Asymmetric opening of styrene oxide with *p*-toluidine catalyzed by BINOL polyols and their lithium complexes

Yu. N. Belokon ',* V. I. Maleev, M. A. Moskalenko, Yu. V. Samoilichenko, A. S. Peregudov,⁺ and A. T. Tsaloev

 ^aA. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (495) 135 5085. E-mail: yubel@ineos.ac.ru

Opening of racemic styrene oxide with p-toluidine catalyzed by chiral BINOL-derived polyols proceeded regioselectively mainly with the formation of 2-phenyl-2-(p-tolylamino)-ethanol with low *ee* values.

Key words: asymmetric organic catalysis, chiral polyols, α -amino alcohols, kinetic resolution, oxiranes.

The epoxide ring opening with nucleophiles is an important reaction in organic chemistry.¹ Achiral² and chiral³ Lewis acids are widely used as catalysts in this reaction. Attempts to use organic catalysis, including its asymmetric version,^{4,5} were also undertaken. It is important to note that the natural enzymes accomplishing the epoxide ring opening do not contain metal ions, and their active groups responsible for the catalysis are phenol groups of the protein thyroxine residues.⁶



Recently, we introduced⁷ a new chiral organic catalyst BIMBOL (3,3'-bis[hydroxy(diphenyl)methyl]-1,1'-binaphthalene-2,2'-diol (1)). This tetraol containing two phenol groups has proved an efficient catalyst of a number of asymmetric conversions, including synthesis of amino acids and Michael reaction.^{7,8} The presence of four hydroxy groups in the structure of one molecule provides their synergetic interaction in the reaction activated complexes and, as a consequence, superiority of BIMBOL over diols, in particular, BINOL (2).8 It could have been expected that BIMBOL and its more acidic analogs (BICBOL (3); FBIMBOL (4)) would also be efficient organic catalysts in the asymmetric opening of epoxide with those nucleophiles which are not strong bases. Tetraol BIMBOL, like diol BINOL, possesses good chelating ability with respect to metal ions, therefore, its complexes can be efficient catalysts simultaneously exhibiting Lewis acidity due to the metal ion and Brønsted acidity due to the hydroxy groups.

In the present work, we report an opening of enantiomerically pure and racemic styrene oxides (5) with p-toluidine (6) catalyzed by polyols 1-4, as well as by lithium derivatives of compound 1 (Scheme 1).



Published in Russian in Izvestiya Akademii Nauk. Seriya Khimicheskaya, No. 6, pp. 1371–1376, June, 2013.

1066-5285/13/6206-1371 © 2013 Springer Science+Business Media, Inc.

Results and Discussion

The synthesis of compounds 1 and 2 was reported.^{9,10} Catalysts 3 and 4 were obtained according to the procedures suggested by us earlier.

The opening of styrene oxide (5) with *p*-toluidine (6) in the presence of polyols 1–4 mainly led to isomer 7a, namely, 2-phenyl-2-(p-tolylamino)ethanol, whereas regioisomer 7b, 1-phenyl-2-(p-tolylamino)ethanol, was formed in considerably lower amounts (Table 1, entries 1-10). The rate of the process was found to very strongly depend on the catalyst acidity and structure. Diol 2 (5 mol.%, CH₂Cl₂, room temperature) catalyzed the reaction, providing a 12% yield of product 7a within three days, with the asymmetric induction being absent (entry 1). The use of 5 mol.% of catalyst 1 under the same conditions gave product 7a in 28% yield and a slight enantiomeric enrichment, 5% ee (entry 2). When catalyst 3 was used under the same conditions, the yield of 7a was 39% with the enantiomeric excess ee 5% (entry 3), and the full conversion of styrene oxide was reached within ten days (entry 4). The catalytic activity of compound 4 was low, and the yield of the product was only 8% (2.5 mol.% of catalyst, 72 h, entry 5) at no enantiomeric enrichment.

The reaction was accelerated by the elevation of temperature to 55 °C (solvent toluene), and after 11 h (5 mol.% of 1) the yield of product 7a reached 37% (entry 6), however, the enantio-discrimination practically disappeared. As it was expected, diol 3 proved more active catalyst and under the same conditions gave the product in 36 and 80% yield on using 5 and 10 mol.% of the catalyst, respectively, however, without enantiomeric enrichment (entries 7 and 8). The reaction in toluene without heating catalyzed by diol 3 gave 20% of product 7a with 12% *ee* within 24 h (entry 9). Catalyst **2** at 55 °C in toluene within 11 h provided 36% of **7a** without enantiomeric enrichment (entry *10*).

The catalytic activity of polyols 1-4 clearly enough correlated with their acidity. Since the acidity of the phenol groups in compounds 1, 3, and 4 differs only slightly, the main factor determining the difference in their catalytic activity is the acidity of the carboxy and triphenylcarbinol groups in 3 and in 1, 4, respectively. The pK_a values of this groups in DMSO exceed 25 for 1 (see Ref. 11), 10.8 for 4 (see Ref. 12), and are within 10–12 for 3 (see Ref. 11). Since the acidity constant of the protonated form of aniline in DMSO is 3.6, toluidine can ionize neither the phenol OH groups (pK_a 17–18), nor other acid groups in compounds 1–4, and the catalysts retain their initial acidic properties in its presence.

It is obvious that the catalysis of the epoxide opening is provided by the formation of strong hydrogen bonds of the OH groups of the catalyst with the oxygen atom of styrene oxide in the activated complex. The presence of the conjugated system of hydrogen bonds in molecules 1, 3, and 4 facilitates the proton transfer from the forming ammonium group to the generating alkoxide group in the transition state of the amino alcohol formation. This can explain the superiority of organic catalysts 1, 3, and 4 over 2. The formation of the excess of isomer 7a allows us to suggest that the character of the transition state of the styrene oxide opening is shifted toward the S_N1 and considerable carbocationic character of this state is stabilized by the phenyl ring of styrene oxide. This is also indicated by the decrease in the amount of the second isomer 7b formed when more acidic catalyst 3 is used (see Table 1, entry 3).

It is obvious that an increase in the acidity of polyol catalyst leads to the increase in its activity in the reaction

Entry	Polyol	<i>C</i> (mol.%)	Solvent	T/°C	t/h	Yield ^{<i>b</i>} (%)		ee (%)
						7a	7b	
1	(<i>R</i>)- 2	5.0	CH ₂ Cl ₂	25	72	12	2.0	0
2	<i>(S)</i> -1	5.0	CH ₂ Cl ₂	25	72	28	4.5	5 (<i>R</i>)
3	(R)-3	5.0	CH ₂ Cl ₂	25	72	39	2.7	5(S)
4	(R)-3	5.0	CH ₂ Cl ₂	25	240	92	6.0	_
5	(R)-4	2.5	CH ₂ Cl ₂	25	72	8		0
6	<i>(S)</i> -1	5.0	Toluene	55	11	37	6.0	1 (<i>R</i>)
7	(R)-3	5.0	Toluene	55	11	36	4.5	0
8	(R)-3	10.0	Toluene	55	11	80	9.0	0
9	(R)-3	5.0	Toluene	25	24	20	6.0	12 (S)
10	(<i>R</i>)-2	5.0	Toluene	55	11	36	12.0	0

Table 1. Opening of racemic styrene oxide with *p*-toluidine catalyzed by compounds $1-4^a$

^a Reagents: catalyst (0.0118 mmol), styrene oxide 5 (0.237 mmol), p-toluidine (0.332 mmol), solvent (0.5 mL).

^b Was determined using ¹H NMR spectroscopy from the ratio of signals for the product **7a** at δ 6.54 (2 H) and the unreacted styrene oxide at δ 2.87 (1 H), regioisomer **7b** was formed in the trace amounts; unreacted styrene oxide **5** remained in the reaction mixture without changes.

^c Trace amounts.

of the styrene oxide opening with *p*-toluidine. It is known that the Brønsted acidity of hydroxy groups can be raised by the activation with Lewis acids (LBA).¹³ This suggestion was tested by the use of (S)-1 with the equimolar additive of lithium tetraphenylborate as the catalytic system (Table 2).

The reaction proceeded rapidly (within 20 min) to reach 18% yield of product 7a and then it stopped: the yield did not change during the next 2 h (see Table 2, entries 1-3). This fact indicates the disappearance from the reaction medium of activating species (the ¹H NMR spectroscopic data showed that the starting *p*-toluidine and styrene oxide remained in the mixture). The catalyst 1 itself without activating additives has low activity (entry 2). This means that lithium ion are completely removed from the catalytic cycle, probably, by the competing chelation by the reaction product, β -amino alcohol **7a**. The reaction can take place without catalyst 1 only in the presence of lithium tetraphenylborate, though slower and with low yield, which can be caused by the same reason (entry 4). As it was expected, the amount of product 7b decreased with the increase in the acidity of the catalytic system resulted from the addition of LiBPh₄ (cf. Table 1, entry 2 and Table 2, entries 1-3).

It could have been expected that ionization of **1** upon the action of a base would make it more efficient catalyst of this process. The ionized tetraol **1** becomes better chelating agent, that allows us to suppress the competing chelation of lithium ions with the forming β -amino alcohol, which leads to the termination of the reaction. In this case, two additional catalytic centers emerge (Fig. 1). The first center is basic (the ionized hydroxy group), the second one is acidic (Lewis acid, Li⁺ ion). The Lewis acid together with the Brønsted acid groups (the unionized hy-

Table 2. Opening of racemic styrene oxide with *p*-toluidine catalyzed by the system (S)-1–LiBPh₄^{*a*}

Entry	t/min	Yield	ee ^c (%)	
		7a	7b	
1	20	18.0	1.0	2 (<i>R</i>)
2	60	18.0	1.0	2(R)
3	120	18.0	1.0	0
4^d	60	11.5	3.5	0

^{*a*} Reagents: (*S*)-1 (0.0118 mmol, 5 mol.%), LiBPh₄ (0.0118 mmol, 5 mol.%), styrene oxide 5 (0.237 mmol), *p*-toluid-ine (0.332 mmol), CH_2Cl_2 (0.5 mL).

^b Was determined using ¹H NMR spectroscopy from the ratio of signals for the product **7a** at δ 6.54 (2 H), regioisomer **7b** at δ 4.93 (1 H), and unreacted styrene oxide **5** at δ 2.87 (1 H).

^c Enantiomeric purity of compound **7a** was determined by HPLC (see Experimental).

^{*d*} Experiment was carried out with 5 mol.% of LiBPh₄ and without (S)-1.



Fig. 1. Polyfunctional character of monolithium salt 1[Li].

droxy groups of the catalyst) should activate the oxygen atom of styrene oxide. At the same time, the ionized hydroxy group of the catalyst increases the nucleophilicity of p-toluidine following the general base catalysis mechanism.

The monolithium salt was obtained by the reaction of **1** with the equimolar amount of BuLi. The exclusive formation of the monolithium salt **1**[Li] was confirmed by the mass spectrometry (electrospray ionization). The mass spectrum exhibited a positive ion with m/z 657 corresponding to the protonated monolithium salt with no signals corresponding to the higher amount of lithium per one molecule of **1**.

To confirm the suggested hypothesis for the activation of the catalyst, we carried out a quantitative comparison of the reaction rates depending on the catalyst used. Figure 2 represents the accumulation of the reaction product in the catalysis with (R)-1, (R)-2, (R)-3, and lithium salt (R)-1[Li]. All the experiments were carried out in NMR



Fig. 2. Accumulation of product **7a** in the course of the opening of racemic styrene oxide **5** with *p*-toluidine catalyzed by (*R*)-**1** (5 mol.%), (*R*)-**2** (10 mol.%), (*R*)-**3** (5 mol.%), and lithium salt (*R*)-**1**[Li] (5 mol.% Li, 5 mol.% (*R*)-**1**) in CD₂Cl₂ at 25 °C. For the linear dependence of catalysis with lithium salt (*R*)-**1**[Li], the convergence factor $R^2 = 0.9927$.

tubes in CD_2Cl_2 , and the reaction progress was monitored by the changes in the ¹H NMR spectra of the reaction mixture.

The yield was determined from the ratio of the integral intensity of the signal for product **7a** at δ 6.54 (2 H) and the total integral intensity of the signals for the unreacted *p*-toluidine at δ 6.67 (2 H) and regioisomer **7b** at δ 6.66 (2 H). Allowance was made for the initial excess of *p*-toluidine and its consumption in the formation of some second isomer **7b**.

The formation of a noticeable amount of **7b** (up to 6.2%) was observed only when lithium salt 1[Li] was used; the ratio of regioisomers **7a** : **7b** = 20 : 3 remained practically unchanged as the reaction progressed.

Monolithium salt 1[Li] exhibited considerably higher catalytic activity under the indicated reaction conditions: the yield was 41% after 93 h, the enantiomeric purity of the product was 12% (S). The order of activity of the catalysts other than lithium salts corresponded to their acidity, which confirmed the data obtained earlier (see Table 1). As it was expected, the highest reaction rate was observed in the case of diol (R)-3, possessing the highest acidity, in the case of less acidic tetraol (R)-1, the rate of the reaction was slower. Despite the fact that the comparison of the catalytic activity in this experiment was carried out using 10 mol.% of catalyst (R)-2 containing two OH groups in the molecule, the reaction turned out to be the slowest, that agreed with its lowest acidity. A relatively small increase in the reaction rate when catalyst (R)-3 was used as compared to (R)-1 was caused by the low solubility of (R)-3 (see Experimental).

To select the most efficient catalytic system, we obtained lithium salt containing different amounts of lithium by the reaction of tetraol 1 with BuLi taken in different ratios. The monolithium salt of diol (R)-2 was obtained for comparison. The results of the catalytic experiments are represented in Table 3.

As it is seen from these data, the most efficient catalytic system is the one obtained by the reaction of the equimolar amounts of BuLi and tetraol (S)-1, *i.e.* salt 1[Li] (Table 3, entry 1): its amount of 5 mol.% in CH₂Cl₂ at room temperature provided the 40% total yield of the reaction products 7a and 7b within 24 h, the enantiomeric purity of 7a was 41% (R). Dilithium salt of tetraol 1 was less active catalyst (entry 2), the catalytic ability of the system decreased with the decrease in the amount of the BuLi added (entry 3). It should be noted that monolithium salt (R)-2[Li] was much less active as compared to the monolithium salt (S)-1[Li] (entry 4).

To study the mechanism of the reaction catalyzed by monolithium salt 1[Li], we measured the reaction rate in the experiments with enantiomerically pure (*R*)-styrene oxide. The yield of product **7a** linearly depends on the reaction time in the case of catalysis with both lithium salt (*R*)-1[Li] and lithium salt (*S*)-1[Li] (Fig. 3).

Table 3. Opening of racemic styrene oxide catalyzed by lithium salts (R)-1[Li] and $(R)-2[Li]^a$

Entry	Polyol	BuLi : Polyol	<i>t/</i> h	$\operatorname{Yield}^{b}(\%)$		ee (%) ^c
		(mol.% : mol.%)		7a	7b	
1	(<i>S</i>)-1	5:5	24	36	3.6	41
2	(S)-1	10:5	24	8	1.2	2
3	(S)-1	2.5:5	24	2	d	7
4	(<i>R</i>)-2	40:40	24	10	d	—

^{*a*} Reagents: catalyst (0.0118 mmol, 5 mol.%), styrene oxide (0.237 mmol), *p*-toluidine (0.332 mmol), CH_2Cl_2 (0.5 mL).

^b Was determined using ¹H NMR spectroscopy from the ratio of signals for the product **7a** at δ 6.54 (2 H), regioisomer **7b** at δ 4.93 (1 H), and unreacted styrene oxide **5** at δ 2.87 (1 H).

^c Enantiomeric purity of compound **7a** was determined by HPLC (see Experimental).

^d Trace amounts.

The ratio of rate constants of the reaction of (R)-styrene oxide in the presence of (R)-1[Li] (k_{RR}) and (S)-1[Li] (k_{RS}) is $k_{RR} : k_{RS} = 2.64$ (the ratio of the constants k_{RR} and k_{RS} is equal to the ratio of the slopes of the corresponding straight lines, see Fig. 3). The ratio of rate constants of the reaction of each of the enantiomers is the stereoselectivity factor (s), whereas its value differing from 1 (2.64), according to the known formula¹⁴ $s = \ln[1 - C(1 +$ + ee')] : $\ln[1 - C(1 - ee')]$, indicates a possibility of kinetic resolution in this reaction. The low s value indicates that the further modification of the catalytic system is necessary in order to increase the efficiency of the resolution, and such works are in progress.

In the experiments on the opening of enantiomerically pure (R)-styrene oxide, the enantiomerically enriched



Fig. 3. Accumulation of product **7a** in the course of the opening of racemic styrene oxide **5** with *p*-toluidine catalyzed by monolithium salts (*S*)-**1**[Li] and (*R*)-**1**[Li] (5 mol.% Li, 5 mol.% **1**) in CD₂Cl₂ at 25 °C. The approximation of the linear dependencies for the catalysis by salt (*R*)-**1**[Li] was made using the equation y = 0.4938x, the convergence factor $R^2 = 0.996$; for the catalysis by salt (*S*)-**1**[Li], using the equation y = 0.1852x, $R^2 = 0.991$.

product 7a was formed predominantly in (S)-configuration in the case of catalysis with both (R)-1[Li] and (S)-1[Li]. However, the enantiomeric purity of 7a in the case of catalysis with (R)-1[Li] is 96.4% (S), whereas in the case of (S)-1[Li], 91.3% (S). In the case of the classic $S_{\rm N}$ l-type mechanism, the stereochemistry of the reaction product would have been determined by only the configuration of the catalyst and would have differed depending on whether (R)-1[Li] or (S)-1[Li] was used. It is obvious that this clearly contradicts to the conclusions drawn earlier. On the one hand, the regioselectivity of the styrene oxide ring opening indicates a considerable degree of the carbocationic character of the transition state of the process and, consequently, the $S_N 1$ mechanism of the reaction. On the other hand, the retention of the enantiomeric purity in the reaction product indicates a considerable S_N 2-character of the opening. We suggest that in this case the reaction follows the $S_N l$ mechanism with one of the sides of the planar carbocation being shielded by the alkoxide anion of the forming amino alcohol and, thus, the $S_N 2$ mechanism is simulated.

Experimental

¹H, ¹³C and ¹⁹F NMR spectra were recorded on Bruker AvanceTM 300, 400, 600 spectrometers. Chemical shifts (δ) in the ¹H NMR spectra were measured relative to the residual protons of the solvent, in the ¹³C NMR spectra, relative to the signal of the deuterated solvent, in the ¹⁹F NMR spectra, relative to the external standard CFCl₃ (δ = 0.00). The spectra were recorded in CDCl₃ and CD₂Cl₂. Optical rotation was measured on a Perkin—Elmer 341 polarimeter in a temperature-controlled cuvette (*l* = 5 cm) at 25 °C.

Silica gel 60 purchased from Merck was used in the work.

Enantiomeric purity of BINOL (2) was analyzed on a liquid chromatograph using a Chiralcel[®] IB-3 column (eluent hexane—PrⁱOH (90 : 10), the rate of the eluent flow 1.0 mL min⁻¹, UV detector ($\lambda = 254$ nm)).

Enantiomeric purity of 2-(*p*-tolylamino)-2-phenylethanol (7a) was analyzed on a liquid chromatograph using an AmyCoat column (150×4.6 mm) (eluent hexane—PrⁱOH (95 : 5), the rate of the eluent flow 1.0 mL min⁻¹, UV detector ($\lambda = 254$ nm)); $t_0 = 2$ min, $t_S = 11.4$ min, $t_R = 17.3$ min.

All the solvents used were purified according to the standard procedures. $^{\rm 15}$

Elemental analysis of all the compounds obtained was performed in the Laboratory of Elemental Analysis of A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences.

(*R*)-BINOL ((*R*)-2) was synthesized according to the known procedure.¹⁰

(*S*)-**BIMBOL** ((*S*)-**1**) was synthesized according to the known procedure⁹ starting from (*S*)-**BINOL** (*ee* 99.9%, t_{ret} 5.058 min); $[\alpha]_D^{25}$ -107.3 (*c* 1.00, CHCl₃) (*cf.* Ref. 9: $[6]_D^{20}$ -109.5 (*c* 1.00, CHCl₃). M.p. 186–188 °C (*cf.* Ref. 16: m.p. 176–179 °C). ¹H NMR (CDCl₃), δ : 4.79 (s, 2 H, OH); 6.70 (s, 2 H, OH); 7.14–7.17 (m, 2 H, Ar); 7.19 (s, 2 H, Ar); 7.28–7.40 (m, 24 H, Ar); 7.65–7.68 (m, 2 H, Ar). Found (%): C, 79.2;

H, 5.8. $C_{46}H_{34}O_4 \cdot 2H_2O \cdot Me_2CO$. Calculated (%): C, 78.9; H, 5.9.

(*R*)-BIMBOL ((*R*)-1) was synthesized according to the known procedure⁹ starting from (*R*)-BINOL ((*R*)-2) (*ee* 99.9%, t_{ret} 5.499 min); $[\alpha]_{\text{D}}^{25}$ + 109.8 (*c* 1.00, CHCl₃) (*cf.* Ref. 9: $[\alpha]_{\text{D}}^{20}$ + 113.4 (*c* 1.00, CHCl₃)).

(*R*)-MOM-BINOL ((*R*)-1) was synthesized according to the known procedure¹⁷ starting from (*R*)-BINOL ((*R*)-2).

(R)-BICBOL ((R)-2,2⁻-dihydroxy-1,1⁻-binaphthalene-3,3⁻dicarboxylic acid, (R)-3). A 2.5 M solution of BuLi in hexane (14 mL, 0.0348 mol) was added dropwise to a solution of (*R*)-MOM-BINOL (bis-methoxymethylene ether (*R*)-BINOL) (4.36 g, 0.0116 mol) in 1,4-dioxane (50 mL) at -15 °C under argon, and the mixture was stirred for 3 h at -5-0 °C. Then dry CO₂ was passed through the reaction mixture over 1 h, followed by the addition of water (20 mL), diethyl ether (50 mL), and 1% aqueous HCl until acidic pH. The organic layer was separated, the aqueous layer was additionally extracted with diethyl ether (2×50 mL). The combined organic extracts were dried with sodium sulfate, the solvent was evaporated at reduced pressure. The intermediately obtained (R)-MOM-BICBOL was used in the next step without additional purification. For this, a 6 M solution of HCl in 1,4-dioxane (30 mL) was added to its solution in THF (30 mL), and the mixture was kept for 3 h. Then the solvent was evaporated at reduced pressure, followed by the addition of water (20 mL) and extraction with ethyl acetate (3×50 mL). The combined organic layer was dried with sodium sulfate, the solvent was evaporated at reduced pressure. The residue was recrystallized from a mixture of ethyl acetate-toluene. The yield of product (*R*)-3 was 2.18 g (50%), m.p. >290 °C. ¹H NMR (DMSO-d₆), δ: 3.20 (br.s, 2 H, COOH); 7.00–7.02 (m, 2 H); 7.32-7.35 (m, 4 H); 8.02-8.04 (m, 2 H); 8.70 (s, 2 H); 11.14 (br.s. OH).

(*R*)-FBIMBOL (3,3´-bis[(hydroxy)bis(pentfluorophenyl)methyl]-1,1´-binaphthamine-2,2´-diol, (*R*)-4).

Step 1. Thionyl chloride (5 mL, 8.19 g, 0.069 mol) was added dropwise to a solution of compound (R)-3 (1 g, 0.0027 mol) in methanol (30 mL), and the reaction mixture was refluxed for 6 h and then concentrated at reduced pressure. The residue was treated with water and extracted with ethyl acetate. The combined organic layer was dried with sodium sulfate, then passed through a short layer of silica gel, and the solvent was evaporated at reduced pressure. The yield of dimethyl ester of compound (R)-3 was 0.93 g (87%). ¹H NMR (CDCl₃), δ : 4.07 (s, 6 H); 7.15–7.19 (m, 2 H); 7.34–7.38 (m, 4 H); 7.91–7.95 (m, 2 H); 8.70 (s, 2 H); 10.72 (s, 2 H).

<u>Step 2.</u> A 2.5 *M* solution of BuLi in hexane (0.64 mL, 1.6 mmol) was placed into a flask under argon, followed by the addition of a solution of C_6F_5Br (0.395 g, 1.6 mmol) in diethyl ether (5 mL) at -70 °C and the stirring of the mixture at this temperature for 2 h. A solution of dimethyl ester of (*R*)-3 (0.1 g, 0.25 mmol) obtained in step 1 in diethyl ether (40 mL) was added dropwise to the obtained solution of pentfluorophenyl-lithium¹⁸ at -70 °C. The mixture was stirred for 16 h, with the temperature allowing to reach the ambient. Then, 10% aq. HCl was added dropwise to the reaction mixture, followed by the extraction with diethyl ether (3×50 mL) and drying with Na₂SO₄. Diethyl ether was evaporated at reduced pressure, the product was isolated by chromatography on silica gel (eluent ethyl acetate—hexane (1 : 4), *R*_f 0.6). The isolated material was visualized in the system diethyl ether—hexane (1 : 9) as two spots: com-

pound (*R*)-4 had lower R_f 0.2. The yield of the product was 0.038 g (15%). ¹⁹F NMR (CDCl₃), δ : (-83.74)–(-83.36) (m, 2 F); (-74.98) (dt, 1 F, J = 55.0, J = 21.3 Hz); (-60.25) (dd, 2 F, J = 88.4 Hz, J = 19.4 Hz). ¹³C NMR (CDCl₃), δ : 29.72 (s), 112.53 (s), 117.28 (m), 123.96 (s), 125.43 (s), 128.34 (s), 128.64 (s), 128.89 (s), 129.22 (s), 133.48 (s), 136.26 (m), 139.62 (m), 142.97 (m), 143.65 (m), 146.98 (m), 150.36 (c).

Monolithium salt (S)-1[Li]. Tetraol (S)-1 (7.7 mg, 0.0118 mmol) and a 0.075 M solution of BuLi (0.158 mL, 0.0118 mmol) in hexane were placed in a round-bottom flask with a magnetic stirrer under argon, and the mixture was stirred for 5 min. The solvent was evaporated at reduced pressure. The solid compound obtained was directly used as a catalyst in the reaction of the styrene oxide opening with p-toluidine.

Reaction of styrene oxide (5) with *p*-toluidine (general procedure). *A*. The catalyst (5 mol.% of (*S*)-1, 7.7 mg, 0.0118 mmol) in CH₂Cl₂ (0.5 mL) was placed in a round-bottom flask with a magnetic stirrer under argon. Then, styrene oxide (5) (27 μ L, 0.237 mmol) and *p*-toluidine (6) (35 mg, 0.332 mmol) were added. After the reaction reached completion, the mixture was passed through a short layer of silica gel (eluent light petroleum—ethyl acetate (5:1)). The yields of products **7a** and **7b** were determined from the ¹H NMR spectra, which agreed with those described in the literature.^{19,20}

2-Phenyl-2-(*p*-tolylamino)ethanol (7a). ¹H NMR (CDCl₃), δ : 2.24 (s, 3 H); 3.72 (dd, 1 H, J = 11.1 Hz, J = 7.4 Hz); 3.93 (dd, 1 H, J = 11.1 Hz, J = 4.2 Hz); 4.49 (dd, 1 H, J = 7.4 Hz, J = 4.2 Hz); 6.54 (d, 2 H, J = 8.2 Hz); 6.96 (d, 2 H, J = 8.3 Hz); 7.35–7.39 (m, 5 H).

1-Phenyl-2-(*p*-tolylamino)ethanol (7b). ¹H NMR (CDCl₃), δ : 2.31 (s, 3 H); 3.30 (dd, 1 H, J = 13.1 Hz, J = 8.7 Hz); 3.43 (dd, 1 H, J = 13.1 Hz, J = 3.9 Hz); 4.93 (dd, 1 H, J = 8.7 Hz, J = 3.9 Hz); 6.66 (d, 2 H, J = 8.0 Hz); 7.06 (d, 2 H, J = 8.1 Hz); 7.32–7.45 (m, 5 H).

B. NMR experiment. The catalyst (5 mol.% of (*S*)-1, 7.7 mg, 0.0118 mmol) in CD₂Cl₂ (0.6 mL) was placed in an NMR tube, followed by the addition of styrene oxide (5) (27 μ L, 0.237 mmol), shaking, and addition of *p*-toluidine (6) (35 mg, 0.332 mmol), then the tube was shaken until its complete dissolution. The ¹H NMR spectra were recorded on a Bruker Avance 600 spectrometer, chemical shifts (δ) were measured relative to the residual signal of the undeuterated solvent, CD₂Cl₂. The yield was determined from the ratio of the integral intensities of the signal for the signals for the unreacted *p*-toluidine at δ 6.67 (2 H) and regioisomer 7b at δ 6.66 (2 H). Allowance was made for the initial excess of *p*-toluidine and its consumption in the formation of isomer 7b.

Yield (%) =
$$R_{\text{exc}} \cdot I_{7a} / (I_{7a} + I_{7b} + I_{\text{tol}}) \cdot 100\%$$

where R_{exc} is the initial molar ratio *p*-toluidine : styrene oxide; I_{7a} and I_{7b} are the integral intensities of the indicated signals of products **7a** and **7b**, respectively; I_{tol} is the integral intensity of the signal for the unreacted *p*-toluidine.

The authors are grateful to N. S. Ikonnikov for the carrying out the mass spectrometric analysis.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 11-03-00206).

References

- L. P. C. Nielsen, E. N. Jacobsen, in *Aziridines and Epoxides in Organic Synthesis*, Ed. A. K. Yudin, Wiley-VCH, Weinheim, 2006, p. 229.
- A. T. Placzek, J. L. Donelson, R. Trivedi, R. A. Gibbs, S. K. De, *Tetrahedron Lett.*, 2005, 46, 9029 (and references cited therein).
- 3. B. Plancq, T. Ollevier, *Chem. Commun.*, 2012, **48**, 3806 (and references cited therein).
- U. Das, B. Crousse, V. Kesavan, D. Bonnet-Delpon, J. P. Bogue, J. Org. Chem., 2000, 65, 6749.
- T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, Org. Lett., 2008, 10, 1513.
- A. R. Gallimore, C. B. W. Stark, A. Bhatt, B. M. Harvey, Y. Demydchuk, V. Bolanos-Garcia, D. J. Fowler, J. Staunton, P. F. Leadlay, J. B. Spencer, *Chem. Biol.*, 2006, 13, 453.
- Y. N. Belokon, Z. T. Gugkaeva, K. V. Hakobyan, V. I. Maleev, M. A. Moskalenko, V.N. Khrustalev, A. S. Saghyan, A. T. Tsaloev, K. K. Babievsky, *Amino Acids*, 2012, 43, 299.
- 8. Y. N. Belokon, Z. T. Gugkaeva, V. I. Maleev, M. A. Moskalenko, A. T. Tsaloev, V. N. Khrustalev, K. V. Hakobyan, *Tetrahedron: Asymmetry*, 2011, **22**, 167.
- 9. Q. Wang, X. Chen, L. Tao, L. Wang, D. Xiao, X.-Q. Yu, L. Pu, J. Org. Chem., 2007, 72, 97.
- H.-J. Schanz, M. A. Linseis, D. G. Gilheany, *Tetrahedron:* Asymmetry, 2003, 14, 2763.
- 11. F. G. Bordwell, Acc. Chem. Res., 1988, 21, 456.
- P. Christ, A. G. Lindsay, S. S. Vormittag, J.-M. Neudorfl, A. Berkessel, A. C. O'Donoghue, *Chem. Eur. J.*, 2011, 17, 8524.
- 13. H. Yamamoto, K. Futatsugi, Angew. Chem., Int. Ed., 2005, 44, 1924.
- 14. H. B. Kagan, J. C. Fiaud, Top. Stereochem., 1988, 18, 249.
- 15. A. J. Gordon, R. A. Ford, *The Chemist's Companion: A Handbook of Practical Data, Techniques, and References*, John Wiley and Sons, New York, 1972.
- 16. Y.-L. Zhang, Q.-H. Fan, J. Chem. Res., Synop., 2005, 778.
- X. Yang, W. Su, D. Liu, H. Wang, J. Shen, C. Da, R. Wang, A. S. C. Chan, *Tetrahedron*, 2000, 56, 3511.
- 18. T. V. Talalaeva, K. A. Kocheshkov, Metody elementoorganicheskoi khimii Li, K, Na, Rb, Cs. Kn. 1 [Methods of Organoelement Chemistry of Li, K, Na, Rb, Cs. Book 1], Nauka, Moscow, 1971, 412 (in Russian).
- 19. S. B. Pujala, A. K. Chakraborti, J. Org. Chem., 2007, 72, 3713.
- 20. Z. Xu, S. Zhu, Y. Liu, L. He, Z. Geng, Y. Zhang, *Synthesis*, 2010, 811.