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Stereoselective Synthesis of Azetidines and Pyrrolidines from *N*-*tert*-Butylsulfonyl(2-aminoalkyl)oxiranes†

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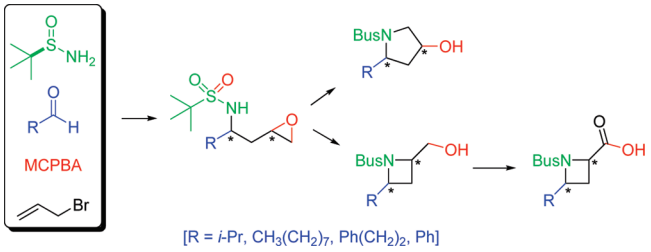

Base-induced cyclization of enantiopure (2-aminoalkyl)oxiranes allowed the stereospecific formation of pyrrolidin-3-ols and/or 2-(hydroxymethyl)azetidines, depending on the reaction conditions. The oxidation of 2-(hydroxymethyl)azetidines led to azetidine-2-carboxylic acids in high yields.

Introduction

Among small- and medium-size aza-heterocycles, azetidines[1] have attracted less attention than aziridines,[2] pyrrolidines,[3] and piperidines,[4] mainly due to the lack of general methods for their preparation. Recently, four-membered nitrogen-containing heterocycles have found applicability in pharmacy as highly biologically active compounds.[5] However, five-membered pyrrolidines have well-known biological activities and are widely represented in Nature. Proline derivatives in particular have garnered much attention due to their central role in organocatalysis.[6] For all these reasons, methodologies which allow access to enantiomerically pure both azetidines and pyrrolidines are of great interest in the context of discovering new drugs and more efficient organocatalysts. Many methodologies have been developed for the preparation of nitrogen-containing heterocycles, with the intramolecular nitrogen nucleophilic displacement of a leaving group being one of the most commonly used. On the

† Dedicated to Professor Peter Stanetty on occasion of his 60th birthday.

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other hand, one of the most direct and reliable methods for the asymmetric synthesis of amine derivatives is the addition of an organometallic reagent (mainly organomagnesium,[7] organolithium,[8] organozinc[9] and organoindium[10] derivatives) to the C=N bond of enantiopure *N*-sulfinylimines. In this context, *N*-*tert*-butylsulfinyl derivatives[11] have found high applicability in synthesis as electrophiles because both enantiomers are accessible in large-scale processes[12] and because the chiral auxiliary is easily removed under acidic conditions.[8b] In addition, practical processes for recycling the *tert*-butylsulfinyl group upon deprotection of *N*-*tert*-butylsulfinylamines have also been reported.[13] We described recently[10a] the stereoselective allylation of *N*-*tert*-butylsulfinyl aldimines with allylindium species[14] which can be generated in the presence of the imine from allylic bromides and indium metal under mild reaction conditions and exhibit high tolerance to a wide range of functional groups in many solvents.[15] The resulting enantiopure *N*-*tert*-butylsulfinyl homoallylamines were easily oxidized to give a diastereomeric mixture of the corresponding *N*-*tert*-butylsulfonyl(2-aminoalkyl)oxiranes, which upon treatment under basic conditions led to *cis*- and *trans*-pyrrolidin-3-ols.[16] We report here a full account of our studies of the base-induced cyclization of (2-aminoalkyl)oxirane derivatives of type **I** which, depending on the reaction conditions, could undergo a 4-*exo*-*tet* or a 5-*endo*-*tet* ring closure, leading to the corresponding 2-(hydroxymethyl)azetidine **II** or 3-hydroxypyrrolidine derivatives **III**, respectively (Scheme 1). There are only two examples in the literature of 4-*exo*-*tet* ring closure in aminooxiranes of type **I**. One is the thermal

SCHEME 1. Base-Induced Cyclization Pathways of (2-Aminoalkyl)oxirane Derivatives

decomposition of 5-aryl-2-methyl-5-methoxy-4-(cyclohexylamino)-1,2-epoxypentan-3-one boron trifluoride complexes leading to the corresponding azetidinone,[17] and the other one is the cyclization of *N*-tosyloxiraneethylamines, which upon treatment with aqueous sodium hydroxide afforded either 2-(hydroxymethyl)azetidine or 3-hydroxylpyrrolidine derivatives, depending on the location of a pentamethylene substitution in the chain connecting the nitrogen with the oxirane ring.[18]

Results and Discussion

N-*tert*-Butylsulfinyl amines **2** were prepared with high both chemical yields and diastereoselectivities by the reaction of different *N*-*tert*-butylsulfinyl aldimines **1** with allyl bromide and indium powder in THF at 60 °C (Table 1).[10a] For (R_S)-aldimines, the nucleophilic attack takes place almost exclusively at the *Si* face of the imino group and, logically, at the *Re* face for (S_S)-enantiomers. The sense of the stereoinduction has been explained by a chairlike model in which the metal is chelated both by the oxygen and the nitrogen of the imine moiety.[10a] In this way, homoallylamine derivatives **2** are accessible in enantiomerically pure form after column chromatography since the reaction products of the indium-mediated allylation are diastereomers. The oxidation of compounds **2** with 3 equiv of *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at room temperature yielded *N*-*tert*-butylsulfonyl(2-aminoalkyl)oxiranes **3** in almost quantitative yields (Table 1). The oxidation of the sulfinyl group to the corresponding sulfonyl group (*t*-BuSO_2 or Bus) took place fairly rapidly. Subsequent epoxidation under these reaction conditions occurred without any stereoselection in spite of the presence of a stereogenic center in the molecule (a ca. 1:1 diastereomeric mixture was always obtained). All attempts to separate diastereoisomers **3** (column chromatography, silica gel, hexane/ethyl acetate) failed.[16]

We initially explored the base-induced cyclization of the diastereomeric mixture of (2-aminoalkyl)oxiranes (2*R**,2′*S*)-**3d** (derived from the aldimine of benzaldehyde and (R_S)-*N*-*tert*-butylsulfinyl amine). After some experimentation, we found that the treatment of the crude reaction mixture of (2*R**,2′*S*)-**3d** (without purification after the oxidation step, that means that *m*-CPBA and *m*-CBA are present along with the diastereomeric mixture of epoxides **3d**) with potassium carbonate in *N*,*N*-dimethylformamide (DMF) at 100 °C for 24 h led, with total conversion, to a mixture of pyrrolidin-3-ol derivatives (5*S*)-**4d** and (5*S*)-**5d**, which were easily separated by column chromatography (Table 2, entry 1).[16] The pyrrolidin-3-ols (5*S*)-**4d** (*cis*-isomer) and (5*S*)-**5d** (*trans*-isomer) are formed through a disfavored 5-*endo*-*tet* ring

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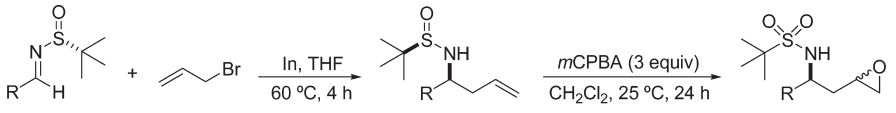
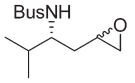
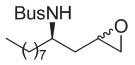
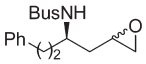
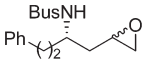
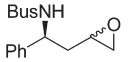
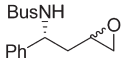
TABLE 1. Preparation of (2-Aminoalkyl)oxiranes 3 from Chiral Aldimines 1[a]

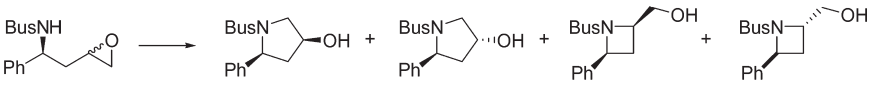


1 2 3

	Aldimine		Homoallyl amine			(2-Aminoalkyl)oxirane[d]	
Entry	No.	R	No.	dr[b]	Yield (%)[c]	No.	Structure
1	(S_S)-**1a**	*i*-Pr	(R_C,S_S)-**2a**	92:8	82	(2*R**,2′*R*)-**3a**	
2	(R_S)-**1b**	$CH_3(CH_2)_7$	(R_C,R_S)-**2b**	96:4	91	(2*R**,2′*R*)-**3b**	
3	(R_S)-**1c**	$Ph(CH_2)_2$	(R_C,R_S)-**2c**	91:9	79	(2*R**,2′*R*)-**3c**	
4	(S_S)-**1c**	$Ph(CH_2)_2$	(S_C,S_S)-**2c**	91:9	75	(2*R**,2′*S*)-**3c**	
5	(R_S)-**1d**	Ph	(S_C,R_S)-**2d**	94:6	94	(2*R**,2′*S*)-**3d**	
6	(S_S)-**1d**	Ph	(R_C,S_S)-**2d**	94:6	90	(2*R**,2′*R*)-**3d**	

[a]Reactions carried out using 1.0 mmol of aldimine **1**, 1.2 mmol of allyl bromide, and 1.2 mmol of In in 5 mL of THF for the allylation step. [b]Diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixtures. [c]Isolated yields after column chromatography based on the starting aldimine **1**. [d]Yields were always > 95%.

TABLE 2. Optimization of the Base-Induced Cyclization of (2-Aminoalkyl)oxiranes (2*R,2′*S*)-3d[a]**



(2*R**,2′*S*)-**3d** (5*S*)-**4d** (5*S*)-**5d** (4*S*)-**6d** (4*S*)-**7d**

			reaction products (%)[c]			
entry	reaction conditions	conversion[b] (%)	(5*S*)-**4d**	(5*S*)-**5d**	(4*S*)-**6d**	(4*S*)-**7d**
1[d]	K_2CO_3 (3 equiv), DMF (1 mL), 100 °C, 24 h	100	53	47		
2	K_2CO_3 (3 equiv), DMF (1 mL), 100 °C, 24 h	100	23	38	24	12
3	K_2CO_3 (3 equiv), KI (1 equiv), DMF (1 mL), 100 °C, 24 h	100	51	49		
4	K_2CO_3 (3 equiv), DMF (1 mL), 80 °C, 24 h	100	33	31	17	19
5	K_2CO_3 (3 equiv), DMF (1 mL), MW (65−70 W), 100 °C, 15 min	72	43	25	19	13
6	K_2CO_3 (1,1 equiv), DMF (1 mL), MW (5−15 W), 60 °C, 2 h	51	72	12	11	6
7	TfOH (1 mol %), THF (1 mL), 25 °C, 24 h	100	53	38		9
8	K_2CO_3 (1 g), no solvent, 100 °C, 48 h	100	18	14	36	32
9	K_2CO_3 (1 g), no solvent, 80 °C, 48 h	100	19	13	35	33
10	$KHCO_3$ (1 g), no solvent, 80 °C, 48 h	92	32	20	22	26
11	K_2CO_3 (3 equiv), 1,4-dioxane (2 mL), 80 °C, 48 h	0				
12	K_2CO_3 (3 equiv), 1,4-dioxane (2 mL), 100 °C, 48 h	63	69	14	9	7
13	K_2CO_3 (3 equiv), toluene (2 mL), 80 °C, 48 h	0				
14	K_2CO_3 (3 equiv), toluene (2 mL), 100 °C, 48 h	91	37	19	26	18

[a]Reactions carried out using 1 mmol of pure (2*R**,2′*S*)-**3d**. [b]Determined by GC analysis. [c]Yields reported were determined by GC analysis of the crude reaction mixtures and are given in percent independently of the epoxide conversion. [d]Starting epoxide was used without purification after the oxidation step.

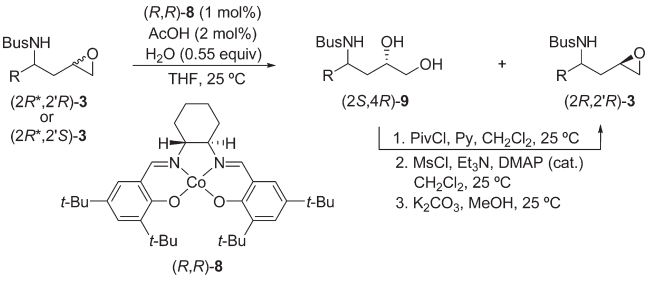
closure instead of a favored 4-*exo*-*tet* process according to Baldwin's rules.[19] Surprisingly, when pure (2*R**,2′*S*)-**3d** (*m*-CPBA and *m*-CBA were removed after column chromatography) was treated under the same reaction conditions a mixture of pyrrolidin-3-ols (5*S*)-**4d**, (5*S*)-**5d**, 2-(hydroxymethyl)azetidines (5*S*)-**6d** (*cis*-isomer), and (5*S*)-**7d** (*trans*-isomer) were obtained (Table 2, entry 2). It seems that *m*-CPBA or *m*-CBA present in the crude reaction mixture favored the formation of the five-membered ring over the four-membered one, probably through an intermolecular nucleophilic

(19) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

opening of the epoxide followed by intramolecular cyclization. In order to confirm this hypothesis, the reaction was performed with pure (2*R**,2′*S*)-**3d** in the presence of 1 equiv of potassium iodide. As anticipated, the pyrrolidin-3-ols (5*S*)-**4d** and (5*S*)-**5d** were the only reaction products (Table 2, entry 3). This is proposed to occur via an iodohydrine intermediate that results from iodide nucleophilic opening of the epoxide, which easily would undergo intramolecular nitrogen nucleophilic displacement leading to the pyrrolidines **4** and **5**. In order to expand the synthetic interest of (2-aminoalkyl)oxiranes **3** as precursors of azetidines, experiments were carried out trying to favor the 4-*exo*-*tet* process. Temperature seems to have little influence in the cyclization pathway since similar results were obtained when the process was performed at 100 and 80 °C (Table 2, entries 2 and 4, respectively). On the other hand, microwave irradiation at different temperatures and reaction times with potassium carbonate as a base led to poorer conversion, with pyrrolidines being the major reaction products (Table 2, entries 5 and 6). Acid-catalyzed cyclization with 1 mol % of triflic acid in THF led almost exclusively to pyrrolidines (5*S*)-**4d** and (5*S*)-**5d** (Table 2, entry 7). The best results for the formation of azetidines (5*S*)-**6d** and (5*S*)-**7d** were obtained when the cyclization was performed at 100 or 80 °C without any solvent and when the starting (2-aminoalkyl)oxiranes (2*R**,2′*S*)-**3d** were supported on potassium carbonate. Under these reaction conditions, pyrrolidines/azetidines were in a 1:2 ratio (Table 2, entries 8 and 9) and in a 1:1 ratio when the cyclization was performed with potassium bicarbonate at 80 °C (Table 2, entry 10). Cyclization in 1,4-dioxane or toluene took place only at 100 °C (Table 2, entries 11−14), leading to pyrrolidines (5*S*)-**4d** and (5*S*)-**5d** as the major reaction products.

Access to enantiomerically pure (2-aminoalkyl)oxiranes **3** is of great synthetic utility because a single pyrrolidine or azetidine stereoisomer could be prepared through this methodology. As commented above, *m*-CPBA oxidation of homoallylamine derivatives **2** gave an almost 1:1 mixture of diastereomeric (2-aminoalkyl)oxirane derivatives **3** which could not be separated (Table 1). Better diastereoselectivity was obtained when the oxidation was performed with a system consisting of 35% H_2O_2 and a catalytic amount of methyltrioxorhenium(VII) (MTO, 2 mol %) in the presence of pyridine (10 mol %) in CH_2Cl_2.[20] For instance, oxidation of (S_C,R_S)-**2d** gave a 2:1 mixture of (2*S*,2′*S*)-**3d** (Table 3, entry 10) and (2*R*,2′*S*)-**3d** (Table 3, entry 9), respectively, instead of an 1:1 diastereomeric mixture. Sharpless asymmetric dihydroxylation[21] of homoallylamine derivatives **2** also provided an inseparable diastereomeric mixture of diols **9**, which thus could not be converted into enantiomerically pure epoxides **3**. We were pleased to find that Jacobsen hydrolytic kinetic resolution (HKR)[22] of a 1:1 diastereomeric mixture of (2-aminoalkyl)oxiranes **3** (Table 1), using chiral cobalt complex (*R*,*R*)-**8** or its enantiomer, allowed the access to the corresponding enantiomerically pure epoxide **3** and diol **9**.

SCHEME 2. Hydrolytic Kinetic Resolution of (2-Aminoalkyl)-oxirane Derivatives 3



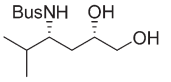
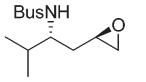
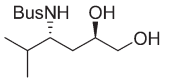
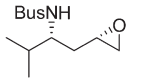
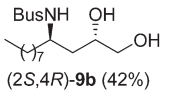
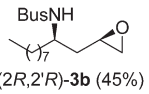
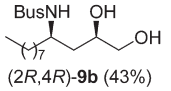
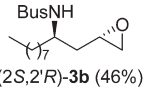
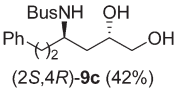
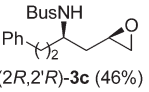
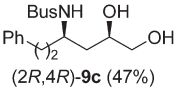
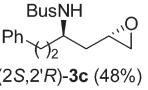
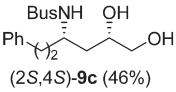
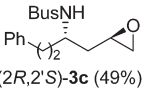
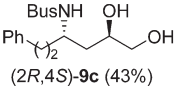
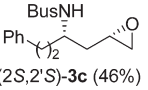
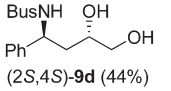
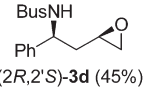
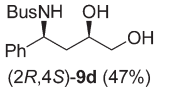
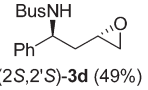
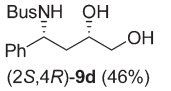
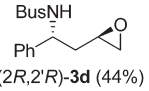
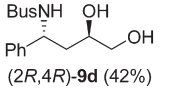
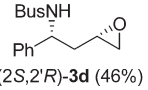
Conversion of diol **9** to epoxide **3** occurred through a three-step process which involved (a) successive selective acylation of the primary alcohol with pivaloyl chloride, (b) mesylation of the secondary alcohol and (c) final basic hydrolysis of the pivaloyl ester (Scheme 2).[23] Yields of epoxides **3** and diols **9** were over 40% in all cases (Table 3). Regarding the influence of the stereogenic center present in epoxides **3**, slightly higher yields were obtained in the HKR leading to *syn*-aminodiol derivatives **9** and the corresponding epoxides **3** (Table 3; entries 1, 4, 6, 7, 10, and 11). In this case, the catalyst and substrate seem to be a match combination. Through this methodology, a diastereomeric mixture of (2-aminoalkyl)oxiranes **3** was converted into each diastereoisomer in approximately 70% overall yield, depending on the configuration of the salen cobalt complex **8** used in the HKR (Table 3; compare entries 1−2, 3−4, etc.). The configuration of enantiopure oxiranes **3** and diols **9** was thus assigned on the basis of the known indium-promoted allylation step[10a] and Jacobsen HKR.[22,24]

Base-induced cyclization of enantiomerically pure (2-aminoalkyl)oxiranes **3** could be directed to the synthesis of pyrrolidines (**4** or **5**) or azetidines (**6** or **7**), depending on the reaction conditions (Table 2). Thus, the treatment of enantiomerically pure oxiranes **3** with potassium carbonate and potassium iodide in *N*,*N*-dimethylformamide (DMF) at 100 °C for 24 h (method A) led to pyrrolidines **4** (*cis*-isomers) or **5** (*trans*-isomers) in high yield, depending on the relative configuration of the starting oxirane (Table 4). Surprisingly, when the cyclization was performed at 80 °C and the chiral oxiranes **3** were supported on potassium carbonate (method B), azetidines **6** (*cis*-isomers) or **7** (*trans*-isomers) were the only isolated reaction products in the case of oxiranes **3a**−**c** (Table 4, entries 1−8). However, in the case of oxiranes **3d**, the corresponding pyrrolidines were also formed (Table 2, entry 8, and Table 4, entries 9−12). The yields of these 4-*exo*-*tet* ring closures were slightly higher in the case of *cis*-isomers **6** (Table 4, entries 1, 4, 6, and 7).

The configuration of the pyrrolidines **4** and **5** and the azetidines **6** and **7** was assigned on the basis of the proposed configuration of the starting oxiranes **3**, assuming that the intramolecular nucleophilic ring-opening of the epoxide

(20) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189.
(21) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(22) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
(23) Smith, A. B. III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547.
(24) (a) Smit, M. S.; Labuschagne, M. *Curr. Org. Chem.* **2006**, *10*, 1145. (b) Tokunaga, M.; Aoyama, H.; Kiyosu, J.; Shirogane, Y.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *J. Organomet. Chem.* **2007**, *692*, 472. (c) Kumar, P.; Naidu, V; Gupta, P. *Tetrahedron* **2007**, *63*, 2745. (d) Kumar, P.; Gupta, P. *Synlett* **2009**, 1367.

TABLE 3. Preparation of Enantiomerically Pure Oxiranes from a Mixture of Diastereoisomeric Oxiranes 3[a]

Entry	Starting oxirane	Catalyst	HKR reaction products[b] Diol **9**	HKR reaction products[b] Oxirane **3**	**9** → **3** Yield (%)[c]	Combined yield (%)[d]
1	(2*R**,2'*R*)-**3a**	(*R*,*R*)-**8**	 (2*S*,4*R*)-**9a** (45%)	 (2*R*,2'*R*)-**3a** (47%)	58	73
2	(2*R**,2'*R*)-**3a**	(*S*,*S*)-**8**	 (2*R*,4*R*)-**9a** (42%)	 (2*S*,2'*R*)-**3a** (44%)	60	69
3	(2*R**,2'*R*)-**3b**	(*R*,*R*)-**8**	 (2*S*,4*R*)-**9b** (42%)	 (2*R*,2'*R*)-**3b** (45%)	66	72
4	(2*R**,2'*R*)-**3b**	(*S*,*S*)-**8**	 (2*R*,4*R*)-**9b** (43%)	 (2*S*,2'*R*)-**3b** (46%)	61	73
5	(2*R**,2'*R*)-**3c**	(*R*,*R*)-**8**	 (2*S*,4*R*)-**9c** (42%)	 (2*R*,2'*R*)-**3c** (46%)	71	75
6	(2*R**,2'*R*)-**3c**	(*S*,*S*)-**8**	 (2*R*,4*R*)-**9c** (47%)	 (2*S*,2'*R*)-**3c** (48%)	67	79
7	(2*R**,2'*S*)-**3c**	(*R*,*R*)-**8**	 (2*S*,4*S*)-**9c** (46%)	 (2*R*,2'*S*)-**3c** (49%)	64	78
8	(2*R**,2'*S*)-**3c**	(*S*,*S*)-**8**	 (2*R*,4*S*)-**9c** (43%)	 (2*S*,2'*S*)-**3c** (46%)	68	75
9	(2*R**,2'*S*)-**3d**	(*R*,*R*)-**8**	 (2*S*,4*S*)-**9d** (44%)	 (2*R*,2'*S*)-**3d** (45%)	56	69
10	(2*R**,2'*S*)-**3d**	(*S*,*S*)-**8**	 (2*R*,4*S*)-**9d** (47%)	 (2*S*,2'*S*)-**3d** (49%)	58	76
11	(2*R**,2'*R*)-**3d**	(*R*,*R*)-**8**	 (2*S*,4*R*)-**9d** (46%)	 (2*R*,2'*R*)-**3d** (44%)	59	67
12	(2*R**,2'*R*)-**3d**	(*S*,*S*)-**8**	 (2*R*,4*R*)-**9d** (42%)	 (2*S*,2'*R*)-**3d** (46%)	64	72

[a]Reactions carried out starting from 1 mmol of a 1:1 diastereomeric mixture of oxiranes **3**. [b]Isolated yields after column chromatography based on the starting diastereomeric mixture of oxiranes **3** are given in parentheses. [c]Isolated yield after column chromatography based on the starting diol **9**. [d]Combined yield of the enantiomerically pure oxirane **3** considering the HKR step and the cyclization of diol **9** based on the starting diastereomeric mixture of oxiranes **3**.

takes place through a S_N2 mechanism with concomitant inversion of the stereocenter involved in the case of azetidines. This assumption was confirmed by crystal X-ray analysis (see the Supporting Information) of the solid compounds pyrrolidine (5*S*)-**4c**[25] (Table 4, entry 7), and azetidines (4*R*)-**6c**[26] (Table 4, entry 6) and its diastereomer (4*R*)-**7c**[27] (Table 4, entry 5).

In order to explore the synthetic potential of 2-(hydroxymethyl)azetidine derivatives **6**, we studied their oxidation with a ruthenium trichloride−sodium periodate combination.[28]

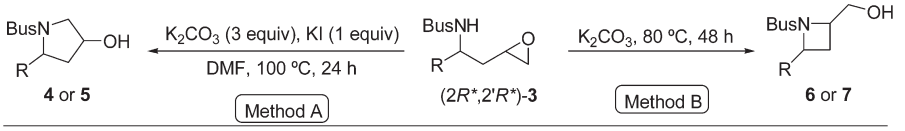
(25) Crystal data (excluding structure factors) deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 684401.

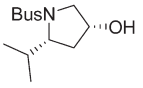
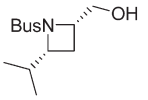
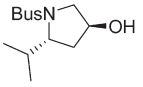
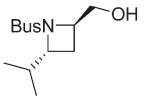
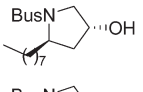
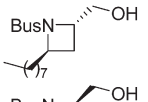
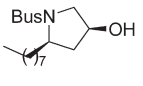
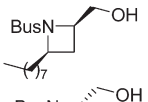
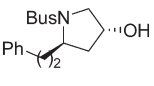
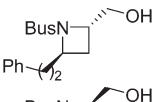
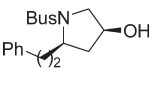
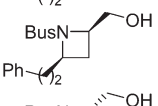
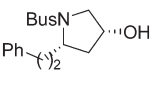
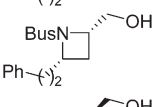
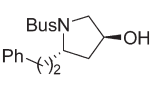
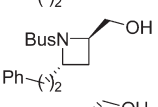
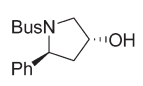
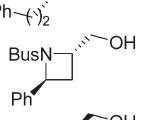
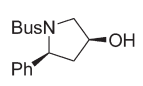
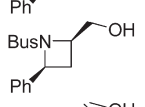
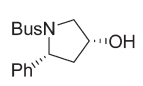
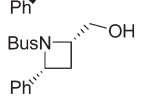
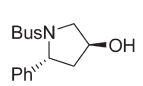
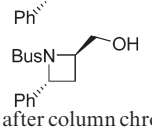
(26) Crystal data (excluding structure factors) deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 741719.

(27) Crystal data (excluding structure factors) deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 741869.

(28) Figadere, B.; Franck, X. *Sci. Synth.* **2006**, *20a*, 173.

TABLE 4. Synthesis of Pyrrolidines 4 or 5 and Azetidines 6 or 7 from Enantiomerically Pure Oxiranes 3[a]

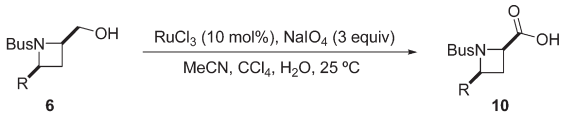


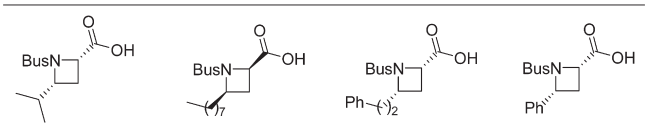
		Method A			Method B		
Entry	Starting oxirane	No.	Structure	Yield (%)[b]	No.	Structure	Yield (%)[b]
1	(2*R*,2'*R*)-**3a**	(5*R*)-**4a**		92	(4*R*)-**6a**		89
2	(2*S*,2'*R*)-**3a**	(5*R*)-**5a**		94	(4*R*)-**7a**		71
3	(2*R*,2'*R*)-**3b**	(5*R*)-**5b**		95	(4*R*)-**7b**		68
4	(2*S*,2'*R*)-**3b**	(5*R*)-**4b**		96	(4*R*)-**6b**		86
5	(2*R*,2'*R*)-**3c**	(5*R*)-**5c**		94	(4*R*)-**7c**		74
6	(2*S*,2'*R*)-**3c**	(5*R*)-**4c**		98	(4*R*)-**6c**		90
7	(2*R*,2'*S*)-**3c**	(5*S*)-**4c**		95	(4*S*)-**6c**		88
8	(2*S*,2'*S*)-**3c**	(5*S*)-**5c**		93	(4*S*)-**7c**		72
9	(2*R*,2'*S*)-**3d**	(5*S*)-**5d**		92	(4*S*)-**7d**		61[c]
10	(2*S*,2'*S*)-**3d**	(5*S*)-**4d**		94	(4*S*)-**6d**		64[d]
11	(2*R*,2'*R*)-**3d**	(5*R*)-**4d**		96	(4*R*)-**6d**		65[e]
12	(2*S*,2'*R*)-**3d**	(5*R*)-**5d**		89	(4*R*)-**7d**		61[f]

[a]Reactions carried out starting from 0.5 mmol of enantiomerically pure oxirane **3**. [b]Isolated yield after column chromatography based on the starting oxirane **3**. [c]Pyrrolidine (5*S*)-**5d** was also isolated in 24% yield. [d]Pyrrolidine (5*S*)-**4d** was also isolated in 26% yield. [e]Pyrrolidine (5*R*)-**4d** was also isolated in 20% yield. [f]Pyrrolidine (5*R*)-**5d** was also isolated in 31% yield.

The corresponding 4-substituted azetidine-2-carboxylic acids **10**, compounds homologous to proline, were obtained in good yields, and it is worth mentioning that no epimerization occurred at the oxidation step and further workup (Table 5).

TABLE 5. Synthesis of 4-Substituted Azetidine-2-carboxylic Acids 10[a]





[a]Reactions carried out starting from 0.25 mmol of azetidines **6**. [b]Isolated yield after column chromatography based on the starting azetidine **3** are given in parentheses.

Conclusions

In conclusion, enantiomerically pure pyrrolidin-3-ols **4** and **5** and/or 2-(hydroxymethyl)azetidines **6** and **7** are accessible from *N*-*tert*-butylsulfonyl-(2-aminoalkyl)oxiranes **3** through a base-catalyzed cyclization reaction by simply choosing the appropriate reaction conditions. Since all these reactions are stereospecific, the stereochemistry of the reaction products **4**−**7** is determined by the configurations of the starting aldimine **1** (allylation step) and the salen cobalt complex **8** (HKR). Moreover, oxidation of 2-(hydroxymethyl)azetidines leads to azetidine-2-carboxylic acids **10** in high yields.

Experimental Section

General Procedure for the Synthesis of Pyrrolidin-3-ols (Method A). A mixture of the corresponding *N*-*tert*-butylsulfonyl(2-aminoalkyl)oxirane **3** (0.5 mmol), KI (0.5 mmol, 0.084 g), and K_2CO_3 (1.5 mmol, 0.208 g) in *N*,*N*-dimethylformamide (3 mL) was stirred for 24 h at 100 °C. Then, the resulting mixture was hydrolyzed with water (5 mL), extracted with EtOAc (3 × 15 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **4** or **5**.

(3*R*,5*R*)-*N*-*tert*-Butylsulfonyl-5-isopropylpyrrolidin-3-ol [(5*R*)-4a]. Following the general procedure, but using 0.5 mmol of starting oxirane (2*R*,2′*R*)-**3a**, after workup, chromatography on silica gel eluting first with 5:1 and then 3:1 hexane/EtOAc afforded 119 mg (92% yield) of (5*R*)-**4a** as a white solid: $[\alpha]^{22}_D$ +34 (*c* 0.79, CH_2Cl_2); mp 92−93 °C (hexane/CH_2Cl_2); R_f 0.55 (hexane/EtOAc: 1/1); IR ν (KBr) 3545−3497, 2960, 2873, 1465, 1389, 1311, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J = 6.9, 3H), 0.93 (d, J = 6.9, 3H), 1.37 (s, 9H), 1.56 (dt, J = 12.4, 9.0, 1H), 2.07−2.20 (m, 2H), 2.42 (br s, 1H), 2.80 (dd, J = 10.7, 9.1, 1H), 3.83 (dd, J = 10.2, 9.1, 1H), 4.15−4.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 19.2, 24.4 (CH_3), 30.8 (CH), 32.1, 56.5 (CH_2), 60.4 (C), 62.9, 70.4 (C); LRMS (EI) m/z 249 (M^+, 0.1), 86 (100), 68 (14), 57 (39); HRMS (EI) calcd for $C_8H_{16}NSO_3$ (M − *i*-Pr) 206.0851, found 206.0837.

General Procedure for the Synthesis of 2-(Hydroxymethyl)-azetidines (Method B). To a solution of *N*-*tert*-butylsulfonyl(2-aminoalkyl)oxirane **3** (0.5 mmol) in CH_2Cl_2 (1 mL) was added K_2CO_3 (6.0 mmol, 1 g) and the mixture stirred at room temperature for 15 min. After that, the solvent was removed in a rotary evaporator (15 Torr), and the resulting solid residue was heated at 80 °C for 48 h. It was then hydrolyzed with water (15 mL), extracted with EtOAc (3 × 15 mL), dried over anhydrous $MgSO_4$, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **6** or **7**.

(2*R*,4*R*)-*N*-*tert*-Butylsulfonyl-2-hydroxymethyl-4-(2-phenylethyl)-azetidine [(4*R*)-6c]. Following the general procedure, but using 0.5 mmol of starting oxirane (2*S*,2′*R*)-**3c**, after workup, chromatography on silica gel eluting first with 5:1 and then 3:1 hexane/EtOAc afforded 140 mg (90% yield) of (4*R*)-**6c** as a white solid: $[\alpha]^{22}_D$ −25 (*c* 1.62, CH_2Cl_2); mp 57−59 °C (hexane/CH_2Cl_2); R_f 0.27 (hexane/EtOAc 2/1); IR ν (KBr) 3500−3235, 3068, 3025, 2970, 2868, 1474, 1360, 1294, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.78−1.88 (m, 1H), 2.04−2.27 (m, 3H), 2.54−2.60 (m, 2H), 3.56−3.69 (m, 2H), 4.29−4.39 (m, 1H), 7.15−7.21 (m, 3H), 7.26−7.30; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_2), 24.0 (CH_3), 30.7 (CH_2), 37.8 (CH_2), 58.4 (C), 59.6 (CH), 60.7 (CH), 64.0 (CH_2), 126.0 (CH), 128.2 (CH), 128.4 (CH), 140.9 (C); LRMS (EI) m/z 280 (M − CH_2OH), 191 (19), 190 (18), 161 (12), 160 (100), 117 (32), 91 (44), 86 (14), 57 (47); HRMS (EI) calcd for $C_{15}H_{22}NSO_2$ (M − CH_2OH) 280.1371, found 280.1370.

General Procedure for the Synthesis of Azetidine-2-carboxylic Acids. To a solution of CH_3CN (2.2 mL), CCl_4 (0.8 mL) and H_2O (2.0 mL) were added successively at room temperature $NaIO_4$ (0.120 g, 0.54 mmol) and $RuCl_3 \cdot 3H_2O$ (7.5 mg, 0.027 mmol). The resulting mixture was stirred for 30 min at the same temperature and then added into a solution of the corresponding 2-(hydromethyl)azetidine **6** (0.25 mmol) in CH_3CN (4.5 mL). To the resulting dark solution was added an additional lot of $NaIO_4$ (0.060 g, 0.27 mmol), and the mixture was stirred at room temperature for 30 min. The resulting salts were removed by filtration through a Celite pad, washing thoroughly with MeOH. The combined filtrate was concentrated under reduced pressure (15 Torr) and the residue purified by column chromatography (silica gel, EtOAc/MeOH, 3:1) to yield products **10**.

(2*R*,4*R*)-*N*-(*tert*-Butylsulfonyl)-4-octylazetidine-2-carboxylic Acid (10b). Following the general procedure, but using 0.25 mmol of starting 2-(hydroxymethyl)azetidine (4*R*)-**6b**, after workup, chromatography on silica gel eluting with 3:1 EtOAc/MeOH afforded 73 mg (88% yield) of **10b** as a colorless oil: $[\alpha]^{20}_D$ +19 (*c* 0.99, CH_2Cl_2); R_f 0.44 (hexane/EtOAc 1/3); IR ν (film) 3560−3140, 2927, 2855, 1720, 1458, 1313, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0, 3H), 1.18−1.34 (m, 10H), 1.38 (s, 9H), 1.52−1.68 (m, 2H), 1.75−1.81 (m, 1H), 1.97−2.06 (m, 1H), 2.37−2.43 (m, 1H), 2.56−2.65 (m, 1H), 4.36−4.42 (m, 1H), 4.81 (dd, J = 9.2, 8.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2), 23.8 (CH_2), 23.9 (CH_3), 25.3 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.7 (CH_2), 36.0 (CH_2), 56.9 (CH), 59.2 (C), 60.5 (CH), 175.6 (C); LRMS (EI) m/z 333 (M^+, 0.2), 288 (4), 254 (6), 168 (100), 99 (30), 74 (20), 57 (56); HRMS (EI) calcd for $C_{15}H_{30}NSO_2$ (M − CO_2H) 288.1997, found 288.2001.

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Supporting Information Available: Experimental procedures, full characterization and copies of ^1H and ^{13}C NMR spectra of all compounds, and X-ray crystal data for compounds (5*S*)-**4c**, (4*R*)-**6c** and (4*R*)-**7c**. This material is available free of charge via the Internet at http://pubs.acs.org.