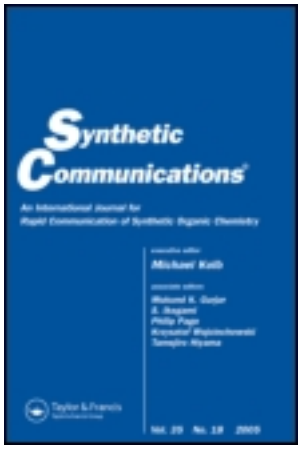

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Najeh Tka [a], Jamil Kraïem [a] & Béchir Ben Hassine [a]

[a] Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène, Faculté des Sciences de Monastir, Monastir, Tunisia

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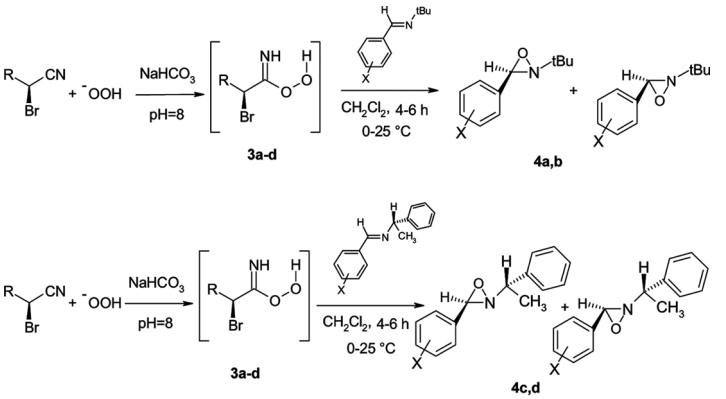
ENANTIO- AND DIASTEREOSELECTIVE OXIDATION OF *N*-ALKYLIMINES USING CHIRAL α-BROMONITRILES AND HYDROGEN PEROXIDE SYSTEM

Najeh Tka, Jamil Kraïem, and Béchir Ben Hassine
Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène, Faculté des Sciences de Monastir, Monastir, Tunisia

GRAPHICAL ABSTRACT



Abstract *Chiral α-bromonitriles were prepared with good chemical and optical yields starting from natural α-amino acids by dehydrating the corresponding α-bromoamides with thionyl chloride. The combined system α-bromonitriles/hydrogen peroxide was examined for the enantio- and diastereoselective oxidation of* N*-alkylimines in basic media at room temperature. The oxidation of* N*-tertiobutylarylimines leads to optically active oxaziridines with moderate enantiomeric excess. However, the oxidation of (S)-1-phenylethylarylimines affords the corresponding oxaziridines with good diasteromeric excess up to 97/3 as proved by gaseous-phase chromatography.*

Keywords Chiral α-bromonitriles; chiral bromoalkylperoxyimidic acids; chiral oxaziridines; oxidation of *N*-alkylimines

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Address correspondence to Béchir Ben Hassine, Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène, (01 UR 1201), Faculté des Sciences de Monastir, Avenue de l'Environment, 5019, Monastir, Tunisia. E-mail: bechirbenhassine@yahoo.fr

INTRODUCTION

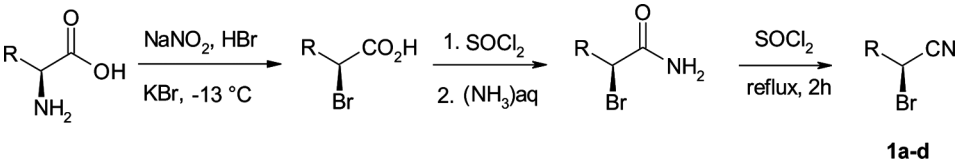
Oxaziridines are a topic of increasing interest in medicinal chemistry. They have received attention as antitumour agents[1,2] and analogs of penicillin.[3] Furthermore, the oxaziridine ring has been the focus of several studies mainly because of the presence of an inherently weak N–O bond, which makes the molecule unusually reactive. As a result, oxaziridines have been used as both oxygenating[4–7] and aminating[8–11] agents in reactions with a wide variety of nucleophiles. Furthermore, oxaziridines constitute a highly reactive functional group that can serve as versatile synthetic intermediates for the synthesis of many heterocyclic compounds.[12] Recently, Marilene et al. have described an efficient cycloaddition reaction of a variety of aryl alkenes with 2-*tert*-butyl-3-aryloxaziridines leading to 3,5-diarylisoxazolidines.[13] We have recently shown that cycloaddition of 2-alkyl-3-aryloxaziridines with chlorosulfonylisocyanate occurs with cleavage of the C–N bond of the oxaziridine ring and gives the corresponding 1,2,4-oxadiazolidin-3-one.[14]

Several synthetic methods have been employed for the synthesis of oxaziridines.[15–18] Among them, the oxidation of imines with different oxidizing agents continues to be the favored method. The commercially available *m*-chloroperbenzoic acid (MCPBA) is one of the most widely used reagents.[19] However, we have previously reported that the trichloroacetonitrile–hydrogen peroxide system can compete with MCPBA at the levels of costs reactivity, and yields of oxaziridines.[20,21]

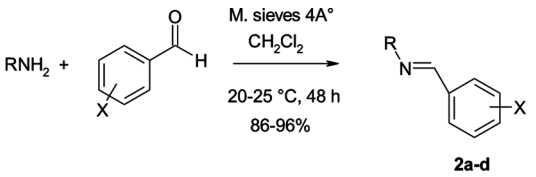
As part of our work to synthesize optically pure oxaziridines and investigate the preparation of new chiral heterocyclic compounds, herein we report the investigation of an optically active α-bromonitriles/hydrogen peroxide system for the enantio- and diastereoselective oxidation of *N*-alkylimines and the study of the asymmetric induction of in situ formed chiral bromoalkylperoxyimidic acids when transferring oxygen to *N*-tertiobutylarylimines and (*S*)-1-phenylethylarylimines. This oxidant system can compete at the levels of cost and reactivity with chiral peroxy acids, which have been widely used since 1968.

RESULTS AND DISCUSSION

The synthetic route to the target α-bromonitriles **1a–d** from the corresponding α-amino acids is outlined in Scheme 1. Optically pure α-bromoacids prepared according to the procedure described by Larchevêque and petit[22] were easily converted to α-bromoamids by treatment with thionyl chloride followed by aqueous ammonia and then dehydrated with thionyl chloride to afford the corresponding α-bromonitriles **1a–d** with good yields and enantiomeric purity.



Scheme 1. Synthesis of α-bromonitriles **1a–d** from the corresponding natural amino acids. **a**: R = Me; **b**: R = i-Pr; **c**: R = i-Bu; **d**: R = *sec*-Bu.



Scheme 2. Synthesis of prochiral and chiral N-alkylarylimines **2a**–**d**. **a**: R = tBu-, X = H; **b**: R = tBu-, X = OCH_3; **c**: R = PhMeHC*-, X = H; **d**: R = PhMeHC*-. X = OCH_3.

The synthetic route to the prochiral and chiral imines **2a–d** is outlined in Scheme 2.

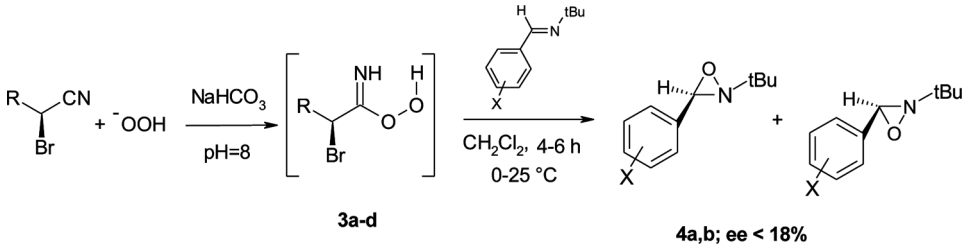
N-Alkylimines **2a**–**d** were obtained as one geometrical isomer by reacting tertiobutylamine or optically pure (*S*)-1-phenylethylamine with the corresponding aryl aldehydes in the presence of molecular sieves.

The synthetic route to oxaziridines **4a** and **b** is outlined in Scheme 3. The chiral α-bromonitriles **1a–d** react with hydrogene peroxide under basic media to generate in situ the corresponding chiral bromoalkylperoxyimidic acids **3a-d**, which oxidize the *N*-tertiobutylarylimines **2a** and **b** to provide the corresponding optically active oxaziridines **4a** and **b**. The latter compounds were obtained as a mixture of two enantiomers with good chemical yields and moderate enantiomeric excesses.

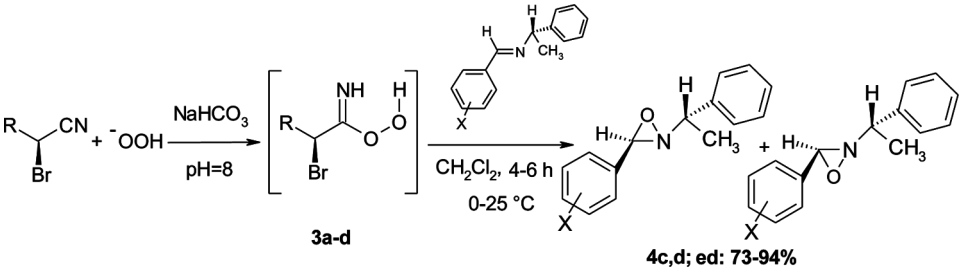
The synthetic route to oxaziridines **4c,d** is outlined in Scheme 4. The α-bromonitriles/hydrogene peroxide system is used to oxidize chiral (*S*)-1-phenylethylarylimines **2c** and **d** under basic media to afford the corresponding oxaziridines **4c** and **d** with good diastereomeric excesses.

The activation of the nitrile by hydrogen peroxide to form peroxycarboximidic acid was first described by Payne et al.[23] Since that, an interesting variation of the Payne system has been introduced.[24] We have previously reported the use of a trichloroacetonitrile–hydrogen peroxide system to oxidize several imines in a symmetric manner, giving racemic oxaziridines. Our dual objective in the present study is to develop an efficient, inexpensive, asymmetric, oxidizing reagent based upon chiral α-bromonitriles and 30% H_2O_2 that could lead to chiral oxaziridines with good optical purity.

We have already reported the synthesis of new enantiomerically pure aminonitriles[25] and their application to prepare some chiral biologically active heterocyclic compounds.[26–28] Following the same strategy, we have prepared four new



Scheme 3. Enantioselective synthesis of oxaziridines **4a** and **b** from the corresponding prochiral imines **2a** and **b**. **a**: R = Me; **b**: R = i-Pr; **c**: R = i-Bu; **d**: R = *sec*-Bu. X = OCH_3.



Scheme 4. Diastereoselective synthesis of oxaziridines **4c** and **d** from the corresponding chiral imines **2c** and **d**. R = Me; **b**: R = i-Pr; **c**: R = i-Bu; **d**: R = *sec*-Bu. X = OCH_3.

enantiomerically enriched α-bromonitriles from natural aminoacids by dehydrating the corresponding α-bromoamides with thionyl chloride. Desired α-bromonitriles were obtained with chemical yields ranging from 88% to 92% and good enantiomeric excess. Enantiomeric ratios were measured by high-performance liquid chromatography (HPLC), showing in all cases a slight racemization of less than 5%.

This asymmetric oxidation of *N*-alkyl imines involves two steps. The first step is the in situ formation of chiral peroxycarboximidic acid by adding hydrogen peroxide to optically active α-bromonitriles in basic media. This step is promoted by $NaHCO_3$, which is added in an appropriate amount to the aqueous H_2O_2 to adjust the pH to 8. This pH favors the increase of concentration of ion HOO^-, which activates the α-bromonitriles **1a–d** to form in situ the chiral bromoalkylperoxyimidic acids **3a–d**. The second step is the electrophilic transfer of oxygen from peroxycarboximidic acids to imines **2a–d**.

As described in the literature,[29] prochiral and chiral imines were prepared by reacting tertiobutylamine or optically pure (*S*)-1-phenylethylamine with the corresponding aryl aldehydes in the presence of molecular sieves in anhydrous methylene chloride. Imines **2a** and **d** were obtained as one geometrical isomer, presumably the thermodynamically favored *anti*-imine. Oxaziridines **4a** and **d** were obtained with good yields in a reasonably short time, ranging from 4 to 6 h by oxidizing the corresponding imines **2a** and **d** using 1.2 equivalents of α-bromonitriles and 6 equivalents of H_2O_2.

As shown in Scheme 3, the enantioselective oxidation of *N*-tertiobutylarylimines **2a** and **b** using the combined system of α-bromonitriles **1a** and **d** and hydrogen peroxide leads to a mixture of two enantiomeric oxaziridines **4a** and **b** with good chemical yields. We note that both enantiomers were obtained exclusively in a *trans*-configuration and the less stable (Z)-isomer could not be obtained because of the bulkiness of the substituents. Unfortunately, we have found that oxaziridines were formed with relatively low enantiomeric excess not exceeding 18%, as shown in Table 1. The enantiomeric excess of obtained oxaziridines were found to be moderate because the central chirality of the peroxyimidic acid is relatively far from the site of oxygen transfer. Therefore, the interaction between the stereocentre and the substituents of the imines remains too low as shown in Figure 1.

Unlike *N*-tertiobutylarylimines **2a** and **b**, the oxidation of (*S*)-1-phenylethylarylimines **2c** and **d** proceeded with fairly good stereoselectivity. This high stereoselectivity of the reaction is the outcome of asymmetric induction exerted by two

Table 1. Chemical yields and enantiomeric excess of obtained oxaziridines **4a** and **b**

Oxaziridines	MeC · HBrCN		iPr-C · HBrCN		tBu-C · HBrCN		Sec-BuC · HBrCN	
R	Yield (%)	*Ee*[a]	Yield (%)	*Ee*[a]	Yield (%)	*Ee*[a]	Yield (%)	Ee[a]
Ph	71	55:45	72	58:42	75	57:43	78	59:41
4-CH_3O-C_6H_4	74	57:43	70	56:44	76	54:46	74	57:43

[a]The enantiomeric ratios have been assigned by NMR using chiral solvating agents as reported by Pirkle and Rinaldi.[30]

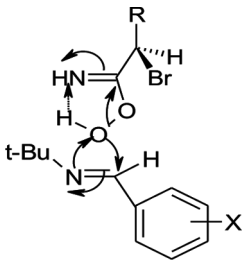


Figure 1. Electrophilic oxygen transfer from chiral bromoalkylperoxyimidic acid to imines.

stereocenters present in the chiral imines and the chiral peroxycarboximidic acids. From each optically pure imine **2c** and **d**, two diastereomeric oxaziridines were generated with good diastereomeric ratios ranging from 74% to 94% as shown in Table 2. However, Troisi et al.[31] have shown that diastereoselective oxidation of imines **2c**, and **d** using achiral oxidant (MCPBA) gives the corresponding oxaziridines with diastereomeric ratios ranging from 20% to 60%.

Both diastereomers were obtained with good chemical yields in a *trans*-configuration and the less stable *cis*-isomer has not been obtained because of the bulkiness of the substituents. For example, the addition of hydrogen peroxyde to the (2*S*)-2-bromopropane nitrile **1a** generates in situ the (2*S*)-2-bromopropylperoxyimidic acid **2a**, which oxidizes chiral imine **2c** to afford a mixture of both nonequimolar oxaziridines **4c** and **4c′**. The diastereomeric excess of the obtained oxaziridines was measured by gaseous-phase chromatography, showing a

Table 2. Chemical yields and diastereomeric excess of obtained oxaziridines **4c** and **d**

Oxaziridines	MeC · HBrCN		iPr-C · HBrCN		tBu-C · HBrCN		Sec-BuC · HBrCN	
R	Yield (%)	*De*[a]	Yield (%)	*De*[a]	Yield (%)	*De*[a]	Yield (%)	*De*[a]
Ph	80	87:13	81	89:11	85	92:8	88	97:3
4-CH_3O-C_6H_4	82	88:12	83	86:14	86	90:10	84	95:5

[a]The diastereomeric excess of obtained oxaziridines was measured by gaseous-phase chromatography.

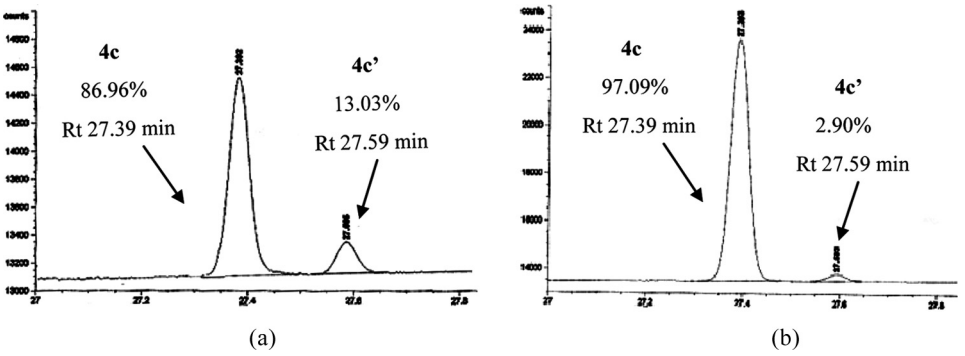


Figure 2. Analyses by gaseous-phase chromatography of the mixture of oxaziridines **4c** and **4c′** obtained using (a) (2S)-2-bromopropane nitrile–hydrogen peroxyde system and (b) (2S,3S)-2-bromo-3-methylpentanenitrile–hydrogen peroxyde system.

diastereomeric excess of 73% (Fig. 2). The best result was observed with chiral (2*S*,3*S*)-2-bromo-3-methylpropylperoxyimidic acid formed in situ by adding hydrogen peroxyde to the (2*S*,3*S*)-2-bromo-3-methylpentanenitrile. As shown in the gas chromatogram (Fig. 2), both oxaziridine diastereoisomer **4c** and **4c′** were isolated with a diastereomeric ratio of 94%.

The absolute configuration of major diastereomers isolated in the enantiomerically pure form after column chromatography on silica gel is given by comparing the specific rotation values with the known products described in the literature. As a result, we suggest that imines **2c** and **d** were attacked by the oxygen of the bromoalkylperoxyimidic acid from the upper side affording a new stereogenic carbon of oxaziridinic ring having the R configuration. However, an attack from the bottom leads to the minor diastereomer having the S configuration.

Finally, the investigated method for asymmetric oxidation of imines was found to be more stereoselective with chiral *N*-alkylimines. This method seems to be simple and inexpensive because available amino acids were used as starting materials.

CONCLUSION

We reported the enantioselective and diastereoselective synthesis of oxaziridines by oxidation of the corresponding imines using the combined system of chiral α-bromonitriles and hydrogen peroxide. The enantiomeric excesses of the prepared oxaziridines were moderate, whereas the diastereomeric excesses were high, up to 97/3, as proved by gaseous-phase chromatography. We intend to optimize experimental conditions to further improve the chemical and optical yields of the obtained oxaziridines and their use to synthesize new biologically active compounds.

EXPERIMENTAL

Chiral α-Bromonitriles 1a–d

General procedure. A mixture of α-bromoacid (10 mmol), $SOCl_2$ (50 mmol), and three drops of dry DMF in anhydrous dichloromethane was stirred overnight at

room temperature. After removal of the excess of $SOCl_2$ under vacuum, the residue was added slowly to a cold solution of aqueous ammonium hydroxide and stirred for 2 h. The mixture was filtered, and the resultant α-bromoamides were collected, purified, and dissolved in 20 mL of freshly distilled thionyl chloride. The mixture was refluxed for 2 h, the excess of thionyl chloride was removed, and the reaction residue was mixed with crushed ice, and extracted with ethylacetate, and dried with anhydrous $MgSO_4$. After removing the solvent, the crude product was purified by column chromatography on a neutral alumina gel to afford the chiral α-bromonitriles **1a–d**.

HPLC analysis of α-bromonitriles **1a–d** were carried out using a chiral Chirobiotic V column 4.6 mm × 250 mm under the following conditions: heptane/isopropanol (98:2) as mobile phase, rt, $\lambda = 254$ nm, flow rate = 0.6 mL/min. Retention times of α-bromonitriles **1a–d** are **1a**, 15.25 min; **1b**, 17.66 min, **1c**, 19.01 min, and **1d**, 21.81 min.

(2S)-2-Bromopropanenitrile 1a. Yield = 90%; colorless oil; $[\alpha]_D$ −50.0 (c 0.25%, $CHCl_3$); HRMS-ESI calcd. for C_3H_4BrN 132.95274; found 132.95279; IR (cm^{-1}); $\nu_{CN} = 2249$; ^1H NMR (300 MHz, $CDCl_3$): δ 1.97(d, 3H, $J = 7.2$ Hz); 4.38 (q, 1H, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ δ 21.21; 23.91; 118.26 (CN).

(2S)-2-Bromo-3-methylbutanenitrile 1b. Yield = 88%; colorless oil; $[\alpha]_D$ −55.0 (c 0.25%, $CHCl_3$); HRMS-ESI calcd. for C_5H_8BrN 160.98403; found 160.98408; IR (cm^{-1}); $\nu_{CN} = 2239$; ^1H NMR (300 MHz, $CDCl_3$): δ1.15 (d, 3H, $J = 2.4$ Hz); 1.18 (d, 3H, $J = 2.4$ Hz), 2.16 (m, 1H), 4.24 (d, 1H, $J = 5.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 19.09, 19.59, 33.89, 35.75, 116.60 (CN).

(2S)-2-Bromo-4-methylpentanenitrile 1c. Yield = 92%; color less oil; $[\alpha]_D$ −60.0 (c 0.25%, $CHCl_3$); HRMS-ESI calcd. for $C_6H_{10}BrN$ 174.99969; found 174.99972; IR (cm^{-1}); $\nu_{CN} = 2242$; ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (m, 6H); 1.87–2.02 (m, 3H); 4.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.64, 25.66, 26.63, 45.17, 52.65, 117.66 (CN).

(2S,3S)-2-Bromo-3-methylpentanenitrile 1d. Yield = 90%; color less oil; $[\alpha]_D$ −65.0 (c 0.25%, $CHCl_3$); HRMS-ESI calcd. for $C_6H_{10}BrN$ 174.99969; found 174.99974; IR (cm^{-1}); $\nu_{CN} = 2240$; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, $J = 7.5$ Hz); 1.17 (d, 3H, $J = 6.6$ Hz), 1.48 (m, 1H), 1.69 (m, 1H), 1.97 (m, 1H); 4.33 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ 11.38, 16.03, 26.98, 34.22, 40.39, 116.43 (CN).

Chiral Oxaziridines 4a–d from the Corresponding Imines 2a–d

General procedure. A solution of H_2O_2 (30%) (30 mmol) over a period of 5 min was added to a stirred solution of imines **2a**–**d** (5 mmol) and α-bromonitrile **1** (5.5 mmol) in CH_2Cl_2 (30 ml) at 0 °C. The pH of the 30% aqueous H_2O_2 was adjusted to 8 prior to addition with the appropriate amount of $NaHCO_3$. The reaction mixture was allowed to come to room temperature and then stirred until the imine was consumed (TLC). Then, the mixture was washed with water (250 mL) and extracted with three 50-mL portions of CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure ($T < 30$ °C). The crude residue was cooled, diluted with 100 mL hexane, and filtered to remove

precipitated α-bromoamide. The solvant was evaporated, and the residue was purified by flash chromatography on silica gel (cyclohexane/acetate 85:15) to afford pure (*E*) oxaziridines **4a–d**. All oxaziridines mentioned have previously been reported: **4a**, **b**[32] and **4c, d**.[31]

Analysis of different oxaziridines was performed using a gas chromatograph type HP 5890 equipped with a flame ionization detector and a polar capillary column 50 m long and 0.32 mm in diameter. The carrier gas used was nitrogen at a pressure of 0.552 bar and chromatography is developed with temperature programming from 180 to 250 °C.

(*E*)-2-*tert*-Butyl-3-phenyloxaziridine 4a. Yield = 71–78%; yellow oil; *ee* 10–18%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 9H), 4.69 (s, 1H), 7.38–7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 25.34, 58.51, 73.71, 127.56, 128.52, 129.83.

(*E*)-2-*tert*-Butyl-3-paramethoxyphenyloxaziridine 4b. Yield = 70–76%; yellow oil; *ee* 08–14%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, 9H), 3.81 (s, 3H) 4.64 (s, 1H) 6.31 (d, 2H, $J = 8.7$ Hz); 6.89 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$), δ 25.32, 55.38, 58.34, 73.53, 113.93, 127.66, 128.98, 160.89.

(*E*)-(1′S,3R)-2-(1′-Phenylethyl)-3-phenyloxaziridine 4c. Yield = 80–88%; yellow oil; *de* 74–94%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (d, 3H, $J = 6.3$ Hz) 3.29 (q, 1H); 4.56 (s, 1H); 7.29–7.33 (m, 5H); 7.41–7.54 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 21.84, 71.36, 79.54, 124.21, 127.12, 128.02, 128.85, 129.21, 131.69, 133.75, 139.97.

(*E*)-(1′S,3R)-2-(1′-Phenylethyl)-3-paramethoxyphenyloxaziridine 4d. Yield = 82–86%; yellow oil; *de* 72–90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (d, 3H, $J = 6.3$ Hz) 3.37 (q, 1H) 3.85 (s, 3H) 4.67 (s, 1H); 7.12 (d, 2H, $J = 8.4$ Hz) 7.30–7.34 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 20.54, 56.24, 71.34, 80.55, 113.84, 125.55, 127.74, 128.55, 128.97, 129.45, 137.77, 160.94.

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