Diastereoselective bromination of (*R*)-*N*-cinnamoyl-4-phenyloxazolidin-2-one in the presence of Lewis acids

Yu. N. Belokon', Yu. N. Bubnov, T. D. Churkina, A. A. Chesnokov, K. A. Kochetkov, N. Yu. Kuznetsov, V. N. Khrustalev, and N. I. Raevskii*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,
28 ul. Vavilova, 117813 Moscow, Russian Federation.
Fax: 007 (095) 135 5085. E-mail: yubel@ineos.ac.ru

The stereochemistry of addition of Br_2 to *E*- and *Z*-(*R*)-*N*-cinnamoyl-4-phenyloxazolidin-2-ones was studied. It was established that both the *E*- and *Z*-isomers give only two out of four possible diastereoisomers in the presence of Lewis acids (BPr_3 or $AlBr_3$). The absolute configurations of the diastereoisomers [(2*S*',3*R*') and (2*R*',3*S*') of the side chain] were established by X-ray structural analysis. The stereochemistry observed is a consequence of the stepwise bromination and the absence of bridging bromine atoms along the reaction coordinate. In the case of the *Z*-isomer, the diastereoselectivity of the reaction was high, whereas it is low in the case of the *E*-isomer. It was suggested that at the first stage of addition of Br_2 at the C=C bond, the attack of the Br^+ cation occurs at the α position, and the second stage of transfer of Br^- occurs with the participation of boron or aluminum complexes in the intermediate state of the bromination reaction. This hypothesis as well as the results of calculations of the initial conformations of the substrates provide an explanation of the regularities observed.

Key words: (*R*)-*N*-cinnamoyl-4-phenyloxazolidin-2-one, *E* and *Z* isomers, bromination; diastereomeric excess; Lewis acids.

Diastereoselective (*de* > 90%) addition of one Br atom to a molecule of a chiral organic compound was advantageously carried out with the use of various chiral auxiliary reagents.[1—3] Lesser success has been achieved in diastereoselective bromination of the C=C bond in the chiral environment.[4,5] Recently, it was demonstrated that the direction of the primary attack of Br_2 can be determined by an OH substituent of the chiral auxiliary reagent. The latter forms a hydrogen bond with Br_2, thus activating and determining the direction of the attack of Br_2 from one side of the prochiral double bond.[5] We suggested that these functions should be performed by a metal ion or Lewis acids, which form an intermediate complex with the auxiliary reagent. With the aim of testing this hypothesis, in this work we studied addition of Br_2 to *E*- and *Z*-(*R*)-*N*-cinnamoyl-4-phenyloxazolidin-2-ones (**1**) in the presence of Lewis acids ($AlBr_3$ and BPr_3). The reactions of **1** with nucleophiles were studied previously.[3] Adducts of organometallic compounds[3] and cycloaddition products[6] were obtained from the derivatives of *E*-**1** in the presence of Lewis acids with high diastereoselectivity. The participation of intermediate complexes of substrate with metal in the intermediate state of cycloaddition is well known.[7]

Results and Discussion

The initial compound *E*-**1** was synthesized by condensation of *E*-cinnamoyl chloride with 4-(*R*)-phenyloxazolidin-2-one. Isomer *E*-**1** was subjected to photoisomerization to give product *Z*-**1**, which was isolated chromatographically (see Experimental).

Bromination of isomers *E*-**1** and *Z*-**1** at 25 °C in the presence of the $BPr_3—Br_2$ system[13] (**1** : BPr_3 : Br_2 = 1 : 5 : 5) yielded only two diastereomeric products (**2** and **3**), which were isolated chromatographically on SiO_2 (a 4 : 1 : 1 $C_6H_{14}—PhH—Et_2O$ mixture was used as the eluent).

The structures of compounds **2** (the highest value of R_f) and **3** were confirmed by the data of elemental analysis and the ^1H NMR spectra. The absolute configurations of three asymmetrical centers (C(4), C(7), and C(8)) of compounds **2** and **3** were established by X-ray structural analysis. The atomic coordinates and equivalent isotropic temperature factors for compounds **2** and **3** and the geometric parameters of the molecules are given in Tables 1—6. The bond lengths and bond angles in two crystallographically independent molecules **2**, which are conformers that differ in the position of the Ph group in the acyl substituent, are identical to within the experimental error. It was found that compounds **2** and **3** are the (2*S*',3*R*')- and (2*R*',3*S*')-dibromodihydrocinnamoyl derivatives, respectively (Figs. 1 and 2).

It was demonstrated by special experiments that under the reaction conditions, interconversion of diastereoisomers **2** and **3** did not occur. Therefore, both *E*-**1** and *Z*-**1** added bromine in the presence of BPr_3 to give exclusively *anti* isomers (in the kinetically controlled

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 5, pp. 1022—1028, May, 1997.

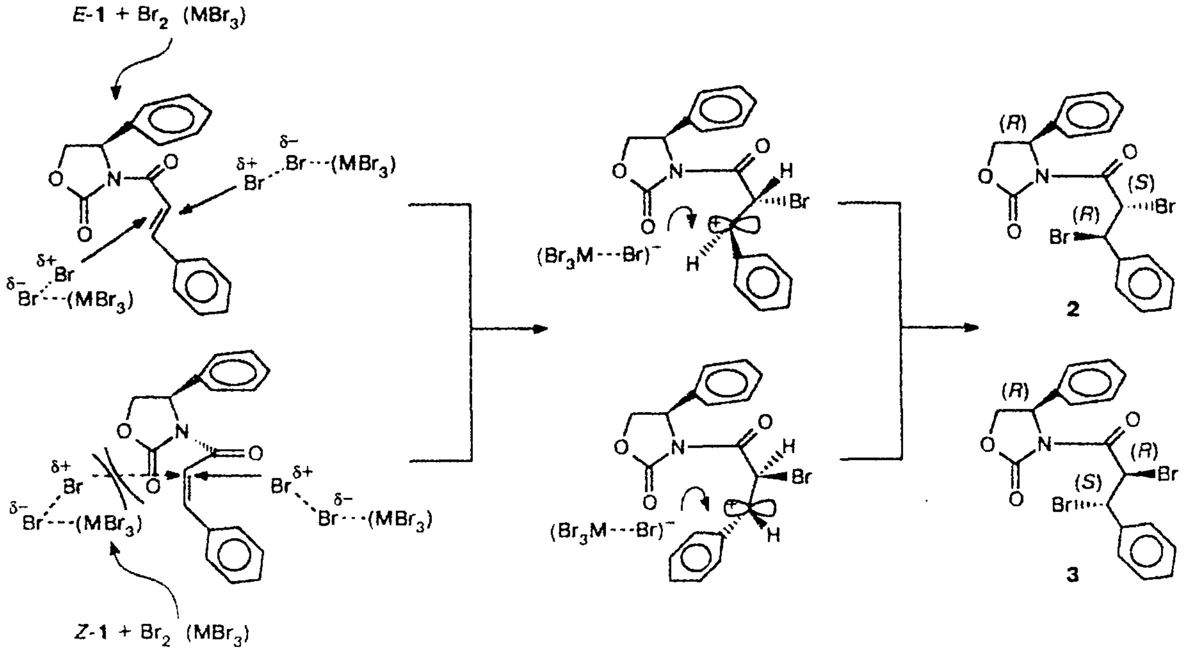
Table 1. Coordinates of nonhydrogen atoms ($\times10^4$) and equivalent isotropic temperature parameters ($U_{eq}\times10^3$) in the structure of **2**

Atom	x	y	z	U_{eq}/Å^2	Atom	x	y	z	U_{eq}/Å^2
		Molecule I					Molecule II		
Br(1)	4022(1)	8782(1)	7766(1)	46(1)	Br(1′)	7830(1)	15641(1)	9576(1)	52(1)
Br(2)	1297(1)	9845(1)	5739(1)	58(1)	Br(2′)	8137(1)	17896(1)	7203(1)	64(1)
O(1)	4995(6)	8140(5)	4506(4)	42(1)	O(1′)	12240(6)	15904(6)	8617(4)	49(2)
O(2)	5587(6)	9476(6)	5717(4)	53(2)	O(2′)	11303(7)	16977(6)	9367(4)	59(2)
O(3)	1442(6)	7163(5)	6162(4)	42(1)	O(3′)	7930(6)	15166(5)	7338(4)	45(2)
N(3)	3359(7)	7799(6)	5425(4)	32(2)	N(3′)	10121(7)	15721(6)	8053(4)	33(2)
C(2)	4760(9)	8594(8)	5266(6)	37(2)	C(2′)	11221(9)	16286(8)	8752(6)	42(2)
C(4)	2798(8)	6674(6)	4819(5)	26(2)	C(4′)	10394(9)	14860(7)	7448(6)	39(2)
C(5)	3720(9)	7115(8)	4083(6)	41(2)	C(5′)	11963(10)	15261(9)	7734(7)	50(2)
C(6)	2582(9)	7963(7)	6080(5)	33(2)	C(6′)	8822(9)	15802(7)	7943(5)	33(2)
C(7)	3236(8)	9178(7)	6667(5)	29(2)	C(7′)	8555(8)	16631(7)	8608(5)	33(2)
C(8)	2143(8)	9640(7)	6901(5)	30(2)	C(8′)	7425(9)	17033(8)	8234(5)	38(2)
C(9)	2702(9)	10840(7)	7479(5)	32(2)	C(9′)	7082(9)	17838(7)	8874(5)	36(2)
C(10)	1755(9)	11156(8)	7901(6)	41(2)	C(10′)	5710(10)	17433(9)	9096(6)	49(2)
C(11)	2196(12)	12258(9)	8415(6)	53(3)	C(11′)	5355(13)	18142(12)	9680(7)	65(3)
C(12)	3602(12)	13067(8)	8518(6)	52(3)	C(12′)	6354(15)	19256(12)	10053(7)	70(4)
C(13)	4574(11)	12762(9)	8117(6)	49(2)	C(13′)	7730(14)	19685(10)	9850(7)	66(3)
C(14)	4115(10)	11658(7)	7598(5)	38(2)	C(14′)	8108(11)	18967(8)	9261(6)	52(2)
C(15)	2944(8)	5613(7)	5234(5)	30(2)	C(15′)	9514(8)	13537(7)	7540(5)	33(2)
C(16)	1956(9)	4427(7)	4956(6)	41(2)	C(16′)	9395(10)	12657(8)	6862(6)	43(2)
C(17)	2105(11)	3440(8)	5291(7)	55(3)	C(17′)	8604(11)	11425(9)	6905(7)	53(3)
C(18)	3213(11)	3627(9)	5914(7)	52(2)	C(18′)	7912(11)	11057(9)	7623(9)	66(3)
C(19)	4198(11)	4796(9)	6189(6)	52(3)	C(19′)	8008(11)	11901(9)	8318(7)	56(3)
C(20)	4068(10)	5788(8)	5848(6)	43(2)	C(20′)	8810(10)	13138(8)	8285(6)	45(2)

reaction, Scheme 1) in various ratios. In the case of isomer *Z*-**1**, the major bromination product was the (2*R*′,3*S*′)-adduct **3** (84%, *de* 68%), whereas *E*-**1** yielded predominantly the (2*S*′,3*R*′)-adduct **2** (66%, *de* 32%) (see Table 7, runs *3* and *4*).

Bromination of isomers *E*-**1** and *Z*-**1** in the presence of $AlBr_3$ at −65 °C yielded also only two diastereomeric products, namely, *anti*-isomers **2** and **3**. The major product of bromination of isomer *Z*-**1** was the (2*R*′,3*S*′)-adduct **3** (76%, *de* 52%), whereas *E*-**1** gave predomi-

Scheme 1



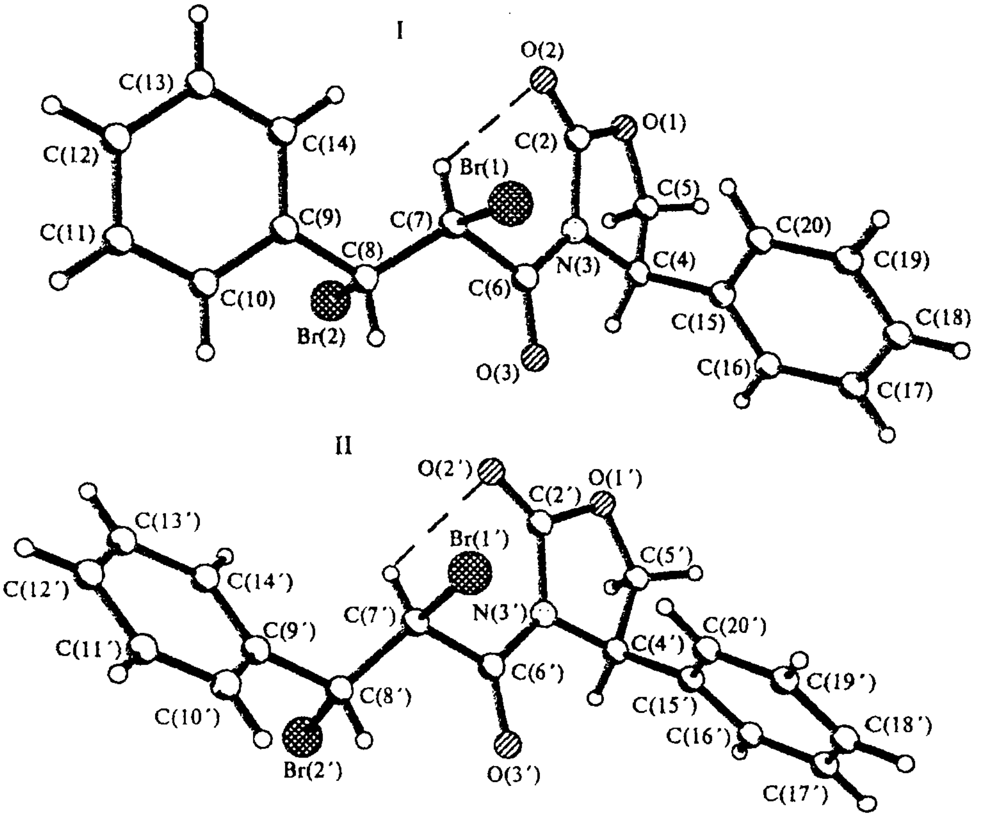


Fig. 1. Structures of two crystallographically independent molecules (I and II) of diastereoisomer **2**.

Table 2. Bond lengths (*d*) in the structure of **2**

Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å
Molecule I				Molecule II			
Br(1)—C(7)	1.976(7)	C(8)—C(9)	1.50(1)	Br(1')—C(7')	1.960(8)	C(8')—C(9')	1.50(1)
Br(2)—C(8)	1.986(7)	C(9)—C(14)	1.38(1)	Br(2')—C(8')	1.967(9)	C(9')—C(14')	1.39(1)
O(1)—C(2)	1.33(1)	C(9)—C(10)	1.39(1)	O(1')—C(2')	1.35(1)	C(9')—C(10')	1.39(1)
O(1)—C(5)	1.45(1)	C(10)—C(11)	1.37(1)	O(1')—C(5')	1.45(1)	C(10')—C(11')	1.37(1)
O(2)—C(2)	1.18(1)	C(11)—C(12)	1.37(1)	O(2')—C(2')	1.18(1)	C(11')—C(12')	1.36(2)
O(3)—C(6)	1.204(9)	C(12)—C(13)	1.39(1)	O(3')—C(6')	1.213(9)	C(12')—C(13')	1.38(2)
N(3)—C(6)	1.39(1)	C(13)—C(14)	1.38(1)	N(3')—C(6')	1.40(1)	C(13')—C(14')	1.40(1)
N(3)—C(2)	1.43(1)	C(15)—C(20)	1.37(1)	N(3')—C(2')	1.40(1)	C(15')—C(16')	1.39(1)
N(3)—C(4)	1.455(9)	C(15)—C(16)	1.38(1)	N(3')—C(4')	1.47(1)	C(15')—C(20')	1.41(1)
C(4)—C(15)	1.52(1)	C(16)—C(17)	1.39(1)	C(4')—C(15')	1.50(1)	C(16')—C(17')	1.38(1)
C(4)—C(5)	1.52(1)	C(17)—C(18)	1.36(1)	C(4')—C(5')	1.52(1)	C(17')—C(18')	1.36(2)
C(6)—C(7)	1.52(1)	C(18)—C(19)	1.36(1)	C(6')—C(7')	1.50(1)	C(18')—C(19')	1.39(2)
C(7)—C(8)	1.52(1)	C(19)—C(20)	1.39(1)	C(7')—C(8')	1.53(1)	C(19')—C(20')	1.38(1)

nantly (2*S*',3*R*')-adduct **2** (76%, *de* 52%) (see Table 7, runs *5* and *6*).

In all the cases of uncatalyzed bromination at 25 °C and −65 °C as well as in the presence of $Et_2O \cdot BF_3$ both in air and under an atmosphere of Ar, *syn*-addition products were found in the reaction mixture (up to 30%) in addition to *anti* isomers **2** and **3** (see Table 7, runs *1* and *2*). Bromination of isomer *E*-**1** with bromoacetamide under irradiation with UV light in CH_2Cl_2 gave only diastereoisomers **2** and **3** with a slight predominance of compound **2** (*de* 16%).

Apparently, such alternatives as simultaneous addition of Br_2 or formation of bridging structures as intermediates should give stereochemically different results for the *E*- and *Z*-isomers. In other words, one would expect formation of *syn*- and *anti*-addition products in different ratios. At the extreme, one isomer will give only the *anti* adduct, whereas the second isomer will

Table 3. Bond angles (ω) in the structure of **2**

Angle	ω/deg
Molecule I	
C(2)—O(1)—C(5)	110.8(6)
C(6)—N(3)—C(2)	128.4(7)
C(6)—N(3)—C(4)	120.8(6)
C(2)—N(3)—C(4)	110.7(6)
O(2)—C(2)—O(1)	125.0(8)
O(2)—C(2)—N(3)	127.7(8)
O(1)—C(2)—N(3)	107.2(7)
N(3)—C(4)—C(15)	112.9(6)
N(3)—C(4)—C(5)	99.7(6)
C(15)—C(4)—C(5)	113.4(6)
O(1)—C(5)—C(4)	105.1(6)
O(3)—C(6)—N(3)	120.2(7)
O(3)—C(6)—C(7)	122.7(7)
N(3)—C(6)—C(7)	117.1(7)
C(8)—C(7)—C(6)	112.8(6)
C(8)—C(7)—Br(1)	108.2(5)
C(6)—C(7)—Br(1)	103.4(5)
C(9)—C(8)—C(7)	116.2(7)
C(9)—C(8)—Br(2)	108.2(5)
C(7)—C(8)—Br(2)	104.4(5)
C(14)—C(9)—C(10)	118.2(7)
C(14)—C(9)—C(8)	123.0(7)
C(10)—C(9)—C(8)	118.7(7)
C(11)—C(10)—C(9)	121.5(9)
C(12)—C(11)—C(10)	119.6(9)
C(11)—C(12)—C(13)	120.0(8)
C(12)—C(13)—C(14)	119.7(9)
C(9)—C(14)—C(13)	121.0(9)
C(20)—C(15)—C(16)	118.4(8)
C(20)—C(15)—C(4)	122.1(7)
C(16)—C(15)—C(4)	119.5(7)
C(15)—C(16)—C(17)	120.6(8)
C(18)—C(17)—C(16)	120.5(9)
C(19)—C(18)—C(17)	119.3(9)
C(18)—C(19)—C(20)	120.6(8)
C(15)—C(20)—C(19)	120.7(8)
Molecule II	
C(2′)—O(1′)—C(5′)	110.4(7)
C(6′)—N(3′)—C(2′)	127.5(7)
C(6′)—N(3′)—C(4′)	120.3(6)
C(2′)—N(3′)—C(4′)	111.8(7)
O(2′)—C(2′)—O(1′)	123.6(8)
O(2′)—C(2′)—N(3′)	128.8(8)
O(1′)—C(2′)—N(3′)	107.6(8)
N(3′)—C(4′)—C(15′)	114.0(7)
N(3′)—C(4′)—C(5′)	100.1(7)
C(15′)—C(4′)—C(5′)	112.9(7)
O(1′)—C(5′)—C(4′)	105.4(7)
O(3′)—C(6′)—N(3′)	119.1(7)
O(3′)—C(6′)—C(7′)	122.3(7)
N(3′)—C(6′)—C(7′)	118.5(7)
C(6′)—C(7′)—C(8′)	112.5(6)
C(6′)—C(7′)—Br(1′)	105.0(5)
C(8′)—C(7′)—Br(1′)	108.3(5)
C(9′)—C(8′)—C(7′)	115.1(6)
C(9′)—C(8′)—Br(2′)	109.9(6)
C(7′)—C(8′)—Br(2′)	106.4(5)
C(14′)—C(9′)—C(10′)	119.3(8)
C(14′)—C(9′)—C(8′)	121.6(8)
C(10′)—C(9′)—C(8′)	119.1(8)
C(11′)—C(10′)—C(9′)	121(1)
C(10′)—C(11′)—C(12′)	120(1)
C(11′)—C(12′)—C(13′)	121(1)
C(12′)—C(13′)—C(14′)	120(1)
C(9′)—C(14′)—C(13′)	119(1)
C(16′)—C(15′)—C(20′)	118.1(8)
C(16′)—C(15′)—C(4′)	118.7(8)
C(20′)—C(15′)—C(4′)	123.1(7)
C(17′)—C(16′)—C(15′)	121.6(9)
C(18′)—C(17′)—C(16′)	119.4(9)
C(17′)—C(18′)—C(19′)	121.0(9)
C(18′)—C(19′)—C(20′)	120(1)
C(19′)—C(20′)—C(15′)	119.8(9)

Table 4. Atomic coordinates ($\times 10^4$; $\times 10^3$ for H atoms) and isotropic (equivalent for nonhydrogen atoms) temperature parameters ($\times 10^3$; $\times 10^2$ for H atoms) in the structure of **3**

Atom	*x*	*y*	*z*	U_{iso}/Å^2
Br(1)	−7226(1)	−1887(1)	−8180(1)	49(1)
Br(2)	−5274(1)	−2103(1)	−10422(1)	49(1)
O(1)	−4906(4)	−6211(4)	−7858(3)	42(1)
O(2)	−6685(4)	−5168(4)	−8503(3)	50(1)
O(3)	−4170(4)	−2014(4)	−8335(3)	41(1)
N(3)	−4682(4)	−4158(5)	−8296(3)	30(1)
C(2)	−5549(6)	−5177(6)	−8254(4)	35(1)
C(4)	−3364(5)	−4520(6)	−7822(4)	33(2)
C(5)	−3538(6)	−5979(7)	−7667(5)	41(2)
C(6)	−4982(5)	−2858(6)	−8521(4)	31(1)
C(7)	−6321(5)	−2548(7)	−9012(4)	31(1)
C(8)	−6388(6)	−1500(6)	−9676(4)	32(1)
C(9)	−7721(6)	−1262(6)	−10221(4)	33(1)
C(10)	−8475(7)	−2295(7)	−10595(4)	42(2)
C(11)	−9687(7)	−2072(8)	−11092(4)	42(2)
C(12)	−10138(6)	−793(8)	−11214(4)	43(2)
C(13)	−9390(7)	223(8)	−10852(4)	46(2)
C(14)	−8183(7)	11(7)	−10354(4)	40(2)
C(15)	−2329(5)	−4279(6)	−8297(4)	32(1)
C(16)	−1064(6)	−4298(7)	−7837(5)	38(2)
C(17)	−52(7)	−4172(7)	−8218(5)	48(2)
C(18)	−301(7)	−4017(7)	−9079(5)	49(2)
C(19)	−1539(8)	−3996(8)	−9537(5)	47(2)
C(20)	−2542(7)	−4151(7)	−9161(4)	42(2)
H(4)	−319(5)	−411(5)	−737(3)	2(1)
H(5A)	−326(5)	−656(6)	−806(4)	2(1)
H(5B)	−326(8)	−620(8)	−707(5)	8(3)
H(7)	−677(5)	−325(5)	−924(3)	1(1)
H(8)	−595(5)	−73(6)	−942(3)	2(1)
H(10)	−828(6)	−302(6)	−1055(4)	2(2)
H(11)	−1011(7)	−273(7)	−1129(4)	4(2)
H(12)	−1103(8)	−70(8)	−1149(5)	8(3)
H(13)	−958(6)	104(7)	−1095(4)	4(2)
H(14)	−773(6)	68(6)	−1013(4)	3(2)
H(16)	−93(6)	−430(6)	−730(4)	3(2)
H(17)	90(9)	−403(9)	−781(7)	13(4)
H(18)	54(7)	−388(7)	−925(4)	6(2)
H(19)	−166(6)	−386(7)	−1003(4)	4(2)
H(20)	−332(6)	−412(6)	−943(4)	5(2)

give only the *syn* adduct. If addition occurs successively to form the same intermediate monobromide, both the *E*- and *Z*-isomers would give identical sets of *syn* and *anti* adducts. The first situation was observed when bromination was carried out in the absence of Lewis acids (*cf.* runs *1* and *2* in Table 7), whereas in the presence of Lewis acids, both the *E*- and *Z*-isomers gave only *anti* adducts (*cf.* runs *3* and *4*; *5* and *6* in Table 7). Previously, it was demonstrated that addition of Br$_2$ to substituted styrenes in CCl$_4$ proceeds according to the electrophilic mechanism, and the reaction nonstereospecifically yields *syn/anti* adducts.[8] It can be suggested that under the conditions of runs *1*—*6* (see Table 7), addition proceeds by the electrophilic mechanism. This

Table 5. Bond lengths (*d*) in the structure of **3**

Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å
Br(1)—C(7)	1.962(6)	N(3)—C(2)	1.404(7)	C(9)—C(10)	1.378(9)	C(15)—C(16)	1.391(8)
Br(2)—C(8)	1.990(6)	N(3)—C(4)	1.492(7)	C(9)—C(14)	1.384(9)	C(16)—C(17)	1.376(9)
O(1)—C(2)	1.338(7)	C(4)—C(15)	1.516(9)	C(10)—C(11)	1.383(9)	C(17)—C(18)	1.379(9)
O(1)—C(5)	1.447(7)	C(4)—C(5)	1.522(9)	C(11)—C(12)	1.385(9)	C(18)—C(19)	1.365(9)
O(2)—C(2)	1.192(7)	C(6)—C(7)	1.508(7)	C(12)—C(13)	1.356(9)	C(19)—C(20)	1.367(9)
O(3)—C(6)	1.210(7)	C(7)—C(8)	1.511(9)	C(13)—C(14)	1.377(9)		
N(3)—C(6)	1.389(7)	C(8)—C(9)	1.518(8)	C(15)—C(20)	1.381(9)		

Table 6. Bond angles (ω) in the structure of **3**

Angle	ω/deg	Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
C(2)—O(1)—C(5)	111.1(5)	C(15)—C(4)—C(5)	112.1(5)	C(7)—C(8)—Br(2)	106.7(4)	C(13)—C(14)—C(9)	119.5(7)
C(6)—N(3)—C(2)	126.8(5)	O(1)—C(5)—C(4)	106.3(5)	C(9)—C(8)—Br(2)	108.0(4)	C(20)—C(15)—C(16)	117.6(6)
C(6)—N(3)—C(4)	120.3(5)	O(3)—C(6)—N(3)	119.9(5)	C(10)—C(9)—C(14)	119.3(6)	C(20)—C(15)—C(4)	124.8(5)
C(2)—N(3)—C(4)	110.6(5)	O(3)—C(6)—C(7)	121.8(5)	C(10)—C(9)—C(8)	121.0(6)	C(16)—C(15)—C(4)	117.4(6)
O(2)—C(2)—O(1)	122.9(6)	N(3)—C(6)—C(7)	118.2(5)	C(14)—C(9)—C(8)	119.7(6)	C(17)—C(16)—C(15)	121.8(7)
O(2)—C(2)—N(3)	127.9(6)	C(6)—C(7)—C(8)	114.2(5)	C(9)—C(10)—C(11)	120.7(7)	C(16)—C(17)—C(18)	119.1(7)
O(1)—C(2)—N(3)	109.2(5)	C(6)—C(7)—Br(1)	105.5(4)	C(10)—C(11)—C(12)	119.2(7)	C(19)—C(18)—C(17)	119.6(7)
N(3)—C(4)—C(15)	114.4(5)	C(8)—C(7)—Br(1)	107.9(4)	C(13)—C(12)—C(11)	120.0(6)	C(18)—C(19)—C(20)	121.4(8)
N(3)—C(4)—C(5)	100.8(5)	C(7)—C(8)—C(9)	114.5(5)	C(12)—C(13)—C(14)	121.3(7)	C(19)—C(20)—C(15)	120.5(7)

Table 7. Results of bromination of (*R*)-*N*-cinnamoyl-4-phenyloxazolidin-2-one

Run	*T* /°C	Substrate	Lewis acid	Source of bromine	Product, *anti/syn*	**2** (*2S,3R*) (%)	**3** (*2R,3S*) (%)
1	25	*E*-**1**	—	Br_2	2.8/1.0[b]	66	34
2	25	*Z*-**1**	—	Br_2	4/1[b]	14	86
3	25	*E*-**1**	BPr_3	Br_2	>20/1	66	34
4	25	*Z*-**1**	BPr_3	Br_2	>20/1	16	84
5[a]	−65	*E*-**1**	$AlBr_3$	Br_2	>20/1	76	24
6[a]	−65	*Z*-**1**	$AlBr_3$	Br_2	>20/1	24	76
7	25	*E*-**1**	—	MeCO—NHBr	>20/1	58	42

[a] Runs *5* and *6* were carried out at low temperature because of resinification of the reaction mixture at ~20 °C.

[b] The analogous *anti/syn* ratio was observed in the presence of $Et_2O \cdot BF_3$.

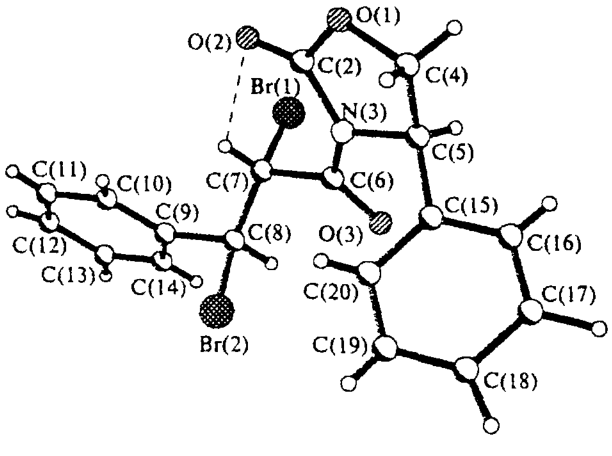
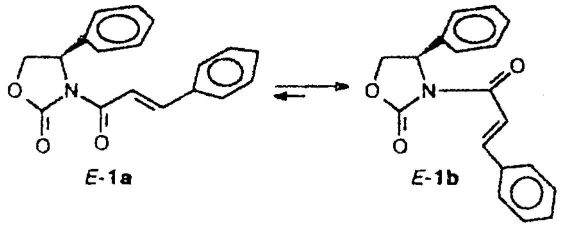


Fig. 2. Structure of diastereoisomer **3**.

is confirmed by the fact that bromination of isomer *E*-**1** with bromoacetamide under irradiation with UV light, which apparently proceeds according to the radical mechanism, gave the *anti* diastereoisomers in a ratio different from the ratios observed in other runs (see *de* in run *7*).

To account for the results of bromination, the following model can be used (see Scheme 1). A polarized Br_2 molecule (see Table 7, runs *1* and *2*) or a Br_2 molecule activated with Lewis acid (see runs *3*—*6*) attacks the C=C bond at the α-C atom because a stable benzyl cation is generated in this case. The configuration of the chiral α-C atom is determined by the relative rates of approach of a bromine molecule to diastereotopic sides of the C=C bond. The lifetime of this benzyl cation stabilized through conjugation is large enough for this cation to rotate about the C—C bond and, thus, to adopt the most favorable conformation identical for isomers *E*-**1** and *Z*-**1**. Then, a Br^- anion (as $[Br_3]^-$, $[BPr_3Br]^-$, or $[MBr_4]^-$) attacks the β-benzyl C atom with the formation of the dibromo derivative and regeneration of Br_2 or MBr_3.

Scheme 2



The low degree of asymmetric induction at the first stage of bromination of isomer *E*-**1** is readily attributable to the structure of the most stable (according to the data of conformational calculations) initial conformation of substrate *E*-**1b** (Scheme 2) in which the O atoms of the carbonyl groups are in *trans* orientation with respect to each other. The cause of an insignificant predominance of compound **2** remains unclear and is not associated with the volume of the substituent at position 4 of the heterocycle because in the most favorable conformer of the *E*-isomer this substituent does not shield the α-C atom of the C=C bond from the attack of Br atoms from either diastereotopic side. Previously, analogous data have been obtained on the stereoselectivity of the attack of electrophilic radicals on the C=C bond in this substrate.[9] In the case of possible coordination of the initial compound to aluminum derivatives ($AlBr_3$) or boron derivatives (BPr_3 and possible products of its bromination, namely, BPr_2Br or $EtCH(Br)BPr_2$, and the product of 1,2-anionotropic rearrangement of the last-mentioned compound, namely, $EtCH(Pr)B(Br)Pr$),[12] the diastereoselectivity should be sharply changed, as was observed previously for other reactions.[3,6,10] A comparison of the results of runs *1*, *3*, and *5*; and *2*, *4*, and *6* (see Table 7) demonstrated that in the case of both substrates, addition of Lewis acid exerted no effect on the stereoselectivity of the primary attack. Apparently, chelated structures of the substrate, which occured in solution, exhibited substantially lower nucleophilicity than the free substrate because the C=C bond was depleted of electrons due to their partial transfer from the carbonyl group of the cinnamoyl residue to the metal cation. Therefore, the primary attack of electrophilic Br_2 occured only on uncoordinated substrate particles. This situation is opposite to that observed[3,6] in the case of nucleophilic addition to isomer *E*-**1**.

In this case, rather high asymmetric induction (*de* 68—72%) in the reaction of isomer *Z*-**1** (see Table 7, runs *2* and *4*) in which compound **3** is the major diastereomeric product is attributed to the fact that in a solution, *Z*-**1** occurs predominantly (according to the quantum-chemical calculations) in the conformation in which the α-C atom of the C=C bond is shielded at the *re* side by the O atom of the carbonyl group of the heterocycle in the most favorable conformation (Fig. 3). The distance between the reaction center of this structure (the α-C atom) and the O atom of the carbonyl group of the heterocycle is only 2.97 Å [C(7)...O(2), see Fig. 3], and the angle between the plane of the C=C bond and the O atom [the O(2)...C(7)—C(8) angle] is 99.7°, which should prevent the attack of a bromine molecule along this direction.

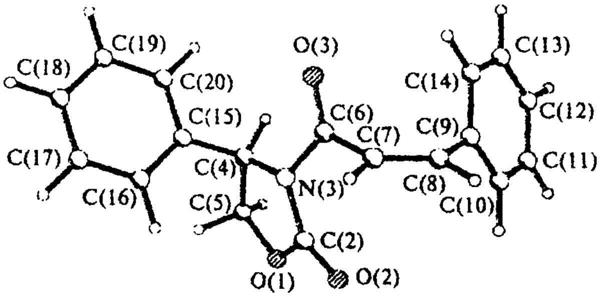


Fig. 3. Structure of the most favorable (according to the quantum-chemical calculations) conformation of *Z*-**1**.

However, the effect of Lewis acid on the stereoselectivity of the reaction was well pronounced at the second stage. As can be seen from the data of Table 7, the probability of formation of the *syn*-addition product is decreased in the presence of Lewis acids in solutions, apparently due to an increase in the size of the particle (for example, the $[MBr_4]^-$ anion), which transfers the Br^- anion on the intermediate carbocation.

In our opinion, this work besides interesting theoretical results offers a route for the highly efficient diastereoselective synthesis of important chiral synthons containing vicinal Br atoms.[14]

Experimental

Dichloromethane was distilled over P_2O_5 under an argon atmosphere. TLC was carried out on Silufol plates. For PTLC, SiO_2 (Merck 60 F254) was used. The ^1H NMR spectra were recorded on Bruker instruments (200 and 400 MHz) with HMDS as the internal standard. The optical rotation was measured on a Perkin—Elmer 241 polarimeter.

The initial 4-(*R*)-phenyloxazolidin-2-one was synthesized according to the procedure reported previously,[11] and then acylated with *E*-cinnamoyl chloride (see Ref. 9).

Photochemical isomerization of compound *E*-1. A solution of *E*-**1** in Pr^iOH was placed in a quartz tube and irradiated with UV light (a PRK-4 lamp) for 10 h. The isomer formed was separated on a column with SiO_2 (C_6H_{14} : PhH : Et_2O = 4 : 1 : 1). The yield of *Z*-**1** was 10%, m.p. 166—167 °C. Found (%): C, 73.43; H, 5.08; N, 4.26. $C_{16}H_{15}NO_3$. Calculated (%): C, 73.70; H, 5.16; N, 4.78. The ^1H NMR spectrum is given in Table 8.

Table 8. Parameters of the ^{1}H NMR spectra of the compounds obtained

Diastereoisomer	δ	*J*/Hz
Z-**1**	4.27 (dd, 1 H, $-\mathrm{OC\underline{H}_aH_b{-}CH_x}$);	3.8 (*vic*)
	4.67 (t, 1 H, $\mathrm{OC\underline{H}_bH_a{-}CH_x}$);	8.8 (*gem*)
	5.44 (dd, 1 H, $\mathrm{NC\underline{H}_x{-}CH_bH_a}$);	3.8 (*vic*)
	6.84 (d, 1 H, CH=);	17.5
	6.9 (d, 1 H, CH(Ph)=);	17.5
	7.33—7.54 (m, 10 H, 2 Ph)	—
E-**1**	4.26 (dd, 1 H, $\mathrm{OC\underline{H}_aH_b{-}CH_x}$);	3.9 (*vic*)
	4.68 (t, 1 H, $\mathrm{OC\underline{H}_bH_a{-}CH_x}$);	8.7 (*gem*)
	5.54 (dd, 1 H, $\mathrm{NC\underline{H}_x{-}CH_bH_a}$);	8.6 (*gem*)
	7.23—7.45 (m, 10 H, 2 Ph);	—
	7.72 (d, 1 H, CH=);	17.5
	7.88 (d, 1 H, CH(Ph)=)	17.5
2	4.37 (dd, 1 H, $\mathrm{OC\underline{H}_aH_b{-}CH_x}$);	4.2 (*vic*)
	4.84 (t, 1 H, $\mathrm{OC\underline{H}_bH_a{-}CH_x}$);	8.9 (*gem*)
	5.49 (d, 1 H, CHBr—);	11.5
	5.5 (dd, 1 H, $\mathrm{NC\underline{H}_x{-}CH_bH_a}$);	4.2 (*vic*)
	6.63 (d, 1 H, CHBr—);	11.5
	7.3—7.5 (m, 10 H, 2 Ph);	—
3	4.39 (dd, 1 H, $\mathrm{OC\underline{H}_aH_b{-}CH_x}$);	3.8 (*vic*)
	4.82 (t, 1 H, $\mathrm{OC\underline{H}_bH_a{-}CH_x}$);	8.8 (*gem*)
	5.44 (d, 1 H, CHBr—);	11.5
	5.58 (dd, 1 H, $\mathrm{NC\underline{H}_x{-}CH_bH_a}$);	3.9 (*vic*)
	6.63 (d, 1 H, CHBr—);	11.5
	7.3—7.5 (m, 10 H, 2 Ph)	—

Bromination of isomers *E*-1 and *Z*-1 in the presence of BPr_3. The reaction with BPr_3 was carried out in an open system as described previously.[12] BPr_3 (0.069 g, 0.095 mL, 0.5 mmol) was added to a solution of *E*-**1** (0.04 g, 0.1 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 10 min, Br_2 (0.026 mL, 0.08 g, 0.5 mmol) was added. The reaction mixture was kept for 40 min. Then the reaction mixture was treated with a 30% H_2O_2 solution (0.2 mL, 1.5 mmol) containing AcONa (0.164 g, 2.0 mmol) to decompose boron complexes. The excess of bromine was washed off with a solution of $Na_2S_2O_3$. The product was extracted with benzene, and the solvent was evaporated. The mixture of products was isolated by PTLC (C_6H_{14} : PhH : Et_2O = 4 : 1 : 1). The yield was 0.05 g (74%). Found (%): C, 47.67; H, 3.37; N, 2.8; Br, 34.84. $C_{18}H_{15}Br_2NO_3$. Calculated (%): C, 47.86; H, 3.31; N, 3.09; Br, 35.32. The mixture of compounds **2** and **3** was separated by PTLC (C_6H_{14} : PhH : Et_2O = 4 : 1 : 1). Purified individual products were analyzed by ^{1}H NMR spectroscopy (see Table 8).

Bromination of isomers *E*-1 and *Z*-1 in the presence of $AlBr_3$. Aluminum bromide (0.027 g, 0.1 mmol) was added to a solution of *E*-**1** (0.04 g, 0.1 mmol) in CH_2Cl_2 (1 mL) at −65 °C. After 10 min, Br_2 (.026 mL, 0.08 g, 0.5 mmol) was added. The reaction mixture was kept for 40 min and then washed with a solution of $Na_2S_2O_3$. The product was extracted with benzene, and the solvent was evaporated. After separation by PTLC, the yield of the mixture of diastereoisomers **2** and **3** was 72%. The mixture of products was analyzed by ^{1}H NMR spectroscopy (see Table 8).

Bromination of isomer *E*-1 with *N*-bromoacetamide. Bromoacetamide (0.028 g, 0.2 mmol) was added to a solution of *E*-**1** (0.04 g, 0.1 mmol) in CH_2Cl_2 (1 mL), and the reaction mixture was irradiated with UV light (a PRK-4 lamp) at 25 °C for 10 min. The product was extracted with benzene, and the solvent was evaporated. The yield of the mixture of diastereoisomers **2** and **3** was 99%. The mixture of the products was analyzed by ^{1}H NMR spectroscopy (see Table 8).

Epimerization of pure diastereoisomer 3. Br_2 and BPr_3 (in the ratio of 1 : 1) were poured into a tube, which was filled with Ar and contained a solution of chromatographically pure compound **3** (0.04 g) in CH_2Cl_2 (0.5 mL), under conditions analogous to those used in bromination of *E*-**1** and *Z*-**1** (see above), but bromine and BPr_3 were added in the reverse order. The mixture was kept for 1 h. The course of the reaction was monitored by TLC (C_6H_{14} : PhH : Et_2O = 4 : 1 : 1). The second diastereoisomer of **2** was not found in the reaction mixture (a comparison with the standard). Epimerization of the mixture of *anti/syn* products **2** and **3** taken in the ratio of 2.8 : 1.0 was carried out analogously (see Table 7, run *I*). In this case, no changes were observed.

X-ray structural studies of diastereoisomers 2 and 3. Crystals of **2** ($C_{18}H_{15}Br_2NO_3$, M = 453.13) are triclinic, space group $P\bar{1}$, at 20 °C a = 10.440(2) Å, b = 12.073(2) Å, c = 15.218(3) Å, α = 93.81(2)°, β = 94.84(2)°, γ = 114.62(2)°, V = 1726.6(6) Å^3, Z = 4, d_{calc} = 1.743 g cm^{-3}. The unit cell parameters and intensities of 7405 reflections were measured on an automated four-circle Siemens P3/PC diffractometer (293 K, λMo-Kα radiation, graphite monochromator, θ/2θ scanning technique, $\theta_{\max}$ = 25°). The structure was solved by the direct method and refined by the full-matrix least-squares method with anisotropic temperature factors for nonhydrogen atoms. The positions of hydrogen atoms were calculated from geometric considerations and included in the refinement with fixed positional (the riding model) and thermal (U_{iso} = 0.08 Å^2) parameters. Crystals **3** are monoclinic, space group $P2_1/n$, at 20 °C a = 10.730(1) Å, b = 10.160(1) Å, c =16.333(2) Å, β = 103.41(1)°, V = 1732.0(1) Å^3, Z = 4, d_{calc} = 1.738 g cm^{-3}. The unit cell parameters and intensities of 3791 reflections were measured on an automated four-circle Siemens P3/PC diffractometer. Hydrogen atoms were located from the difference Fourier synthesis and refined isotropically. The final values of the R factors were as follows: for **2**, R_1 = 0.078 using 6890 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.220 based on a total of 6944 independent reflections; for **3**, R_1 = 0.065 using 2966 reflections with $I > 2\sigma(I)$ and wR_2 = 0.177 based on a total of 3590 independent reflections. All calculations were carried out on an IBM PC/AT-486 computer using the SHELXTL PLUS program package. The final refinement was performed using the SHELXL-93 program.

The following geometric characteristics of the structures of the compounds under study should be noted. The oxazolidine rings adopt an envelope conformation. The C(5) atom deviates from the plane of the remaining atoms of the ring by 0.36 and −0.32 Å in two crystallographically independent molecules **2**, respectively, and by 0.21 Å in molecule **3**. In the molecules, the intramolecular O(2)...H(7)—C(7) hydrogen bond occurs (the O(2)...H(7) distance is 2.2(1), 2.3(1), and 2.29(7) Å, and the O(2)...C(7) distance is 2.86(1), 2.85(1), and 2.842(7) Å for two crystallographically independent molecules **2** and molecule **3**, respectively). The O(2)...H(7)—C(7) angle is 125(5)°, 116(5)°, and 121(3)° for two crystallographically independent molecules **2** and molecule **3**, respectively. In the crystals, molecules **2** and **3** are located at the van der Waals distances. The molecules are packed in stacks along the x axis.

Conformational calculations. The energies of the conformations were calculated using the PM3 and MOPAC programs.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 96-03-33430).

References

1. L. Duhamel, P. Angibaud, J. R. Desmurs, and J. B. Valnot, *Synlet*, 1991, 807.
2. D. A. Evans, T. C. Britton, J. A. Ellman, and R. L. Dorow, *J. Am. Chem. Soc.*, 1990, **112**, 4011.
3. G. Li, C. Russell, M. Jarosinski, and V. J. Hruby, *Tetrahedron Lett.*, 1993, 2565.
4. C. Giordano and G. Cataldi, *J. Org. Chem.*, 1989, **54**, 1470.
5. G. Bellucci, C. Chiappe, and F. D'Andrea, *Tetrahedron, Asymmetry*, 1995, **6**, 221.
6. D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238.
7. K. Gothelf, I. Thomsen, and K. Jorgensen, *J. Am. Chem. Soc.*, 1996, **118**, 59.
8. R. C. Fahey and H. Schneider, *J. Am. Chem. Soc.*, 1968, **90**, 4429.
9. V. I. Tararov, T. F. Savel'eva, Yu. N. Belokon', Yu. T. Struchkov, A. R. Pisarevskii, and N. I. Raevskii, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 640 [*Russ. Chem. Bull.*, 1996, **45**, 600 (Engl. Transl.)].
10. D. A. Evans and J. V. Nelson, *Topics Stereochem.*, 1982, **13**, 1.
11. E. Nicolas, K. C. Russel, and V. J. Hruby, *J. Org. Chem.*, 1993, **58**, 766.
12. B. M. Mikhailov and Yu. N. Bubnov, *Bororganicheskie soedineniya v organicheskom sinteze* [*Organoboron Compounds in Organic Synthesis*], Nauka, Moscow, 1977 (in Russian).
13. J. R. Johnson, H. R. Snyder, and M. G. van Campen, *J. Am. Chem. Soc.*, 1938, **60**, 115.
14. F. D'Angel, P. Marchetti, and V. Bertolusi, *J. Org. Chem.*, 1995, **60**, 4013.

Received November 28, 1996