 128.02 (Ar C), 127.50 (Ar C), 126.45 ($C_q$), 82.80 (CH), 35.21 ($CH_2$). $[\alpha]_D^{25} = -37.4°$ (*c* 0.50 in $CHCl_3$) [lit. −22.10°, *c* 0.9671 in $CHCl_3$] [45], colorless oil, retention times (min): 10.19 (*S*), 11.54 (*R*).

#### (R)-2-Bromo-1-(4′-chlorophenyl) ethanol (4a)

$^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (dt, $J = 8.8$, 2.4 Hz, 2H, Ar H), 7.66 (dt, $J = 8.8$, 2.4 Hz, 2H, Ar H), 4.51 (dd, $J = 3.2$, 2.4 Hz, 1H, CH), 3.67 (dd, $J = 12.4$, 3.2 Hz, 1H, $CH_2$), 3.63 (dd, $J = 12.4$, 2.4 Hz, 1H, $CH_2$), 2.38 (br s, 1H, OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 137.56$ ($C_q$), 134.70 ($C_q$), 129.31 (Ar C), 127.87 (Ar C), 84.22 (CH), 35.08 ($CH_2$). $[\alpha]_D^{25} = -45.8°$ (*c* 2.1 in $CHCl_3$); [lit. −59.5° (*c* 0.9966 in $CHCl_3$)] [45], colorless oil, retention times (min): 11.56 (*S*), 12.30 (*R*).

#### (R)-2-Bromo-1-(4′-methoxyphenyl) ethanol (5a)

$^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.83$ (dt, $J = 9.0$, 3.2 Hz, 2H, Ar H), 7.64 (dt, $J = 9.0$, 2.9 Hz, 2H, Ar H), 4.49 (dd, $J = 4.0$, 3.6 Hz, 1H, CH), 3.81 (s, 3H, $CH_3$), 3.65 (dd, $J = 14.8$, 3.6 Hz, 1H, $CH_2$), 3.60 (dd, $J = 14.8$, 4.0 Hz, 1H, $CH_2$), 2.36 (br s, 1H, OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 159.31$ ($C_q$), 133.60 ($C_q$), 129.90 (Ar C), 114.02 (Ar C), 79.90 (CH), 55.84 ($CH_3$), 35.75 ($CH_2$). $[\alpha]_D^{25} = -41.9$ (*c* 0.5 in $CHCl_3$) [lit. +36.7° (*c* 0.450 in $CHCl_3$), for *S* isomer] [47], colorless oil, retention times (min): 12.15 (*S*), 13.90 (*R*).

#### (R)-2-Bromo-1-naphtylethanol (6a)

$^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.89$–7.79 (m, 4H, Ar H), 7.56–7.49 (m, 3H, Ar H), 4.52 (dd, $J = 3.6$, 3.4 Hz, 1H,

CH), 3.69 (dd, $J = 13.9$, 3.6 Hz, 1H, $CH_2$), 3.64 (dd, $J = 13.9$, 3.4 Hz, 1H, $CH_2$), 2.39 (br s, 1H, OH). *13C* NMR: (100 MHz, $CDCl_3$): $\delta = 144.02$ ($C_q$), 134.62 ($C_q$), 134.61 ($C_q$), 128.74 (Ar C), 128.51 (Ar C), 128.40 (Ar C), 127.50 (Ar C), 127.21 (Ar C), 126.89 (Ar C), 126.66 (Ar C), 81.41, 35.12. $[\alpha]_D^{25} = -42.6°$ ($c$ 0.50 in $CHCl_3$), colorless oil, retention times (min): 10.66 (*S*), 12.47 (*R*).

## General method for the preparation of enantiopure *β*-hydroxytriazoles from *α*-bromohydrins

In the second step, (32 mg, 0.5 mmol) sodium azide was added to (0.5 mmol) chiral $\alpha$-bromohydrins and water (10 mL) in 50 °C. The progress of the reaction was controlled by TLC. After completion of the reaction, terminal acetylene (0.5 mmol), copper sulfate (0.13 mmol) and sodium ascorbate (0.4 mmol) were added. The resulting mixture was stirred at room temperature until complete conversion of starting material, as indicated by TLC. After extraction with ethyl acetate ($3 \times 30$ mL), the organic phases were separated and dried over anhydrous $MgSO_4$, and the solvent was removed under vacuum. The crude products were purified by column chromatography on silica gel using ethyl acetate/*n*-hexane gradient to give the desired product in high purity.

### (R)-1-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl) ethanol (1c)

*1H* NMR (400 MHz, $CDCl_3$): $\delta = 8.05$–8.03 (m, 2H, Ar H), 7.97 (s, 1H, Ar H), 7.90–7.88 (m, 2H, Ar H), 7.72–7.68 (m, 1H, Ar H), 7.59–7.55 (m, 2H, Ar H), 7.47–7.43 (m, 2H, Ar H), 7.38–7.34 (m, 1H, Ar H), 5.36 (dd, $J = 8.8$, 2.4 Hz, 1H, CH), 4.74 (dd, $J = 11.6$, 8.8 Hz, 1H, $CH_2$), 4.68 (dd, $J = 11.6$, 2.4 Hz, 1H, $CH_2$), 3.62 (br s, 1H, OH). *13C* NMR (100 MHz, $CDCl_3$): $\delta = 148.22$ ($C_q$), 136.65 ($C_q$), 135.95 (Ar C), 130.01 ($C_q$), 129.76 (Ar C), 128.84 (Ar C), 128.22 (Ar C), 128.20 (Ar C), 125.83 (Ar C), 121.50 (Ar C), 74.23 (CH), 65.10 ($CH_2$). $[\alpha]_D^{25} = -38.6°$ ($c$ 1.50 in $CHCl_3$), mp: 114–116 °C, retention times (min): 24.4 (*S*), 28.7 (*R*).

### (R)-1-(4′-Bromophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl) ethanol (2c)

*1H* NMR (400 MHz, $CDCl_3$): $\delta = 8.07$–8.05 (m, 2H, Ar H), 7.99 (s, 1H, Ar H), 7.91–7.89 (m, 2H, Ar H), 7.74–7.70 (m, 1H, Ar H), 7.60–7.57 (m, 2H, Ar H), 7.49–7.36 (m, 2H, Ar H), 5.38 (dd, $J = 8.4$, 4.0 Hz, 1H, CH), 4.76 (dd, $J = 12.4$, 8.4 Hz, 1H, $CH_2$), 4.70 (dd, $J = 12.4$, 4.0 Hz, 1H, $CH_2$), 3.64 (br s, 1H, OH). *13C* NMR (100 MHz, $CDCl_3$); $\delta = 148.20$ ($C_q$), 136.63 ($C_q$), 134.93 (Ar C), 129.73 (Ar C), 129.19 ($C_q$), 128.20 (Ar C), 128.17 (Ar C), 128.03 (Ar C), 126.22 (Ar C), 121.48 ($C_q$), 68.69 (CH), 62.99 ($CH_2$). $[\alpha]_D^{25} = -37.1°$ ($c$ 1.00 in $CHCl_3$), mp: 210–212 °C, retention times (min): 28.3 (*S*), 30.5 (*R*).

### (R)-1-(3′-Chlorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl) ethanol (3c)

*1H* NMR (400 MHz, $CDCl_3$): $\delta = 7.89$–7.86 (m, 2H, Ar H), 7.82 (s, 1H, Ar H), 7.80–7.72 (m, 2H, Ar H), 7.70–7.61 (m, 1H, Ar H), 7.51–7.48 (m, 1H, Ar H), 7.40–7.36 (m, 2H, Ar H), 7.31–7.27 (m, 1H, Ar H), 5.41 (dd, $J = 9.6$, 3.6 Hz, 1H, CH), 4.77 (dd, $J = 12.0$, 9.6 Hz, 1H, $CH_2$), 4.71 (dd, $J = 12.0$, 3.6 Hz, 1H, $CH_2$), 3.65 (br s, 1H, OH). *13C* NMR (100 MHz, $CDCl_3$): $\delta = 146.59$ ($C_q$), 140.78 ($C_q$), 135.51 ($C_q$), 130.67 ($C_q$), 130.14 (Ar C), 129.37 (Ar C), 129.00 (Ar C), 128.45 (Ar C), 127.77 (Ar C), 127.23 (Ar C), 126.89 (Ar C), 122.63 (Ar C), 70.84 (CH), 62.93 ($CH_2$). $[\alpha]_D^{25} = -40.8°$ ($c$ 1.00 in $CHCl_3$), mp: 120–123 °C, retention times (min): 27.0 (*S*), 29.1 (*R*).

### (R)-1-(4′-Chlorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl) ethanol (4c)

*1H* NMR (400 MHz, $CDCl_3$): $\delta = 8.12$–8.10 (m, 2H, Ar H), 8.05 (s, 1H, Ar H), 8.03–7.95 (m, 2H, Ar H), 7.94–7.61 (m, 1H, Ar H), 7.53–7.50 (m, 2H, Ar H), 7.45–7.40 (m, 2H, Ar H), 5.43 (dd, $J = 8.0$, 3.2 Hz, 1H, CH), 4.81 (dd, $J = 13.6$, 8.0 Hz, 1H, $CH_2$), 4.74 (dd, $J = 13.6$, 3.2 Hz, 1H, $CH_2$), 3.69 (br s, 1H, OH). *13C* NMR (100 MHz, $CDCl_3$): $\delta = 149.30$ ($C_q$), 135.74 ($C_q$), 133.73 (Ar C), 130.26 ($C_q$), 129.58 ($C_q$), 128.99 (Ar C), 128.62 (Ar C), 128.00 (Ar C), 127.97 (Ar C), 121.28 (Ar C), 69.00 (CH), 63.30 ($CH_2$). $[\alpha]_D^{25} = -48.2°$ ($c$ 1.00 in $CHCl_3$) [lit. +48.93° ($c$ 1.00 in acetone), for *S* isomer] [7], mp: 218 °C, retention times (min): 30.4 (*S*), 33.8 (*R*).

### (R)-1-(4′-Methoxyphenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl) ethanol (5c)

*1H* NMR (400 MHz, $CDCl_3$): $\delta = 7.74$–7.72 (m, 2H, Ar H), 7.67 (s, 1H, Ar H), 7.65–7.57 (m, 2H, Ar H), 7.56–7.33 (m, 1H, Ar H), 7.25–7.22 (m, 2H, Ar H), 7.17–7.13 (m, 2H, Ar H), 5.25 (dd, $J = 9.2$, 2.8 Hz, 1H, CH), 4.63 (dd, $J = 11.6$, 9.2 Hz, 1H, $CH_2$), 4.57 (dd, $J = 11.6$, 2.8 Hz, 1H, $CH_2$), 4.50 (s, 3H, $CH_3$), 3.54 (br s, 1H, OH). *13C* NMR (100 MHz, $CDCl_3$): $\delta = 147.90$ ($C_q$), 141.52 ($C_q$), 136.33 (Ar C), 133.63 ($C_q$), 129.43 ($C_q$), 128.79 (Ar C), 128.42 (Ar C), 127.77 (Ar C), 125.92 (Ar C), 121.18 (Ar C), 68.90 (CH), 63.20 ($CH_2$), 57.78 ($CH_3$). $[\alpha]_D^{25} = -42.5°$ ($c$ 1.00 in $CHCl_3$), mp: 149–152 °C, retention times (min): 29.5 (*S*), 34.3 (*R*).

#### (R)-1-Naphtyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl) ethanol (6c)

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 8.03–8.02$ (m, 2H, Ar H), 8.01 (s, 1H, Ar H), 7.95–7.87 (m, 2H, Ar H), 7.86–7.69 (m, 1H, Ar H), 7.68–7.66 (m, 1H, Ar H), 7.57–7.53 (m, 1H, Ar H), 7.45–7.41 (m, 2H, Ar H), 7.36–7.34 (m, 2H, Ar H), 7.33–7.26 (m, 1H, Ar H), 5.40 (dd, $J = 9.6$, 3.6 Hz, 1H, CH), 4.77 (dd, $J = 12.0$, 9.6 Hz, 1H, $CH_2$), 4.70 (dd, $J = 12.0$, 3.6 Hz, 1H, $CH_2$), 3.65 (br s, 1H, OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 146.59$ ($C_q$), 140.78 ($C_q$), 133.51 ($C_q$), 131.14 (Ar C), 130.67 ($C_q$), 129.37 ($C_q$), 129.00 (Ar C), 128.80 (Ar C), 128.54 (Ar C), 127.77 (Ar C), 127.46 (Ar C), 127.23 (Ar C), 126.79 (Ar C), 126.41 (Ar C), 125.66 (Ar C), 121.39 (Ar C), 72.43 (CH), 60.87 ($CH_2$). $[\alpha]_D^{25} = -45.3°$ ($c$ 1.00 in $CHCl_3$), mp: 230–232 °C, retention times (min): 25.5 ($S$), 29.9 ($R$).

#### (R)-1-Phenyl-2-(4-(1-hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl) ethanol (7c)

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.94–7.92$ (m, 2H, Ar H). 7.86 (s, 1H, Ar H), 7.79–7.77 (m, 2H, Ar H), 7.61–7.57 (m, 1H, Ar H), 5.24 (dd, $J = 9.6$, 2.4 Hz, 1H, CH), 4.40 (dd, $J = 12.0$, 9.6 Hz, 1H, $CH_2$), 4.37 (dd, $J = 12.0$, 2.4 Hz, 1H, $CH_2$), 3.55 (br s, 1H, OH), 3.79 (s, 1H, OH), 1.95–1.80 (m, 2H, $CH_2$), 1.71–1.59 (m, 4H, $CH_2$), 1.49–1.36 (m, 3H, $CH_2$), 1.30–1.21 (m, 1H, $CH_2$). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 147.54$ ($C_q$), 136.02 ($C_q$), 133.46 (Ar C), 130.31 (Ar C), 129.14 (Ar C), 126.00 (Ar C), 73.77 ($C_q$), 64.19 (CH), 60.99 ($CH_2$), 36.12 ($CH_2$), 24.24 ($CH_2$), 22.70 ($CH_2$). Anal. Calcd. for $C_{16}H_{21}N_3O_2$ (287.39): C, 66.86; H, 7.36; N, 14.62; O, 11.13. Found: C, 66.60; H, 7.21; N, 14.73. $[\alpha]_D^{25} = -11.7°$ ($c$ 1.00 in $CHCl_3$), mp: 227–231 °C, retention times (min): 10.7 ($S$), 13.7 ($R$).

#### (R)-1-Phenyl-2-(4-(2-hydroxypropane-2-yl)-1H-1,2,3-triazol-1-yl) ethanol (8c)

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 8.09–8.07$ (m, 2H, Ar H), 7.99 (s, 1H, Ar H), 7.92–7.90 (m, 2H, Ar H), 7.74–7.70 (m, 1H, Ar H), 5.26 (dd, $J = 8.0$, 2.4 Hz, 1H, CH), 4.62 (dd, $J = 11.2$, 8.0 Hz, 1H, $CH_2$), 4.57 (dd, $J = 11.2$, 2.4 Hz, 1H, $CH_2$), 4.20 (s, 1H, OH), 3.49 (br s, 1H, OH), 1.90 (s, 6H, $CH_3$). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 146.96$ ($C_q$), 136.13 ($C_q$), 134.73 (Ar C), 129.09 (Ar C), 128.28 (Ar C), 126.88 (Ar C), 74.23 ($C_q$), 65.10 (CH), 51.17 ($CH_2$), 30.45 ($CH_3$). Anal. Calcd. for $C_{13}H_{17}N_3O_2$ (247.31): C, 63.13; H, 6.92; N, 17.00; O, 12.94. Found: C, 63.02; H, 7.00; N, 17.13. $[\alpha]_D^{25} = -22.6°$ ($c$ 0.50 in $CHCl_3$), mp: 192–194 °C, retention times (min): 16.6 ($S$), 19.3 ($R$).

#### (R)-1-Phenyl-2-(4-ferrocenyl-1H-1,2,3-triazol-1-yl) ethanol (9c)

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 8.09–8.07$ (m, 2H, Ar H), 7.99 (s, 1H, Ar H), 7.92–7.74 (m, 2H, Ar H), 7.73–7.70 (m, 1H, Ar H), 5.56 (dd, $J = 9.6$, 4.0 Hz, 1H, CH), 4.78 (t, $J = 1.6$ Hz, 2H, CH), 4.44 (dd, $J = 14.0$, 9.6 Hz, 1H, $CH_2$), 4.38 (dd, $J = 14.0$, 4.0 Hz, 1H, $CH_2$), 4.20 (t, $J = 1.6$ Hz, 2H, CH), 4.06 (s, 5H, CH), 3.41 (br s, 1H, OH). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 147.29$ ($C_q$), 133.64 ($C_q$), 132.16 (Ar C), 129.47 (Ar C), 122.85 ($C_q$), 119.01 (Ar C), 76.65 (CH), 72.32 (CH), 68.68 (CH), 67.97 (CH), 66.75 (CH), 64.22 ($CH_2$). Anal. Calcd. for $C_{20}H_{19}N_3OFe$ (373.27): C, 64.35; H, 5.12; N, 11.25; O, 4.28; Fe, 14.96. Found: C, 64.20; H, 5.32; N, 11.14. $[\alpha]_D^{25} = -59.9°$ ($c$ 1.00 in $CHCl_3$), mp: 224–226 °C, retention times (min): 11.4 ($S$), 14.9 ($R$).

### General procedure for the synthesis of chiral styrene oxides

For the preparation of chiral styrene oxides, 3 mL NaOH (2 N) was added to $\alpha$-bromohydrin (0.5 mmol) in 6 mL tetrahydrofuran (THF) and then was sttired at room temperature for 1 h. After completing the reaction, the product was extracted by EtOAc and then purified using column chromatography on silica gel using ethyl acetate/$n$-hexane gradient to give the desired product in high purity.

#### (R)-Phenyl oxiran (1d)

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.41–7.27$ (m, 5H, Ar H), 3.70 (dd, $J = 2.8$, 2.6 Hz, 1H, CH), 2.81 (dd, $J = 5.6$, 2.8 Hz, 1H, $CH_2$), 2.53 (dd, $J = 5.6$, 2.6 Hz, 1H, $CH_2$). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 137.04$ ($C_q$), 130.05 (Ar C), 130.00 (Ar C), 129.75 (Ar C), 57.10 (CH), 51.44 ($CH_2$). $[\alpha]_D^{25} = -27.0°$ ($c$ 1.0 in $CHCl_3$), Lit.$[\alpha]_D^{20} = +25.1°$ ($c$ 1.10 in $CHCl_3$, for S enantiomer) [48], colorless oil, retention times (min): 40.8 ($S$), 45.2 ($R$).

#### (R)-4-Bromo-phenyl oxiran (2d)

$^1H$ NMR (400 MHz, $CDCl_3$); $\delta = \delta$(ppm): 7.68–7.63 (m, 2H, Ar H), 7.41–7.38 (m, 2H, Ar H), 3.71 (dd, $J = 4.0$, 2.4 Hz, 1H, CH), 2.81 (dd, $J = 7.6$, 4.0 Hz, 1H, $CH_2$), 2.52 (dd, $J = 7.6$, 2.4 Hz, 1H, $CH_2$). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 136.70$ ($C_q$), 131.66 (Ar C), 127.23 (Ar C), 122.88 ($C_q$), 56.60 (CH), 50.12 ($CH_2$). $[\alpha]_D^{25} = -13.7°$ ($c$ 1.5 in $CHCl_3$); Lit.$[\alpha]_D^{20} = +13.6°$ ($c = 1.46$ in $CHCl_3$ for S enantiomer) [49], colorless oil, retention times (min): 35.03 ($S$), 40.72 ($R$).

#### (R)-3-Chloro-phenyl oxiran (3d)

$^1H$ NMR (400 MHz, $CDCl_3$); $\delta = 7.59–7.50$ (m, 1H, Ar H), 7.46–7.41 (m, 2H, Ar H), 7.38–7.33 (m, 1H, Ar H), 3.62 (dd, $J = 3.2$, 2.8 Hz, 1H, CH), 2.72 (dd, $J = 5.6$, 3.2 Hz, 1H, $CH_2$), 2.43 (dd, $J = 5.6$, 2.8 Hz, 1H, $CH_2$). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 139.96$ ($C_q$), 135.02 (Ar C), 129.67 (Ar C), 129.11 ($C_q$), 127.13 (Ar C), 126.99 (Ar C), 57.10 (CH), 51.68 ($CH_2$). $[\alpha]_D^{25} = -11°$ ($c$ 1.8 in $CHCl_3$), Lit. $[\alpha]_D^{25} = +9°$ ($c$ 1.20 in $CHCl_3$ for S enantiomer) [49], colorless oil, retention times (min): 44.1 (*S*), 48.3 (*R*).

#### (R)-4-Chloro-phenyl oxiran (4d)

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.49–7.45$ (m, 2H, Ar H), 7.23–7.20 (m, 2H, Ar H), 3.60 (dd, $J = 3.2$, 2.8 Hz, 1H, CH), 2.71 (dd, $J = 6.4$, 2.8 Hz, 1H, $CH_2$), 2.42 (dd, $J = 6.4$, 3.2 Hz, 1H, $CH_2$). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 136.56$ ($C_q$), 133.42 ($C_q$), 130.01 (Ar C), 128.46 (Ar C), 57.01 (CH), 50.94 ($CH_2$). $[\alpha]_D^{25} = -21.1°$ ($c$ 1.2 in $CHCl_3$); Lit. $[\alpha]_D^{20} = +19.3°$ ($c = 1.16$ in $CHCl_3$, for S enantiomer) [49], colorless oil, retention times (min): 42.5 (*S*), 46.2 (*R*).

#### (R)-4-Methoxy-phenyl oxiran (5d)

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.49–7.44$ (m, 2H, Ar H), 7.22–7.20 (m, 2H, Ar H), 3.90 (s, 3H, CH3), 3.60 (dd, $J = 4.4$, 3.6 Hz, 1H, CH), 2.70 (dd, $J = 6.8$, 4.4 Hz, 1H, $CH_2$), 2.42 (dd, $J = 6.8$, 3.6 Hz, 1H, $CH_2$). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 157.96$ ($C_q$), 130.00 ($C_q$), 127.50 (Ar C), 113.72 (Ar C), 57.25 ($CH_3$), 56.67 (CH), 51.01 ($CH_2$). $[\alpha]_D^{25} = -31.4°$ ($c$ 1.00 in $CHCl_3$), colorless oil, retention times (min): 39.0 (*S*), 41.9 (*R*).

#### (R)-Naphtyl oxiran (6d)

$^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (d, $J = 9.6$ Hz, 1H, Ar H), 7.89–7.78 (m, 3H, Ar H), 7.77–7.58 (m, 3H, Ar H), 4.07 (dd, $J = 3.2$, 2.8 Hz, 1H, CH), 2.73 (dd, $J = 5.6$, 3.2 Hz, 1H, $CH_2$), 2.44 (dd, $J = 5.6$, 2.8 Hz, 1H, $CH_2$). $^{13}C$ NMR: (100 MHz, $CDCl_3$): $\delta = 139.73$ ($C_q$), 133.35 ($C_q$), 130.05 ($C_q$), 128.59 (Ar C), 127.41 (Ar C), 126.89 (Ar C), 125.26 (Ar C), 124.57 (Ar C), 122.89 (Ar C), 122.00 (Ar C), 58.21 (CH), 51.33 ($CH_2$). $[\alpha]_D^{25} = -23.9°$ ($c$ 1.00 in $CHCl_3$), colorless oil, retention times (min): 35.7 (*S*), 37.2 (*R*).

## Results and discussion

In the first step of our present strategy, we have investigated the bioreduction of $\alpha$-bromoketones (**1**–**6**, shown in Fig. 1) bearing aromatic (phenyl or 2-naphthyl) groups with bromo, chloro or methoxy substituents. We chose *D. carota* as the biocatalyst for the asymmetric reduction of phenacyl bromide derivatives to optically active alcohols due to its operational simplicity, the easy isolation of the reaction products, the inexpensive and readily available biomaterial, the mild conditions and the high yield and enantioselectivity.

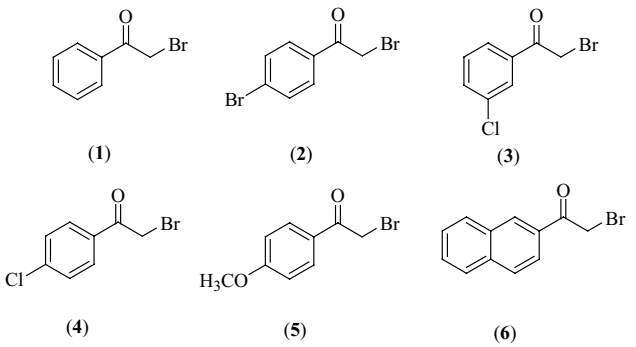
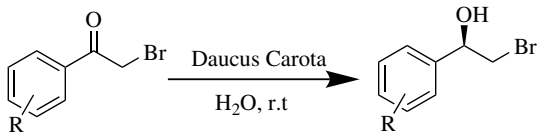



**Fig. 1** $\alpha$-Bromoketones studied in the bioreduction

**Table 1** Bioreduction of $\alpha$-bromoketones to chiral $\alpha$-bromohydrins with *Daucus carota*




**1-6** **1a-6a**

| Entry | Product | Time (h) | Isolated yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | 48 | 65 | 82 (*R*) |
| 2 | **2a** | 30 | 90 | 95 (*R*) |
| 3 | **3a** | 40 | 75 | 85 (*R*) |
| 4 | **4a** | 32 | 90 | 87 (*R*) |
| 5 | **5a** | 35 | 50 | 91 (*R*) |
| 6 | **6a** | 40 | 70 | 80 (*R*) |

Reaction condition: $\alpha$-bromoketones (1.0 mmol), *D. carota* roots (17 g), distilled water (100 mL), at 30 °C

[a]Isolated yield after column chromatography

[b]Determined by HPLC

The results of the stereoselective reduction of phenacyl bromides **1–6** with *D. carota* are summarized in Table 1. The corresponding chiral halohydrins (**1a–6a**) with *R* configuration were formed in high yields with excellent enantiomeric excess. The enantiomeric excess of these alcohols was determined by chiral HPLC analysis. The observed stereochemistry could be explained on the basis of Prelog's rule [50] and the absolute configuration was simply determined by measuring their specific rotations. All of the chiral alcohols

have been prepared previously as single enantiomers and the absolute configurations were assigned by comparison of the optical rotation data measured with values reported in the literature [13, 39, 44, 47].

The asymmetric bioreduction of phenacyl bromides was accomplished by a suspension of freshly sliced *D. carota* roots in water at 30 °C for 30–48 h. As shown in Table 1, the phenacyl bromide (**1**) was converted to its corresponding alcohol in 65% yield with 82% ee. To examine the scope and limitations of the protocol, substituted phenacyl bromides possessing electron-donating and electron-withdrawing groups were reduced under the reaction conditions. The best results were achieved with phenacyl bromides with electron-withdrawing groups *Cl* and *Br* in para-position of phenyl ring (Table 1, entries 2 and 4). Even though *para*-methoxy phenacyl bromide gave moderate yield of the corresponding halohydrin but with high ee (Table 1, entry 5). In addition, the bioreduction of ketones with *meta*-choloro phenyl and 2-naphthyl groups were also proceeded smoothly and gave good yields of the desired products (Table 1, entries 3 and 6).

As mentioned in "Introduction" section, chiral α-halohydrins are important intermediates for the synthesis of enantiopure *β*-Hydroxy 1,2,3-triazoles and also chiral epoxides. The preparation of *β*-hydroxy 1,2,3-triazoles was achieved in a straightforward procedure simply by $S_N2$ reaction of 2-bromo-1-arylethanols with sodium azide in water followed by click reaction with terminal alkynes in the presence of copper catalyst (Scheme 1).

Azido compounds are often unstable to heat and light; therefore, in situ formation of these compounds is advantageous to handle them safely. The $S_N2$ reaction was completed at 50 °C in less than 30 min as monitored by TLC and 2-azidio-1-arylethanols were formed almost quantitatively. The in situ-generated azido alcohols were then reacted with different terminal alkynes using copper sulfate and sodium ascorbate to give the corresponding *β*-hydroxy-1,4-disubstituted-1,2,3-triazoles in high yields. The copper-catalyzed azide-alkyne cycloaddition (CuAAC) is well established and its mechanism was reported [51–53]. Based on the results reported in the literature, it can be assumed that the copper (I) initially forms an acetylide with the terminal alkyne which reacts with azido compounds. Then intramolecular cyclization of resulting intermediates **1** produces the cyclic intermediate **2** which finally transformed to 1,2,3-triazole and regenerates the copper catalyst for further reactions (Scheme 2).

The results for $S_N2$ reaction and its sequential cycloaddition with alkynes are summarized in Table 2.

As shown in Table 2, the present protocol was very effective for the synthesis of *β*-hydroxy 1,2,3-triazoles. Reaction of phenyl acetylene with 2-azido-1-arylethanoles gave excellent yields of the corresponding chiral triazoles in high enantiomeric excess for most cases (Table 2, entries 1–6). A similar trend was also observed for propargyl alcohols (Table 2, entries 7 and 8) and ferrocene acetylene (Table 2, entry 9).

Homochiral styrene oxides are key intermediates for the synthesis of chiral ligands, natural products and chiral drugs in enantiopure form. (*R*)-2-bromo-1-arylethanols prepared from the reduction of the phenacyl bromides by carrot root were applied for the synthesis of chiral styrene oxides. The $S_N2$ ring-closure of 2-bromo-1-arylethanols by treatment with 2*N* NaOH in THF for 1 h afforded the corresponding epoxides in high yields and excellent enantiomeric excess.

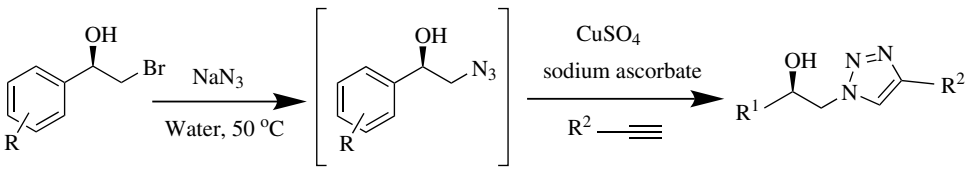
The reaction is an intramolecular variation of the Williamson ether synthesis. The alkoxide anion, formed reversibly by the reaction of bromohydrin with NaOH, displaces bromide ion from the neighboring carbon to afford the desired epoxide (Scheme 3).

The results are summarized in Table 3. The best results were achieved when (*R*)-2-bromo-1-(4′-bromophenyl) ethanol (**2a**) and (*R*)-2-bromo-1-(4′-chlorophenyl) ethanol (**4a**) were transformed to the corresponding epoxides under basic conditions (Table 3, entries 2 and 4).

## Conclusion

In summary, a useful procedure for the synthesis of chiral *β*-hydroxy 1,2,3-triazoles and chiral styrene oxides from *α*- bromoketones has been reported. The procedure consists of the use of cheap and readily available reagents, water as solvent and carrot bits as biocatalysts. Intact cells from cut portions of *D. carota* root mediated efficiently the asymmetric reduction of *α*-bromoketones. The resulting optically active alcohols are the potential chiral building blocks for the synthesis of biologically important molecules. The preparation of optical active *β*-hydroxytriazoles

**Scheme 1** The conversion of 2-bromo-1-arylethanols to *β*-Hydroxy 1,2,3-triazoles




**1a-6a** **1b-6b** **1c-9c**

**Scheme 2** Proposed mechanism of the formation of $\beta$-hydroxy-1,2,3-triazole

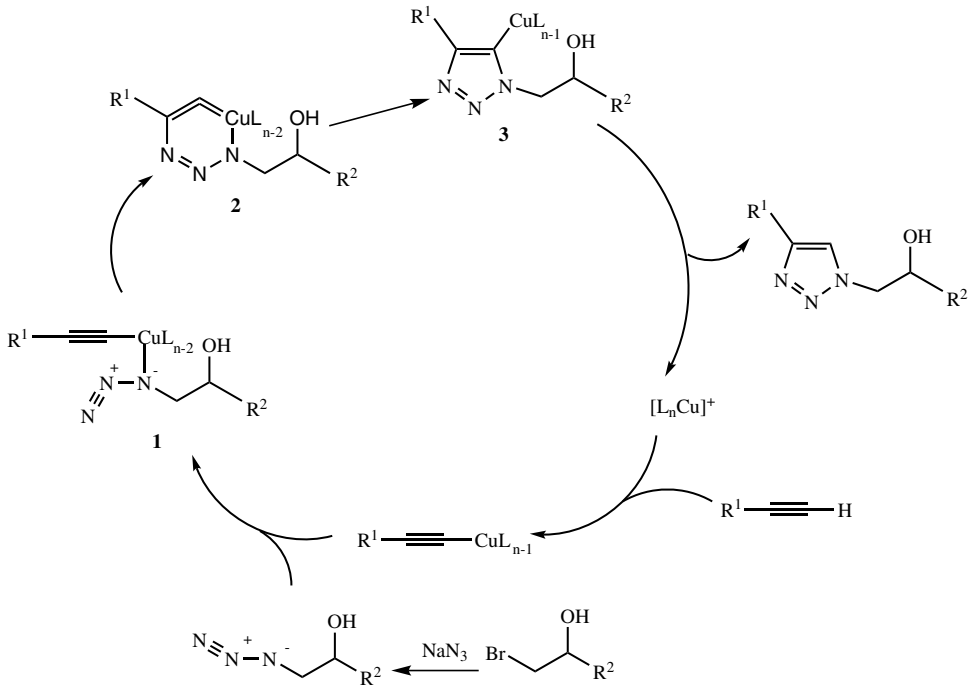
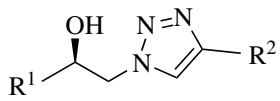


**Table 2** The synthesis of $\beta$-hydroxy 1,2,3-triazoles from 2-bromo-1-arylethanols and terminal alkynes through click reaction[a]

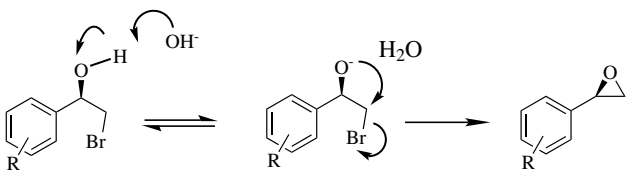


| Entry | $R_1$ | $R_2$ | Products | Time (min) | Isolated yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | Phenyl | Phenyl | **1c** | 55 | 90 | 75 (*R*) |
| 2 | *p*-Bromophenyl | Phenyl | **2c** | 45 | 98 | 97 (*R*) |
| 3 | *m*-Chlorophenyl | Phenyl | **3c** | 50 | 97 | 87 (*R*) |
| 4 | *p*-Chlorophenyl | Phenyl | **4c** | 40 | 98 | 90 (*R*) |
| 5 | *p*-Methoxyphenyl | Phenyl | **5c** | 40 | 91 | 90 (*R*) |
| 6 | 2-Naphtyl | Phenyl | **6c** | 55 | 90 | 90 (*R*) |
| 7 | Phenyl | $CH(OH)(CH_2)_5$ | **7c** | 60 | 90 | 83 (*R*) |
| 8 | Phenyl | $(CH_3)_2CHOH$ | **8c** | 60 | 95 | 79 (*R*) |
| 9 | Phenyl | Ferrocenyl | **9c** | 45 | 93 | 80 (*R*) |

Reaction condition: chiral $\alpha$-bromohydrins (0.5 mmol), sodium azide (0.5 mmol), water (10 mL), in 50 °C in second step, terminal acetylene (0.5 mmol), copper sulfate (32 mg) and sodium ascorbate (80 mg)

[a]Yield of isolated product

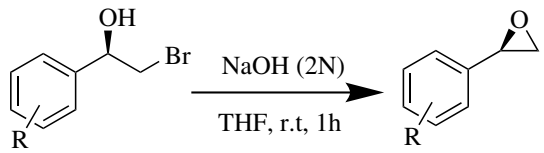
[b]Determined by HPLC



**Scheme 3** Proposed mechanism for the synthesis of chiral styrene oxide

and chiral styrene oxides are two examples and further studies are in progress to obtain other important chiral compounds.

**Table 3** The conversion of 2-bromo-1-arylethanols to styrene oxides




**1a-6a** **1d-6d**

| Entry | Product | R | Isolated yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | **1d** | H | 95 | 83 (*R*) |
| 2 | **2d** | *p*-Br | 98 | 97 (*R*) |
| 3 | **3d** | *m*-Cl | 90 | 86 (*R*) |
| 4 | **4d** | *p*-Cl | 98 | 99 (*R*) |
| 5 | **5d** | *p*-$OCH_3$ | 95 | 93 (*R*) |
| 6 | **6d** | –[c] | 92 | 85 (*R*) |

Reaction condition: chiral $\alpha$-bromohydrins (0.5 mmol), NaOH (2 N, 3 mL), THF (6 mL), at room temperature

[a]Yield of isolated product

[b]Determined by HPLC

[c]2-Bromo-1-naphtylethanol was used

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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