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Regio- and Stereoselective Ring Opening of Enantiomerically Enriched 2-Aryl Oxetanes and 2-Aryl Azetidines with Aryl Borates

Ferruccio Bertolini, Stefano Crotti, Valeria Di Bussolo, Franco Macchia, and Mauro Pineschi*

Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy

pineschi@farm.unipi.it

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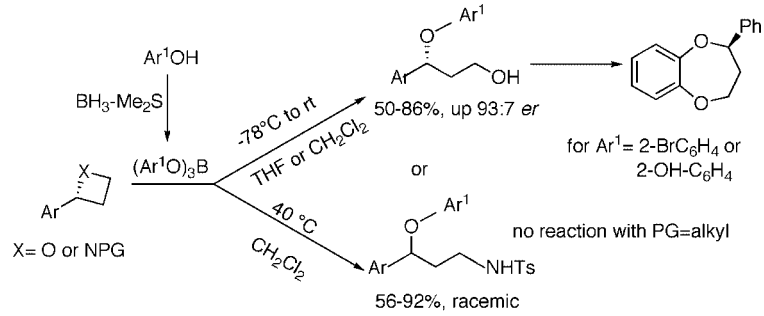

The regioselective ring opening of 2-aryl-substituted four-membered heterocyclic rings with phenols, including catechol, was achieved by the use of aryl borates in mild and neutral reaction conditions without the aid of any transition metal catalysts. While *N*-alkyl azetidines were found not to be reactive, optically active *N*-tosyl azetidines gave the corresponding β-aryloxy amines in a racemic form, thus indicating the considerable carbocationic character of the transition state. The introduction of a hydroxyl group in the azetidine ring (i.e., an azetidinol), able to anchor the aryl borate and to direct the subsequent nucleophilic delivery, was shown to determine the ring-opening process with predominant inversion of configuration. When enantiomerically enriched 2-aryl oxetanes were used, the reduced extent of racemization observed (up to 93:7 er) was rationalized by an intramolecular delivery through a six-membered transition state, giving β-aryloxy alcohols with a predominant retention of configuration (i.e., a *syn*-stereoselective ring opening). The aryloxy alcohols obtained, endowed with suitable functionalities, can be cyclized to give access to enantiomerically enriched 2-aryl-1,5-benzodioxepins.

Introduction

The ring opening of small-ring heterocycles with nucleophiles is a very important topic with a large variety of applications in synthetic organic chemistry. Most of this chemistry concerns the use of epoxides and aziridines,[1] whereas the use of their higher homologues, oxetanes and azetidines, is under-exploited despite their potential broad versatility as building blocks in organic synthesis. For example, oxetanes have a large variety of applications, but mainly in the field of polymers and in material science.[2] As regards the use of oxygen nucleophiles, the acid-catalyzed *anti*-stereoselective ring opening of enantiomerically pure 2-aryl-3,3-dimethyloxetanes with water and alcohols has been described by Kellogg and co-workers.[3] More recently, a ring opening of substituted enantiomerically enriched tertiary oxetanes with hydrogen peroxide and alkyl hydroperoxides catalyzed by Lewis acids, proceeding with moderate and sometimes capricious stereoselection, has been reported.[4] To the best of our knowledge, the ring opening of oxetanes with phenols to give 3-aryloxy alcohols has not yet been reported.

(1) For recent reviews, see: (a) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006. (b) Schneider, C. *Synthesis* **2006**, 3919. (c) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (d) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (e) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979.

(2) For recent examples, see: (a) Bouchekif, H.; Philbin, M. I.; Colclough, E.; Amass, A. J. *Macromolecules* **2008**, *41*, 1989. (b) Crivello, J. V. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 4331. (c) Runzinger, S. J.; Kurt, P.; Brunson, K. M.; Wood, L.; Ohman, D. E.; Wynne, K. J. *Polymer* **2007**, *48*, 4653. (d) Kudo, H.; Nishikubo, T. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 709.

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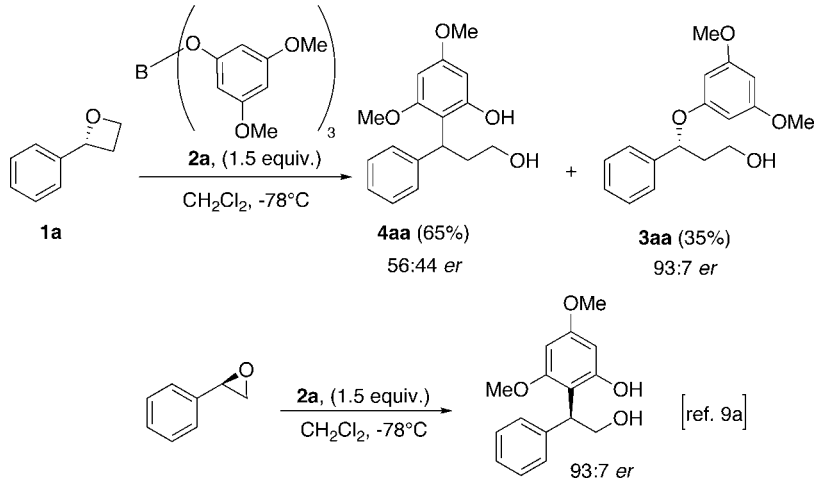
SCHEME 1. Different Reactivity of 2-Phenyloxetane and 1-Phenyloxirane with Borate 2a



This may probably be ascribed to the absence of reactivity of oxetanes in an S_N2-type displacement with the corresponding phenoxide in basic conditions, which is dramatically different from that of epoxides.[5] Likewise, the ring opening of azetidines with phenols in basic conditions is very difficult to obtain, and even the use of an in situ generated azetidinium ion occurred after very long reaction times in drastic reaction conditions with low yields and partial racemization.[6] The synthesis of 1,3-amino ethers by a Lewis acid catalyzed ring opening of 2-aryl-*N*-tosylazetidines with alcohols and phenols has only very recently been reported.[7] However, either the ring opening afforded a mixture of regioisomeric products with a poor yield with phenols,[7a] or the stereoselectivity has not been examined.[7b]

Recently, we found that aryl borates behave as *activating nucleophiles* and readily transfer the phenol moiety to aryl epoxides and aziridines in a stereoselective fashion, without the need for a transition metal catalyst.[8] Depending on the nature of the aryl borate, a competitive Friedel−Crafts-type alkylation represented a very important side reaction, which became exclusive when particularly electron-rich aryl borates were used.[9] Therefore, we envisioned that the reaction of the homologues 2-aryl oxetanes and 2-aryl azetidines with phenols might provide additional information about the reaction mechanism and a new entry to 3-phenyl-3-aryloxy alcohols and 3-phenyl-3-aryloxy amines, respectively, which are synthetically important chiral intermediates for the synthesis of compounds of pharmaceutical interest, widely used for the treatment of anxiety and depression.[10] Alternative simple methods for the synthesis of these compounds in enantiomerically pure form are based on regioselective reduction of optically active 2,3-epoxycinnamyl alcohols,[11] catalytic asymmetric or biological reduction of 3-keto-carboxylates,[12] or asymmetric hydrosilylation of 3-hydroxy-propiophenone.[13] Enzymatic resolutions of racemic 1-phenyl-3-buten-1-ol, followed by ozonolysis of the terminal double bond have also been described.[14] All these methods comprise inter alia a Mitsunobu-etherification of the benzylic secondary alcohol for the installation of the phenol moiety.[11−14] Other straightforward strategies are based on metal-catalyzed stereoselective allylic etherification of cinnamyl derivatives followed by oxidative hydroboration of the terminal double bond.[15]

Here, we report our study on the development of a simple, practical regioselective procedure for the ring opening of enantioenriched 2-aryloxetanes and 2-arylazetidines with phenols, with a particular emphasis on the stereochemical outcome of the reaction.

Results and Discussion

As a preliminary experiment, the reaction of (*R*)-1-phenyloxetane (**1a**),[16] readily available by basic cyclization of (*R*)-3-chloro-1-phenylpropanol, with tris(3,5-dimethoxyphenyl)borate (**2a**) was examined. The reaction occurred at completion in CH_2Cl_2 at −78 °C in 2 h (Scheme 1). Hydroxy phenol **4aa**, a Friedel−Crafts-type *C*-alkylation product, turned out to be

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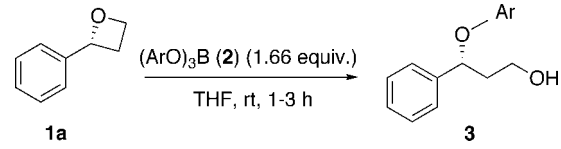
the main reaction product (65% of the crude mixture), and it was obtained with low stereoselectivity (56:44 er). This was accompanied with a significant amount (35% of the crude mixture) of the corresponding *O*-alkylated product **3aa**, showing good stereoselectivity (93:7 er). A comparison of these results with those obtained with structurally related 2-phenyloxirane under the same reaction condition (exclusive formation of Friedel−Crafts-type product with a reduced extent of racemization),[9a] clearly indicated how phenyloxetane **1a** was more prone to the *O*-alkylation ring-opening process than the corresponding phenyloxirane and that it was possible to obtain the corresponding 3-aryloxy alcohol with a slight erosion of enantiomeric enrichment.

On the other hand, the Friedel−Crafts *C*-alkylation seemed to be a less favored and appealing reaction pathway for oxetanes with respect to the same reaction carried out with styrene oxide.

Next we investigated the reaction of commercially available triphenylborate **2b** with (*R*)-2-phenyloxetane **1a** in THF at room temperature. This substrate afforded the desired *β*-aryloxy alcohol **3ab** with complete regioselectivity at the benzylic position and good stereoselectivity (87:13 er), without the formation of any Friedel−Crafts-type reaction products (Table 1, entry 1). The isolated yield of aryloxy alcohol **3ab** was moderate due to the formation of substantial amounts (ca. 30%) of 1-phenyl-1,3-propanediol. In order to study the influence of borates on the stereoselectivity of the ring-opening process, several borates were prepared from the corresponding substituted phenols by acid−base reaction with BH_3-Me_2S,[17] and they were allowed to react with oxetane **1a** in THF at room temperature, giving the corresponding 3-aryloxy alcohols. It was found that by using dichloromethane as well as THF, the outcome of the reaction showed only marginal variations. It should be noted that the attack of the phenol moiety occurred with complete regioselectivity at the benzylic position of the oxetane ring, and only products deriving from an *O*-alkylation ring opening process were found in the crude mixtures. Furthermore, a reduced extent of racemization during the ring opening of oxetane **1a** was found with aryl borates containing electron-withdrawing substituents in the *ortho* position (entries 2−4). In particular, highly stereoselective ring opening was obtained when tris(2-chlorophenyl)borate **2d** (93:7 er) was used (entry 3).

Benzo[*d*][1,3,2]dioxaborol-2-ol (**2f**), which is a compound readily prepared by esterification between boric acid and catechol, proved to be an effective reagent for a mild and unprecedented introduction of a catechol moiety into an oxetane ring (entry 5). This is quite a remarkable result, considering that the reaction protocol occurs under neutral conditions and that not even the use of catechol in drastic alkaline reaction conditions (NaH/EtOH reflux) allowed the ring opening of oxetanes with catechol, unlike the corresponding reaction reported for epoxides.[18] The ring opening occurred smoothly also by the use of borates bearing substituents in a different position of the aromatic ring, giving the corresponding *O*-alkylated products with complete regioselectivity, satisfactory isolated yields, and a reduced extent of racemization (entries 6−10). Even if the reaction can be carried out with only 1.0 equiv of the aryl borate, the present use of 1.66 equiv proved to be optimal with respect to reaction times and stereoselectivities.

TABLE 1. Ring Opening of Oxetane (*R*)-1a with Aryl Borates[a]



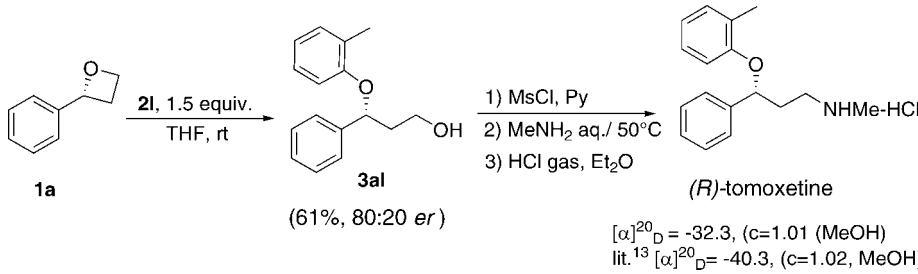
N°	(Ar=) Borate	Product (Yield%)	Er[c]
1	(C_6H_5) **2b**	**3ab** (50)	87:13
2	(2-FC_6H_4) **2c**	**3ac** (78)	88:12
3	(2-ClC_6H_4) **2d**	**3ad** (83)	93:7
4	(2-BrC_6H_4) **2e**	**3ae** (58)	87:13
5	**2f**	**3af** (86)	73:27
6	(4-$OMeC_6H_4$) **2g**	**3ag** (52)	82:18
7	(4-$CF_3C_6H_4$) **2h**	**3ah** (81)	80:20
8[d]	(4-$NO_2C_6H_4$) **2i**	**3ai** (58)	77:23
9	(3-ClC_6H_4) **2j**	**3aj** (79)	82:18
10	(2-I-4-$CO_2MeC_6H_3$) **2k**	**3ak** (68)	72:28

[a] All reactions were carried out in THF at room temperature in accordance with the general procedure, unless stated otherwise. [b] Isolated yields of the product after chromatographic purification (SiO_2). [c] Determined by HPLC analysis on CSPs. [d] Reaction carried out in CH_2Cl_2.

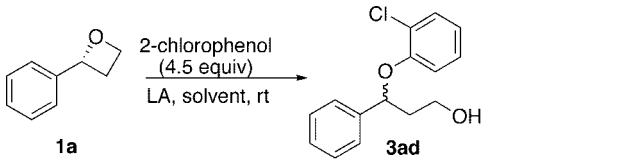
As aryl oxetane **1a** does not react in the reaction with the corresponding phenoxides under basic conditions, the demonstration of the main stereoselective pathway of the ring opening reported in Table 1 by a reference *anti*-stereoselective reaction

(17) Brown, C. A.; Krishnamurthy, S. *J. Org. Chem.* **1978**, *43*, 2731.
(18) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F.; Smith, G. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2249.

SCHEME 2. Absolute Configuration of β-Aryloxy Alcohols: Synthesis of (*R*)-Tomoxetine Hydrochloride



SCHEME 3. Ring Opening of Oxetane (*R*)-1a with 2-Chlorophenol in the Presence of External Lewis Acids



$Sc(OTf)_3$ (10 mol%): 80% yield, 56:44 *er*
$Yb(OTf)_3$ (10 mol%): 30% yield, 58:42 *er*
$Cu(OTf)_2$ (10 mol%): complex mixture
BF_3-Et_2O (100 mol%): Friedel-Crafts type products
$B(OBu)_3$ (100 mol%): 68% yield, 71:29 *er*

and subsequent HPLC analysis on chiral stationary phases was not as simple as for epoxides.[5b,8] To address this issue, we envisioned that our reaction protocol might be used for the synthesis of a compound of known absolute configuration, such as tomoxetine (Scheme 2).[10]

Thus, the ring opening of phenyloxetane **1a** with tris(2-methylphenyl)borate **2l** afforded exclusively aryloxy alcohol **3al** with acceptable isolated yield (61%) and stereoselectivity (80:20 er) (see Supporting Information for details). In accordance with a previously described procedure,[11a] the subsequent mesylation and nucleophilic substitution with 40% aqueous $MeNH_2$ afforded (*R*)-tomoxetine. The measurement of the optical rotatory power of the obtained sample ($[\alpha]^{20}_D = -32.3$, *c* 1.01, MeOH) compared with the literature data indicating that the ring-opening reaction of oxetane **1a** had occurred with a predominant enantioretention of configuration (i.e., a *syn*-stereoselective ring opening). Further confirmation of the stereoselectivity of the ring opening came from the synthesis of scalemic (*R*)-fluoxetine from β-aryloxy alcohol **3ah** (Table 1, entry 7) and comparison of the corresponding optical rotatory power.[19]

In order to check the validity and synthetic utility of our protocol for the ring opening of aryl oxetanes with aryl borates, some alternative procedures based on Lewis acids catalyzed reactions were considered. The use of an external Lewis acid (LA) in combination with a suitable nucleophile represents one of the most common ways of inducing the ring opening of small-ring heterocycles, such as epoxides and aziridines.[1] The reaction of oxetane (*R*)-**1a** with an excess of 2-chlorophenol in the presence of catalytic amounts (10 mol %) of $Cu(OTf)_2$ in THF, or stoichiometric amounts of BF_3-Et_2O in CH_2Cl_2, afforded a complex mixture of products, in which also Friedel−Crafts-type products were found (Scheme 3 and Supporting Information). Low yields of the *O*-alkylated product **3ad** in an almost racemic form (58/42 er) were obtained by the use of catalytic amounts of $Yb(OTf)_3$, while the reaction catalyzed by $Sc(OTf)_3$ in THF afforded good yield of aryloxy alcohol **3ad**, but this compound was likewise recovered in an almost racemic form (56/44 er). The use of stoichiometric amounts of $B(OBu)_3$ in the presence of 2-chlorophenol gave a very sluggish reaction, and only after 48 h was the reaction complete.[20] Subsequent HPLC analysis showed that the major enantiomer was the same obtained by the use of the corresponding aryl borate **2d** (see entry 3, Table 1), albeit an increased racemization was observed (71/29 er).

The fact that, in all of the reactions of oxetane **1a** with aryl borates examined, the phenol attacks exclusively at the benzylic carbon atom seems to imply a considerable cationic character of the transition state. As a result, the possible effect of substituents on the aryl moiety of the oxetane on the stereoselective outcome of the ring-opening reaction was examined.

For this purpose, enantiomerically enriched aryl oxetane **1b** and **1c**, with an electron-withdrawing (*m*-Cl) and an electron-donating group (*p*-Me) on the aryl moiety, respectively, were prepared. (*S*)-2-(3-Chlorophenyl)oxetane **1b** was obtained in enantioenriched form from the corresponding commercially available (*R*)-3-chlorostyrene oxide by means of a homologation reaction which makes use of trimethylsulfoxonium iodide in basic conditions (Scheme 4, eq a).[21] (*S*)-2-*p*-Tolyloxetane **1c** was prepared by asymmetric reduction of 3-chloro-1-*p*-tolyl-propan-1-one with (*R*)-CBS to give (*S*)-3-chloro-1-*p*-tolyl-propan-1-ol **5c** with good yields (76%) and a very high enantioselectivity (ee > 98%).[22] A simple cyclization under basic conditions afforded quantitatively the corresponding enantiomerically pure aryl oxetane **1c** (Scheme 4, eq b). To our surprise, the reaction of aryl oxetane **1b** with tris(2-bromophenyl)borate (**2e**) was complete in 1 h at room temperature and afforded aryloxy alcohol **3be** with good enantiomeric ratio (Scheme 5). The ring opening of *p*-methyl-substituted oxetane **1c** was even faster, and compound **3ce** was obtained with a good isolated yield but with an increased racemization. Considering that unsubstituted phenyl oxetane **1a** reacted with borate **2e** affording the corresponding aryloxy alcohol **3ae** with an 87/13 enantiomeric ratio (see entry 4, Table 1), this qualitatively means that the degree of racemization is directly related to the stability of the cationoid intermediate formed.

Once again, it should be noted the different behavior between three- and four-membered oxygenated rings during ring opening. In fact, in a separate experiment, the related ring opening of 3-chlorostyrene oxide with aryl borate **2e** was much slower (40% conversion in 2 days at room temperature). As these reactions are under electronic control, this different behavior is probably

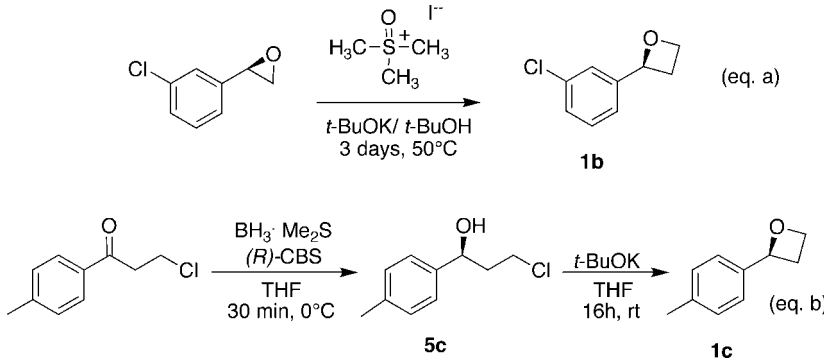
(19) The major enantiomers of the other aryloxy alcohols obtained in this study were assumed to have the same configuration as the known cases.

(20) Simple trialkyl borates such as $B(OBu)_3$ and $B(OMe)_3$ are not reactive with oxetane **1a**.

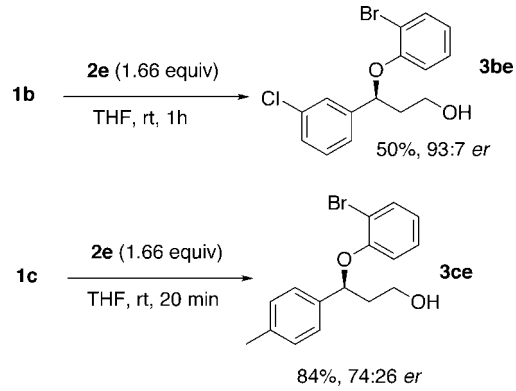
(21) Okuma, K.; Tanaka, K.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, *48*, 5133.

(22) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

SCHEME 4. Synthesis of Optically Active Substituted Aryl Oxetanes 1b and 1c



SCHEME 5. Reactions of Substituted Enantioenriched Aryl Oxetanes 1b and 1c with Borate 1b



due to the higher stability of the carbenium ions formed from oxetanes, compared with that of the corresponding structures deriving from epoxides.[23]

The selective formation of a C−O bond at the benzylic position with a reduced extent of racemization found in our protocol might be reasonably explained by admitting a preferential internal delivery of the aryloxide moiety attached to the former oxetane oxygen by the boron tether in a six-membered transition state, as depicted in Figure 1. First of all, the coordination of boron to the oxygen of oxetane produces the formation of an advanced carbocationic species, such as **A** (Figure 1), which rapidly evolves to a six-membered transition state **B**, which allows the *internal delivery* of the nucleophile, with retention of configuration. It is likely that the more stable carbenium ion derived from oxetane **1c** can be attacked by the oxygen of the phenol in accordance with a S_N1-type mechanism. Clearly, a partial racemization occurring via rotation of 90° around the C_1-C_2 bond after formation of the carbocationic species from the original enantiopure oxetane, followed by an intramolecular delivery of the aryloxide moiety (structure **C**), cannot be ruled out. Accordingly, whenever external Lewis acids have been used (see Scheme 3), an intramolecular delivery of the aryloxide was not conceivable, and a S_N1-type reaction occurred on the intermediate carbocation, giving extensive racemization. Furthermore, in this framework, also other reaction paths, including Friedel−Crafts-type reactions, become possible.

Ring Opening Reactions of 2-Aryl Azetidines and 2-Aryl Azetidinols. We also investigated the ring-opening reaction of differently *N*-protected 2-aryl azetidines **6a** and **6b** with some representative aryl borates (Table 2). As expected, the nature of the nitrogen protecting group is very important, and strongly basic 1-methyl 2-phenyl azetidine did not give any ring-opened products (entry 1, Table 2). It should be noted that unlike from the corresponding ring opening of aryl oxetanes, the ring opening of racemic *N*-tosylazetidine **6a** with borate **2j** in THF at room temperature did not occur at all after 18 h (data not shown in Table 2). A simple change of the reaction solvent to CH_2Cl_2 and a reaction temperature of 40 °C for the same period gave complete conversion, and it was possible to isolate the corresponding 3-aryloxy amine **7aj** with a good yield after chromatographic purification on silica gel (entry 2). However, when the same reaction was carried out with enantiomerically enriched (*R*)-*N*-tosylazetidine **6a** (95:5 er), obtained by a slight modification of the procedure of homologation that makes use of trimethylsulfoxonium iodide in basic conditions reported by Nadir et al.,[24] a complete racemization was observed (entry 3). Considering this stereochemical outcome, all subsequent reactions with differently substituted aryl borates were carried out with racemic azetidine **6a** and gave fair to very good yields of the corresponding ring-opened products, with complete regiocontrol of the nucleophilic attack at the benzylic position (entries 4−8). The complete racemization observed would indicate that a benzylic carbocation is formed without the occurrence in this case of any internal delivery of the phenol moiety to preserve stereochemistry.

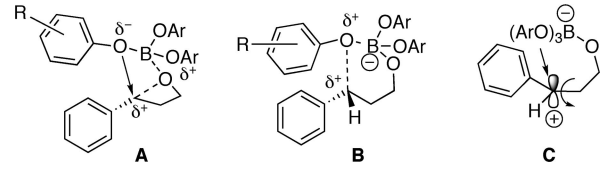


FIGURE 1. Plausible mechanism of the internal delivery of aryloxide moiety.

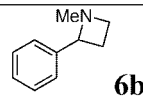
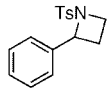
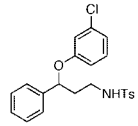
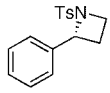
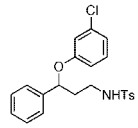
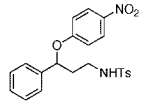
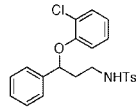
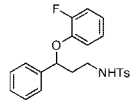
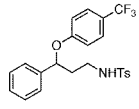
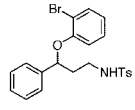
In this framework, we speculated that the presence of a hydroxyl group on the azetidine ring (i.e., an azetidinol) might change the stereochemical outcome of the ring opening by coordination with the aryl borate or anchimeric assistance.

Although there have been several reports describing the reactions of phenols with azetidinols at elevated temperatures in basic conditions to prepare compounds of pharmaceutical interest,[25] the ring opening of activated azetidinols has been minimally explored and a mild procedure is completely lack-

(23) Balsamo, A.; Crotti, P.; Ferretti, M.; Macchia, F. *J. Org. Chem.* **1975**, *40*, 2870.

(24) Nadir, U. K.; Sharma, R. S.; Koul, V. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2015.

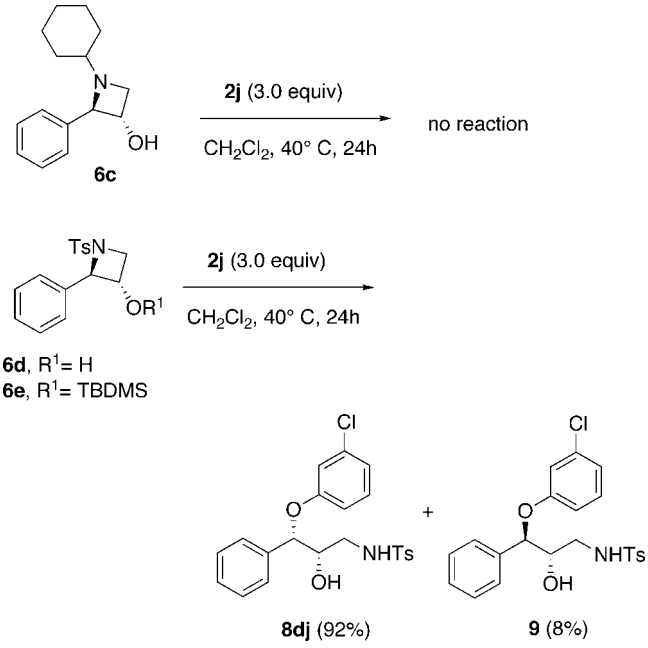
TABLE 2. Ring Opening of Azetidines 6a and 6b with Aryl Borates[a]

entry	borate	azetidine	product (yield%)
1	**2j**	 **6b**	No ring opening
2	**2j**	 **(±)-6a**	 **7aj** (65)
3	**2j**	 **(*S*)-6a**	 **7aj** (65, 52:48 *er*)
4	**2i**	**(±)-6a**	 **7ai** (56)
5	**2d**	**(±)-6a**	 **7ad** (90)
6	**2c**	**(±)-6a**	 **7ac** (92)
7	**2h**	**(±)-6a**	 **7ah** (75)
8	**2e**	**(±)-6a**	 **7ae** (65)

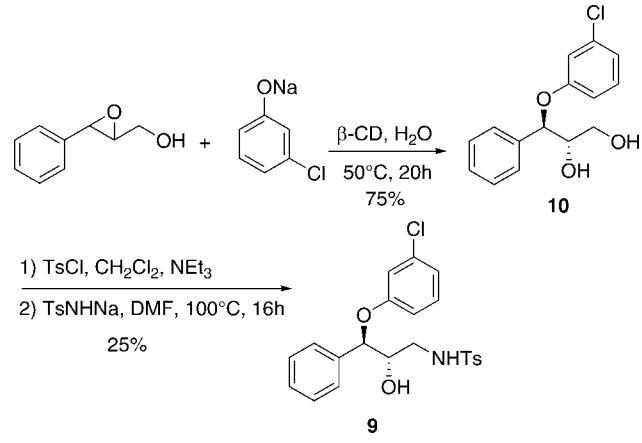
[a] All reactions were carried out in CH_2Cl_2 at 40 °C for 24 h. [b] Isolated yields of the product after chromatographic purification (SiO_2).

ing.[26] We prepared 2-phenyl azetidinols **6c**, **6d**, and **6e** following reported methods[27,28] and allowed them to react with aryl borate **2j**. Coherently with the results obtained with azetidine **6b** (Table 2), 1-cyclohexyl 2-phenyl azetidinol **6c** gave no ring opening after 24 h at 40 °C. On the other hand, the corresponding reaction of (2*R**,3*S**)-*N*-tosyl-protected azetidinol **6d** with borate **2j** occurred at completion and gave a 92:8 mixture of aryloxy amino alcohols **8dj** and **9**, respectively. It was possible to isolate (2*S**, 3*S**)-3-aryloxy amino alcohol **8dj** in diastereoisomerically

SCHEME 6. Ring Opening of Differently Protected Azetidinols with Borate 2j



SCHEME 7. Stereoselective Synthesis of (2*S,3*R**)-Aryloxy Amino Alcohol 9**



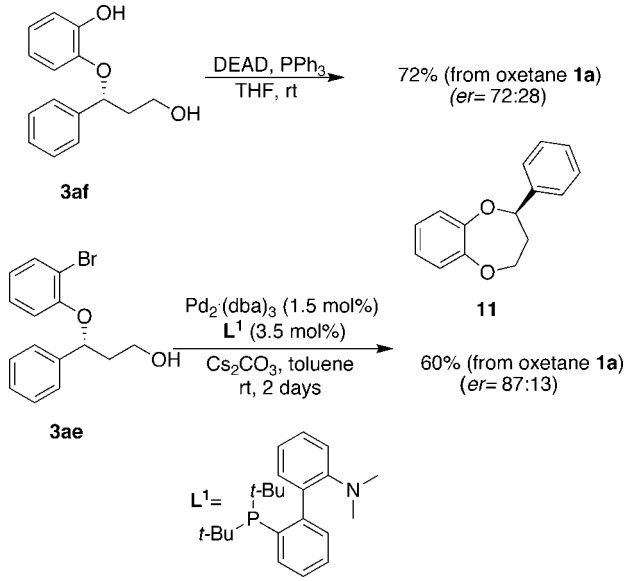
pure form with a satisfactory 62% yield after chromatographic purification. It was significant that the corresponding azetidinol **6e**, bearing a highly hindered *t*-butyldimethylsilyl protecting group, was completely unreactive after 4 days at 40 °C.

As it was not possible to ascertain unequivocally the relative configuration of the ring-opened product **8dj** by NMR analysis, an independent synthesis of the corresponding diastereoisomer **9**, in principle obtainable from the reaction, was undertaken (Scheme 7). Thus, in accordance with a previously described procedure,[29] the regioselective ring opening of phenyl glycidol with sodium 3-chlorophenoxide supported by β-cyclodextrin in

(25) (a) Julia Arechaga, G.; Vila Casas, A. *Spanish Patent ES 541017*, 1985. (b) Vedrilla Veit, D. *Spanish Patent ES 459725*, 1978. (c) Tucker, H. *British Patent GB 1456525*, 1976. (d) Koeppe, H.; Kummer, W.; Staehle, H. German Patent DE 2503222, 1976. (e) Imperial Chemical Industries Ltd., U.K. Jpn. Kokai Tokkyo Koho JP 50032135, 1975. (f) Laboratorio Martin Cuatrecasas, Spanish Patent ES 438367, 1976. (g) Tsukamoto, K.; Suzuki, Y. Jpn. Tokkyo Koho JP 47019259, 1972. (h) Tsukamoto, K.; Suzuki, Y.; Izuni, A.; Hiramatsu, Y. German Patent DE 2058532, 1972. (i) Tsukamoto, K.; Suzuki, Y.; Izuni, A.; Hiramatsu, Y. Jpn. Tokkyo Koho JP 46028534, 1971.

(26) Higgins, R. H.; Faircloth, W. J.; Baughman, R. G.; Eaton, Q. L. *J. Org. Chem.* **1994**, *59*, 2172. and pertinent references therein.

SCHEME 8. Possible Routes to Enantiomerically Enriched 2-Phenyl-1,5-benzodioxepin (11)



H_2O at 50 °C for 20 h afforded aryloxy diol **10** with 75% yield. Subsequent monotosylation of the primary hydroxy functionality and its nucleophilic substitution with *p*-toluenesulfonamide sodium salt in anhydrous DMF at 100 °C for 16 h afforded compound **9** (25% yield for two steps; see Supporting Information for details).

The involvement of the hydroxy functionality in anchimeric assistance during the ring opening of azetidine **6d** would have led to retention of configuration, affording the opposite diastereoisomer, (i.e., (2*S**,3*R**)-aryloxy amino alcohol **9**). Hence, the predominant inversion of configuration of the ring opening found in the reaction of azetidinol **6d** points to a boron atom engaged in the formation of an ate-complex with the free secondary hydroxyl group. In this way the phenol moiety is stereoselectively delivered at the benzylic position in a S_N2 fashion with inversion of configuration. The fact that this reaction manifold is not possible when the hydroxyl group is protected or when basic azetidinol **6c** is used, supports this notion.

Synthesis of 2-Phenyl-1,5-benzodioxepin. As some of the new aryloxy alcohols prepared (see Table 1) from the ring-opening reactions of oxetanes possess reactive functional groups that can undergo substitution reactions, we envisioned that these compounds might be valuable intermediates for the obtainment of 2-aryl-1,5-benzodioxepins.[30] In particular, the Mitsunobu-cyclodehydration of compound **3af** deriving from the ring opening of the optically active oxetane **1a** with benzo[*d*][1,3,2]dioxaborol-2-ol (**2f**) (Table 1, entry 5), afforded 1,5-benzodioxepin **11** with a satisfactory overall yield (72%) and with no loss of optical purity (72:28 er) compared with the ring-opened product **3af** (Scheme 8).[31] Alternatively, it is possible to use *o*-bromophenyloxy alcohol **3ae** (87:13 er) in an intramolecular Pd-catalyzed substitution reaction,[32] to give the same compound **11** with a reduced overall yield and a slight increase in the enantiomeric enrichment.

Conclusions

To sum up, we report that readily available aryl borates behave as activating nucleophiles and react with 2-aryl oxetanes and *N*-sulfonyl 2-aryl azetidines to give the corresponding synthetically useful β-aryloxy alcohols and β-aryloxy amines, respectively, with fair to good yields. The reactions occur regioselectively in mild and neutral reaction conditions and nicely complement the known methods for the ring opening of these somewhat disregarded heterocyclic systems with respect to epoxides and aziridines. In particular, we have shown that the reactions of enantiomerically enriched 2-aryl oxetanes with aryl borates proceed with a predominant retention of configuration (up to 93:7 er), whereas the ring opening in alkaline conditions did not occur at all, and the use of Lewis acid catalyzed protocols afforded a mixture of products and/or extensive racemization. When reactive functionalities are present in the β-aryloxy alcohol, intramolecular cyclization allows a new access to 2-aryl-1,5-benzodioxepins in an enantioenriched form.

Experimental Section

Aryl borates **2a**−**l** were prepared following a previously described procedure[17] and were used immediately after their preparation.

General Procedure for the Ring Opening of Oxetanes (Table 1). A solution of aryl borate (0.5 mmol) in THF (1.0 mL) was added to a stirred solution of the oxetane (0.3 mmol) in THF (0.5 mL) under argon. The reaction was followed by TLC after complete consumption of the starting oxetane. After evaporation of the solvent, the crude reaction mixture was then purified by silica gel column chromatography, to give the pure compounds of type **3**.

(*R*)-3-Phenoxy-3-phenylpropan-1-ol (3ab). (Entry 1, Table 1) Using the general procedure triphenylborate (**2b**) (145.0 mg, 0.5 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*R*)-2-phenyl oxetane (**1a**) (40.2 mg, 0.3 mmol) in THF (0.5 mL). After 3.0 h at room temperature, the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3ab** (34.2 mg, 50%) as an oil. $[\alpha]^{20}_D = +20.0$ (c 2.0, $CHCl_3$, 87:13 er). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.96 (br, s, 1H, OH); 2.00−2.28 (m, 2H); 3.75−3.89 (m, 2H); 5.36 (dd, 1H, J_1 = 8.8 Hz, J_2 = 4.3 Hz); 6.80−6.90 (m, 3H); 7.13−7.40 (m, 7H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.2, 59.9, 78.1, 115.9, 121.0, 125.8, 127.6, 128.7, 129.4, 1415, 157.8. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.56; H, 7.08. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 90/10, retention times (min): 16.7 (S, minor stereoisomer), 19.0 (R, major stereoisomer).

(*R*)-3-(2-Fluorophenoxy)-3-phenylpropan-1-ol (3ac). (Entry 2, Table 1) Using the general procedure, tris(2-fluorophenyl)borate (**2c**) (177.0 mg, 0.5 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*R*)-2-phenyl oxetane (**1a**) (40.2 mg, 0.3 mmol) in THF (0.5 mL). After 1 h at room temperature, the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3ac** (57.6 mg, 78%) as an oil. $[\alpha]^{20}_D = +72.5$ (*c* 0.2, $CHCl_3$, 88:12 er). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.04−2.14 (m, 2H); 2.24−2.30 (m, 1H); 3.73−3.98 (m, 2H); 5.35 (dd, 1H, J_1 = 8.8 Hz, J_2 = 4.3 Hz); 6,74−6.86 (m, 3H); 6.98−7.07 (m, 1H); 7.22−7.39 (m, 5H). ^{13}C NMR (62.5 MHz,

(27) For azetidinol **6c**, see: Okutani, T.; Morimoto, A.; Kaneko, T.; Masuda, K. *Chem. Pharm. Bull. Jpn.* **1974**, *22*, 1490.

(28) For azetidinols **6d** and **6e**, see: Matsuura, F.; Hamada, Y.; Shiori, T. *Tetrahedron* **1994**, *50*, 265.

(29) Narender, M.; Reddy, M. S.; Nageswar, Y. V. D.; Rama Rao., K. *Helv. Chim. Acta* **2007**, *90*, 1107.

(30) Ganesh, T.; Krupadanam, G. L. *Indian J. Chem., Sect. B* **1998**, *37B* (1), 34.

(31) For the recent use of Mitsunobu cyclodehydration for the synthesis of 2,3-dihydrobenzofurans, see: Bertolini, F.; Crotti, P.; Di Bussolo, V.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **2007**, *72*, 7761, and references therein.

(32) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907.

$CDCl_3$) δ 41.0, 60.0, 80.2, 116.0, 116.3, 117.2, 117.3, 121.5, 121.6, 124.1 (2 C); 125.9, 127.9, 128.7, 140.9, 151.2. Anal. Calcd for $C_{15}H_{15}FO_2$: C, 73.15; H, 6.14. Found: C, 73.22; H, 6.21. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 92/8, retention times (min): 19.4 (*R*, major stereoisomer), 22.3 (*S*, minor stereoisomer).

(*R*)-3-(2-Chlorophenoxy)-3-phenylpropan-1-ol (3ad). (Entry 3, Table 1) Using the general procedure, tris(2-chlorophenyl)borate (**2d**) (196.0 mg, 0.5 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*R*)-2-phenyl oxetane (**1a**) (40.2 mg, 0.3 mmol) in THF (0.5 mL). After 1 h at room temperature the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3ad** (65.3 mg, 83%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.08−2.33 (m, 2H); 2.42 (br, s, 1H, *OH*); 3.75− 3.91 (m, 2H); 5.41 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 4.3$ Hz); 6.68 (d, 1H, $J = 8.3$ Hz); 6.76−6.83 (m, 1H); 6.95−7.02 (m, 1H); 7.22−7.31 (m, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.1, 59.8, 79.8, 115.2, 121.6, 125.7, 127.5, 127.9, 128.8, 130.1, 140.7, 153.1, 153.4. Anal. Calcd for $C_{15}H_{15}ClO_2$: C, 68.57; H, 5.75. Found: C, 68.34; H, 5.65. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 94/6, retention times (min): 26.3 (*S*, minor stereoisomer), 27.3 (*R*, major stereoisomer).

(*R*)-3-(2-Bromophenoxy)-3-phenylpropan-1-ol (3ae). (Entry 4, Table 1) Using the general procedure, tris(2-bromophenyl)borate (**2e**) (261.9 mg, 0.5 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*R*)-2-phenyl oxetane (**1a**) (40.2 mg, 0.3 mmol) in THF (0.5 mL). After 1 h at room temperature the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3ae** (53.2 mg, 58%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ δ 2.10−2.42 (m, 2H); 3.73−3.94 (m, 2H); 5.43 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 4.5$ Hz); 6.66 (d, 1H, $J = 7.9$ Hz); 6.68−6.80 (m, 1H); 6.91−7.39 (m, 6H); 7.49 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.4$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.1, 59.8, 79.7, 114.9, 122.0, 125.7, 127.8, 128.1, 128.2, 128.8, 132.2, 140.6, 153.4. Anal. Calcd for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92. Found: C, 58.44; H, 4.86. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 90/10, retention times (min): 18.3 (*S*, minor stereoisomer), 21.3 (*R*, major stereoisomer).

(*R*)-2-(3-Hydroxy-1-phenylpropoxy)phenol (3af). (Entry 5, Table 1) Using the general procedure, benzo[*d*][1,3,2]dioxaborol-2-ol (**2f**) (68.0 mg, 0.5 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*R*)-2-phenyl oxetane (**1a**) (40.2 mg, 0.3 mmol) in THF (0.5 mL). After 2 h at room temperature the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 7:3 to give compound **3af** (63.0 mg, 86%) as a solid. Mp = 92−93 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.00−2.11 (m, 1H); 2.22−2.34 (m, 2H); 3.80−3.89 (m 1H); 3.95−4.03 (m, 1H); 5.19 (dd, 1H, $J_1 = 9.0$ Hz, $J_2 = 3.8$ Hz); 6.58−6.61 (m, 2H); 6.78−6.85 (m, 1H); 6.90 (d, 1H, $J = 7.3$ Hz); 7.03 (br s, 1H, *OH*); 7.25−7.36 (m, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 40.4, 60.2, 81.3, 115.4, 116.8, 119.8, 122.8, 126.1, 128.0, 128.7, 141.3, 145.4, 147.3. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.63; H, 6.71. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 90/10, retention times (min): 22.1 (*S*, minor stereoisomer), 28.0 (*R*, major stereoisomer).

(*R*)-3-(4-Methoxyphenoxy)-3-phenylpropan-1-ol (3ag). (Entry 6, Table 1) Using the general procedure, tris(*p*-methoxyphenyl)borate (190.0 mg, 0.5 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*R*)-**1a** (40.2 mg, 0.3 mmol) in THF (0.5 mL). After 2.0 h at room temperature, the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3ag** (40.3 mg, 52%) as an oil. $[\alpha]^{20}_D = +26.7$ (*c* 1.7, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.00−2.22 (m, 3H); 3.68 (s, 3H); 3.69−3.81 (m, 2H); 5.25 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 5.0$ Hz); 6.70 (d, 2H, $J = 9.0$ Hz); 6.76 (d, 2H, $J = 9.0$ Hz); 7.16−7.35 (m, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.1, 55.6, 60.1, 79.3, 114.5, 117.1, 125.9, 127.6, 128.6, 141.6, 151.9, 153.9. Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 73.93; H, 6.94. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 90/10, retention times (min): 19.5 (*R*, major stereoisomer), 22.3 (*S*, minor stereoisomer).

(*R*)-3-Phenyl-3-(4-(trifluoromethyl)phenoxy)propan-1-ol (3ah). (Entry 7, Table 1) Using the general procedure, tris(*p*-(trifluoromethyl)phenyl)borate (**2h**) (247.0 mg, 0.5 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*R*)-(**1a**) (40.2 mg, 0.3 mmol) in THF (0.5 mL). After 1 h at room temperature, the mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3ah** (71.9 mg, 81%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.77 (br, s, 1H, *OH*); 2.00−2.14 (m, 1H); 2.20−2.31 (m, 1H); 3.70−3.92 (m 2H); 5.41 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 4.5$ Hz); 6.90 (d, 2H, $J = 8.5$ Hz); 7.20−7.35 (m, 5H); 7.41 (d, 2H, $J = 8.5$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.1, 59.4, 77.8, 115.7, 125.7, 126.7 (2 C), 126.8, 126.9, 127.9, 128.8, 140.7. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; N, 5.13; H, 5.53. Found: C, 65.96; N, 5.08; H, 5.42. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 90/10, retention times (min): 14.4 (*R*, major stereoisomer), 15.9 (*S*, minor stereoisomer).

(*R*)-3-(4-Nitrophenoxy)-3-phenylpropan-1-ol (3ai). (Entry 8, Table 1) Using the general procedure, tris(*p*-nitrophenyl)borate (**2i**) (212.5 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added at room temperature to a solution of (*R*)-**1a** (40.2 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL). After 1 h at room temperature the mixture was purified by column chromatography eluting with hexanes/AcOEt 7:3 to give compound **3ai** (47.6 mg, 58%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.99−2.16 (m, 1H); 2.20−2.34 (m 1H); 2.30−2.60 (br, 1H, *OH*); 3.68−3.92 (m, 2H); 5.47 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 5.0$ Hz); 6.88 (d, 2H, $J = 9.0$ Hz); 7.22−7.34 (m, 5H); 8.02 (d, 2H, $J = 9.0$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.0, 58.9, 78.1, 115.6, 115.8, 125.7, 128.2, 129.0, 140.1, 163.1. Anal. Calcd for $C_{16}H_{15}F_3O_2$: C, 64.86; H, 5.10. Found: C, 64.97; H, 5.02. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 90/10, retention times (min): 33.4 (*R*, major stereoisomer), 35.6 (*S*, minor stereoisomer).

(*R*)-3-(3-Chlorophenoxy)-3-phenylpropan-1-ol (3aj). (Entry 9, Table 1) Using the general procedure described above, a solution of tris(3-chlorophenyl)borate (**2j**) (196.0 mg, 0.5 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*R*)-(**1a**) (40.2 mg, 0.3 mmol) in THF (0.5 mL). The mixture was allowed to react for 1 h at room temperature. The mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3aj** (62.1 mg, 79%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.90−2.31 (m, 3H); 3.70−3.92 (m, 2H); 5.34 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 3.8$ Hz); 6.71 (d, 1H, $J = 8.0$ Hz); 6.80−6.89 (m, 2H); 7.03−7.12 (m, 1H); 7.20−7.42 (m, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.1, 59.5, 78.1, 114.1, 116.6, 121.2, 125.8, 127.9, 128.8, 130.1, 134.5, 140.9, 158.6. Anal. Calcd for $C_{15}H_{15}ClO_2$: C, 68.57; H, 5.75. Found: C, 68.34; H, 5.62. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 90/10, retention times (min). 20.0 (*S*, minor stereoisomer), 22.8 (*R*, major stereoisomer).

(*R*)-Methyl 4-(3-hydroxy-1-phenylpropoxy)-3-iodobenzoate (3ak). (Entry 10, Table 1) Using the general procedure, borate **2k** (420.6 mg, 0.5 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*R*)-(**1a**) (40.2 mg, 0.3 mmol) in THF (0.5 mL). After 1 h at room temperature, the mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3ak** (83.8 mg, 68%) as a semisolid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.03−2.39 (m, 3H); 3.73−3.85 (m, 1H); 3.81 (s, 3H); 3.88−4.00 (m, 1H); 5.50 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 4.3$ Hz); 6.60 (d, 1H, $J = 8.8$ Hz); 7.12−7.35 (m, 5H); 7.75 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 1.8$ Hz); 8.40 (d, 1H, $J = 1.8$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.1, 52.1, 59.3, 79.3, 86.3, 112.8, 124.1, 125.7, 128.1, 128.9,

131.2, 139.9, 140.8, 159.8, 165.4. Anal. Calcd for $C_{17}H_{17}IO_4$: C, 49.53; H, 4.16. Found: C, 49.88; H, 4.19. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 90/10, retention times (min): 18.5 (*S*, minor stereoisomer), 21.1 (*R*, major stereoisomer).

(*S*)-3-(2-Bromophenoxy)-3-(3-chlorophenyl)propan-1-ol (3be). (Scheme 5) Using the general procedure, tris(2-bromophenyl)borate (**2e**) (237.1 mg, 0.45 mmol) in THF (1.0 mL) was added at room temperature to a solution of (*S*)-2-(3-chlorophenyl)oxetane (**1b**) (50.5 mg, 0.3 mmol) in THF (0.5 mL). After 1.5 h at room temperature, the mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3be** (51.2 mg, 50%) as an oil. $[\alpha]^{20}_D = +34.2$ (*c* 2.16, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.08−2.38 (m, 3H); 3.70−3.95 (m, 2H); 5.38 (dd, 1H, $J_1 = 8.3$, Hz, $J_2 = 4.3$ Hz); 6.63 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 1.0$ Hz); 6.73−6.80 (m, 1H); 7.02−7.10 (m, 1H); 7.18−7.38 (m, 4H); 7.51 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 41.0, 59.5, 78.8, 114.8, 122.3, 123.9, 125.9, 128.1, 128.3, 130.2, 133.4, 143.0, 153.4. Anal. Calcd for $C_{15}H_{14}BrClO_2$: C, 52.74; H, 4.13. Found: C, 52.90; H, 4.15. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 95/5, retention times (min): 21.6 (*S*, major stereoisomer), 37.5 (*R*, minor stereoisomer).

(*S*)-3-(2-Bromophenoxy)-3-*p*-tolylpropan-1-ol (3ce). (Scheme 5) Using the general procedure, tris(2-bromophenyl)borate (237.1 mg, 0.45 mmol) (**2e**) in THF (1.0 mL) was added at room temperature to a solution of (*S*)-2-*p*-tolyloxetane (**1c**) (44.4 mg, 0.3 mmol) in THF (0.5 mL). After 20 min at room temperature, the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **3ce** (80.6 mg, 84%) as an oil. $[\alpha]^{20}_D = +37.0$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.08−2.35 (m, 5H); 2.42−2.58 (br, 1H); 3.78−3.99 (m, 2H); 5.40 (dd, 1H, $J_1 = 8.2$, Hz, $J_2 = 4.4$ Hz); 6.65−6.77 (m, 2H); 6.95−7.30 (m, 5H); 7.49 (d, 1H, $J = 7.8$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.2, 41.1, 59.9, 79.7, 114.9, 121.9, 125.7, 128.2, 129.1, 129.5, 133.2, 137.6, 154.0. Anal. Calcd for $C_{16}H_{17}BrO_2$: C, 59.83; H, 5.33. Found: C, 59.88; H, 5.28. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 95/5, retention times (min): 22.1 (*S*, major stereoisomer), 31.4 (*R*, minor stereoisomer).

General Procedure for the Ring Opening of Azetidines. (Table 2) A solution of aryl borate (0.5 mmol) in CH_2Cl_2 (1.0 mL) was added to a stirred solution of azetidine (0.3 mmol) in CH_2Cl_2 (0.5 mL). The mixture was allowed to react at 40 °C and was quenched with brine (2.0 mL) after complete consumption of the starting azetidine (24 h). The solution was diluted with Et_2O or CH_2Cl_2 (20 mL) and washed with brine. Evaporation of the dried organic solution afforded a crude reaction mixture that was purified by silica gel column chromatography to give the pure compounds of type **7**.

3-Phenyl-3-(3-chlorophenoxy)-*N*-(4-methylphenyl sulfonyl)-propanamine (7aj). (Entry 2, Table 2) Using the general procedure, tris(3-chlorophenyl)borate (**2j**) (196.0 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added at room temperature to a solution of (*S*)-**6a** (86.1 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL). The mixture was allowed to react for 24 h at 40 °C and then purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **7aj** (80.9 mg, 65%) as a semisolid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.93−2.18 (m, 2H); 2.40 (s, 3H); 3.03−3.24 (m, 2H); 4.62−4.73 (m, 1H, *NH*); 5.12 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 4.5$ Hz); 6.61 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz); 6.71−6.75 (m, 1H); 6.83 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 0.8$ Hz); 7.05 (t, 1H, $J = 8.3$ Hz); 7.12−7.36 (m, 7H); 7.68 (d, 1H, $J = 8.2$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.5, 38.0, 40.0, 77.9, 114.0, 116.5, 121.3, 125.6, 127.1, 128.0, 128.8, 129.7, 130.1, 134.6, 136.4, 140.1, 143.6, 158.2. Anal. Calcd for $C_{22}H_{22}ClNO_3S$: C, 63.53; H, 5.33. Found: C, 63.32; H, 5.28. Enantiomeric ratio determined by chiral HPLC (Chiralcel OD-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 85/15, retention times (min): 36.7 (52%), 56.9 (48%).

3-Phenyl-3-(4-nitrophenoxy)-*N*-(4-methylphenyl sulfonyl)-propanamine (7ai). (Entry 4, Table 2) Using the general procedure, tris(4-nitrophenyl)borate (**2i**) (212.5 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added at room temperature to a solution of **6a** (86.1 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL). The mixture was allowed to react for 24 h at 40 °C and purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **7ai** (71.6 mg, 56%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.90−2.22 (m, 2H); 2.37 (s, 3H); 2.98−3.23 (m, 2H); 5.10−5.18 (m, 1H, *NH*); 5.26−5.35 (m, 1H); 6.79 (d, 2H, $J = 8.0$ Hz); 7.12−7.32 (m, 7H); 7.69 (d, 2H, $J = 8.2$ Hz); 7.99 (d, 2H, $J = 8.0$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.5, 38.2, 39.6, 77.9, 115.7, 125.6, 125.7, 127.0, 128.3, 129.0, 129.8, 136.5, 139.4, 141.5, 143.7, 162.6. Anal. Calcd for $C_{22}H_{22}N_2O_2S$: C, 61.96; N, 6.57; H, 5.20. Found: C, 61.62; N, 6.68; H, 5.18.

3-Phenyl-3-(2-chlorophenoxy)-*N*-(4-methylphenylsulfonyl)-propanamine (7ad). (Entry 5, Table 2) Using the general procedure, tris(2-chlorophenyl)borate (**2d**) (196.0 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added at room temperature to a solution of **6a** (86.1 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL). After 24 h at 40 °C the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **7ad** (112.1 mg, 90%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.00−2.18 (m, 2H); 2.38 (s, 3H); 3.05−3.26 (m, 2H); 5.25 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 4.5$ Hz); 5.46−5.55 (m, 1H, *NH*); 6.55 (d, 1H, $J = 8.3$ Hz); 6.80 (t, 1H, $J = 7.5$ Hz); 6.95 (t, 1H, $J = 7.5$ Hz); 7.08−7.36 (m, 8H); 7.73 (d, 2H, $J = 8.0$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.5, 37.4, 40.1, 79.7, 114.8, 121.7, 122.8, 125.5, 127.2, 127.5, 128.0, 128.8, 129.6, 130.1, 136.8, 139.6, 143.2, 152.6. Anal. Calcd for $C_{22}H_{22}ClNO_3S$: C, 63.53; H, 5.33. Found: C, 63.21; H, 5.14.

3-Phenyl-3-(2-fluorophenoxy)-*N*-(4-methylphenylsulfonyl)-propanamine (7ac). (Entry 6, Table 2) Using the general procedure, tris(2-fluorophenyl)borate (**2c**) (177.0 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added at room temperature to a solution of azetidine **6a** (86.1 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL). After 24 h at 40 °C the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **7ac** (110.2 mg, 92%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.98−2.12 (m, 2H); 2.38 (s, 3H); 3.00−3.30 (m, 2H); 5.18 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 4.3$ Hz); 5.26−5.32 (m, 1H, *NH*); 6.59−6.68 (m, 1H); 6.78−6.85 (m, 2H); 6.96−7.05 (m, 1H); 7.12 −7.46 (m, 7H); 7.73 (d, 2H, $J = 8.2$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.5, 37.7, 40.2, 80.1, 116.0, 116.3, 117.1, 121.6, 121.7, 125.7, 127.2, 128.0, 128.5, 128.7, 129.7, 136.7, 140.1, 143.3. Anal. Calcd for $C_{22}H_{22}FNO_3S$: C, 66.15; H, 5.55. Found: C, 65.96; H, 5.48.

3-Phenyl-3-(4-(trifluoromethyl)phenoxy)-*N*-(4-methyl phenylsulfonyl)-propanamine (7ah). (Entry 7, Table 2) Using the general procedure, tris(*p*-(trifluoromethyl)phenyl)borate (**2h**) (247.0 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added at room temperature to a solution of azetidine **6a** (86.1 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL). The mixture was allowed to react for 24 h at 40 °C. After the usual workup, the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **7ah** (101 mg, 75%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.93−2.18 (m, 2H); 2.36 (s, 3H); 3.00−3.20 (m, 2H); 5.18−5.28 (m, 2H); 6.79 (d, 2H, $J = 8.5$ Hz); 7.16−7.32 (m, 7H); 7.36 (d, 2H, $J = 8.5$ Hz); 7.70 (d, 2H, $J = 8.2$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.5, 38.1, 39.8, 77.5, 115.7, 125.7, 126.7, 126.8, 127.0, 127.1, 128.0, 128.9, 129.7, 136.5, 140.0, 143.6. Anal. Calcd for $C_{23}H_{22}F_3NO_3S$: C, 61.46; N, 3.12; H, 4.93. Found: C, 61.56; N, 3.20; H, 4.85.

3-Phenyl-3-(2-bromophenoxy)-*N*-(4-methyl phenylsulfonyl)-propanamine (7ae). (Entry 8, Table 2) Using the general procedure, tris(2-bromophenyl)borate (**2e**) (261.9 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added at room temperature to a solution of compound **6a** (86.1 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL). After 24 h at 40 °C the crude mixture was purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **7ae** (96 mg, 65%) as an amorphous solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.99−2.17 (m, 2H); 2.38 (s, 3H); 3.05−3.21 (m, 2H); 5.225−5.30 (m, 1H);

5.54−5.58 (m, 1H, *NH*); 6.53 (d, 1H, $J = 7.5$ Hz); 6.68−6.77 (m, 1H); 6.91−7.02 (m, 1H); 7.08−7.27 (m, 7H); 7.47−7.53 (m, 1H); 7.74 (d, 2H, $J = 8.2$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.5, 37.4, 40.0, 79.6, 114.6, 122.2, 125.5, 127.2, 127.9, 128.3, 128.8, 129.6, 133.2, 136.8, 139.5, 143.2, 153.7. Anal. Calcd for $C_{22}H_{22}BrNO_3S$: C, 57.39; H, 4.82. Found: C, 57.45; H, 4.76.

(2*S,3*S**)-2-Hydroxy-3-phenyl-3-(3-chlorophenoxy)-*N*-(4-methylphenylsulfonyl)-propanamine (8dj).** (Scheme 6) Using the general procedure, tris(3-chlorophenyl)borate (**2j**) (352 mg, 0.9 mmol) in CH_2Cl_2 (1.0 mL) was added at room temperature to a solution of azetidinol **6d** (91 mg, 0.3 mmol) in CH_2Cl_2 (1.0 mL). The mixture was allowed to react for 24 h at 40 °C and then purified by column chromatography eluting with hexanes/AcOEt 8:2 to give compound **8dj** (84 mg, 65%) as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.42 (s, 3H); 2.88−2.98 (m, 3H); 3.91−3.97 (m, 1H); 4.89−4.96 (m, 1H); 5.09 (d, 1H, $J = 6.0$ Hz); 6.65−6.70 (m, 1H), 6.85−6.92 (m, 2H); 7.08 (t, 1H, $J = 7.5$ Hz), 7.25−7.43 (m, 8H), 7.68 (d, 2H, $J = 8.1$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 21.5, 43.9, 73.4, 81.38, 99.9, 114.0, 116.7, 121.8, 126.8, 127.1, 128.9, 129.0, 129.8, 130.2, 136.1, 143.6. Anal. Calcd for $C_{22}H_{22}ClNO_4S$: C, 61.18; H, 5.13. Found: C, 60.95; H, 5.05.

(*R*)-2-Phenyl-1,5-benzodioxepine (11). (Scheme 8) To a stirred solution of compound **3af** (29 mg, 0.12 mmol) in anhydrous THF (0.5 mL) were added at rt triphenylphosphine (62.9 mg, 0.24 mmol) and diethylazodicarboxylate (31.3 mg, 0.18 mmol) under argon. The mixture was allowed to react for 18 h at room temperature Column chromatography eluting with hexanes/AcOEt 7:3 afforded pure **11** (23 mg, 84%), as a colorless liquid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.31−2.45 (m, 2H); 3.94−4.19 (m, 1H); 4.33−4.56 (m, 1H); 4.94−5.13 (m, 1H); 6.75−7.08 (m, 4H); 7.14−7.50 (m, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 39.1, 69.8, 82.3, 121.3, 122.0, 123.3, 125.8, 127.8, 128.5, 141.6, 151.4, 153.2. Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.06; H, 5.27. Enantiomeric ratio determined by chiral HPLC (Chiralcel OB-H), flow rate: 0.5 mL/min, mobile phase: hexane/isopropanol 97/3, retention times (min): 15.8 (*S*, minor stereoisomer), 25.7 (*R*, major stereoisomer).

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Supporting Information Available: Text giving detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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