Boron Trifluoride-Induced, New Stereospecific Rearrangements of Chiral Epoxy Ethers. Ready Access to Enantiopure 4-(Diarylmethyl)-1,3-dioxolanes and 4,5-Disubstituted Tetrahydroben...

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Boron Trifluoride-Induced, New Stereospecific Rearrangements of Chiral Epoxy Ethers. Ready Access to Enantiopure 4-(Diarylmethyl)-1,3-dioxolanes and 4,5-Disubstituted Tetrahydrobenzo[*c*]oxepin-4-ols

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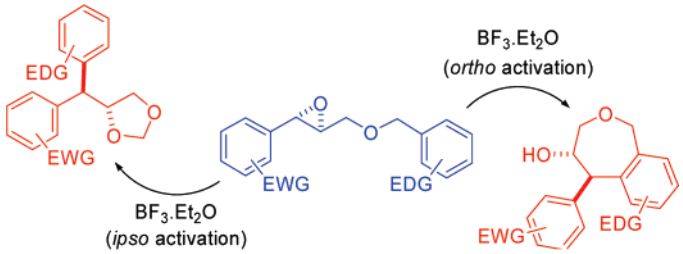

Upon treatment with $BF_3{\cdot}Et_2O$ at low temperature, enantiopure benzyl-type ethers of arylglycidols with electron withdrawing substituents at the skeletal aryl group and electron donating substituents at the benzyl group undergo stereospecific rearrangements of Friedel−Crafts type, leading to enantiopure 4-diarylmethyl-1,3-dioxolanes (**2**) or to enantiopure *trans*-4,5 disubstituted tetrahydrobenzo[*c*]oxepin-4-ols (**5**). The course of the reactions is controlled by the substitution pattern at the benzyl ether: While benzylic systems activated toward ipso substitution afford diarylmethanes **2** through a Friedel−Crafts reaction followed by fragmentation, benzylic systems activated toward ortho attack lead to enantiopure oxepinols **5** through a *7-endo-tet* ring closure of Friedel−Crafts type.

Introduction

Enantiomerically pure diarylmethane derivatives are important chiral building blocks in medicinal chemistry due to the large number of therapeutic agents that possess this structural motif.[1] Despite its increasing demand, methods for their enantioselective preparation are scarce, mostly relying on the catalytic arylation of aldehydes.[2]

On the other hand, epoxides depict an extremely rich and varied reactivity. While nucleophiles easily perform ring opening of the epoxide ring, thus allowing the stereospecific preparation of 1,2-difunctional compounds of many different types, electrophiles (Lewis acids) trigger a variety of rearrangements ultimately leading to carbonyl compound through carbocation or carbocation-like intermediates.[3]

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(1) See, for instance: (a) Silvestri, R.; Artico, M.; De Martino, G.; Ragno, R.; Massa, S.; Loddo, R.; Murgioni, Ch.; Giulia, L. A.; La Colla, P.; Pani, A. *J. Med. Chem.* **2002**, *45*, 1567−1576. (b) *Chiral Drugs*; Challener, C. A., Ed.; Ashgate: Burlington, VT, 2001; p 278.

(2) For recent work on preparation of enantiopure, heterosubstituted diarylmethanes by enantioselective phenyl transfer to aldehydes, see: (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465−3467. (b) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850−14851. (c) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532−2543. (d) Ji, J.-X.; Wu, J.; Au-Yeung, T. T.-L.; Yip, C.-W.; Haynes, R. K.; Chan, A. S. C. *J. Org. Chem.* **2005**, *70*, 1093−1095. (e) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138−4139. For a successful approach based on Ru-catalyzed hydrogenation, see: (f) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659−662. For de-racemization approaches, see: (g) Prat, L.; Mojovic, L.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2509−2516. (h) Prat, L.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J.; Levacher, V. *Tetrahedron Lett.* **2001**, *42*, 4515−4518. For a conjugate addition approach, see: (i) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894−7895.

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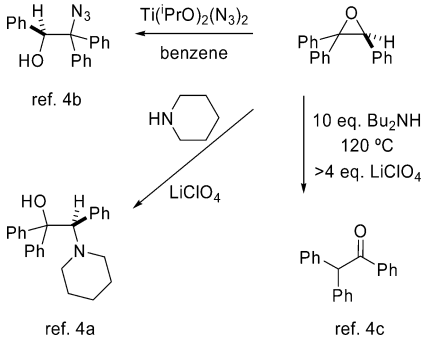
SCHEME 1. Ring Opening and Rearrangement of Triphenylethylene Oxide

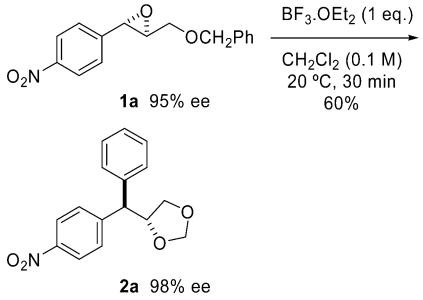


In the Lewis acid-mediated reactions of epoxides, if a nucleophile (either external or internal) is present in the reaction medium, attack on the carbocation intermediate can occur and products similar to those resulting from purely nucleophilic attack can arise, often with regiochemical reversal. This is illustrated in Scheme 1 with examples from our laboratory.[4]

Among these Lewis acid-mediated nucleophilic additions to epoxides, reactions where the nucleophile is an aromatic ring are particularly interesting because of the nature of the resulting systems. They represent a special type of Friedel−Crafts reactions, suitable for the preparation of enantiopure compounds whenever readily available enantiopure epoxides are employed as reactants. Until now, most of examples in this reappraisal of Friedel−Crafts chemistry refer to intermolecular processes, where a variety of Lewis acids have been used to induce the reactions.[5]

Over the past years, we have been involved in the development of modular ligands for asymmetric catalysis from enantiopure epoxy alcohols and epoxy ethers.[6] While working on the boron trifluoride-mediated synthesis of oxazolines[6h] from benzyl-type ethers of phenylglycidol, we discovered that these substrates can experience a regioselective and stereospecific ring-opening hydrofluorination under very mild reaction conditions.[7] We also observed that, when the *p*-methoxybenzyl ether

SCHEME 2. Reaction Conditions for the Stereospecific Rearrangement of 1a Leading to 2a



of phenylglycidol was employed as a substrate, the course of the reaction was completely different, a nonfluorinated rearrangement product being obtained.

We were intrigued by this behavior, and we have now studied in detail this alternate pathway. We report in this paper how enantiomerically pure benzyl-type ethers of arylglycidols containing electron withdrawing groups on the skeletal aryl substituent and properly placed electron donating groups on the benzyl moiety experience stereospecific intramolecular Friedel−Crafts reactions when treated with $BF_3{\cdot}Et_2O$ at low temperature to afford either enantiopure diarylmethanes (through an unprecedented ipso attack followed by fragmentation) or enantiopure *trans*-4,5-disubstituted tetrahydrobenzo[*c*]oxepin-4-ols.

Results and Discussion

Our study of the boron trifluoride-mediated rearrangement of benzyl ethers of arylglycidols began with epoxy ether **1a**, containing a strong electron withdrawing nitro group on the skeletal phenyl group. We anticipated that the presence of this group would decrease the rate of the potentially competitive ring-opening hydrofluorination of the epoxide. According to our expectations, when epoxy ether **1a** was treated with this reagent under very mild conditions (0.3 equiv of $BF_3{\cdot}OEt_2$, 0.1 M CH_2Cl_2, −35 °C, 1 h), the reaction afforded the rearranged compound **2a** as the sole reaction product;[8] however, conversion of the starting material was incomplete (65%). Very gratifyingly, a complete conversion of **1a** into the enantiomerically pure diarylmethane derivative **2a** was recorded when the reaction was carried out at 20 °C in the presence of 1 equiv of $BF_3{\cdot}OEt_2$ (Scheme 2).

It is to be mentioned that the structural assignment of **2a** posed some initial challenge: Whereas ^{13}C NMR experiments clearly indicated the presence of two methylene and two nonaromatic methine groups, two distinct singlets (one proton each) at 4.94 and 5.08 ppm, correlated with one single methylene carbon, were present in the ^1H NMR spectra. Since no situation with $^2J_{HH} = 0$ was easily anticipated for structures related to **1a**, more solid arguments for the structural assignment were sought from X-ray crystallography. In this way, the structure and the

(3) For recent reviews on the chemistry of epoxides, see: (a) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 1−29. (b) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006.

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(8) For recent examples of BF_3-induced rearrangements in epoxides, see: (a) Jung, M. E.; Anderson, K. L. *Tetrahedron Lett.* **1997**, *38*, 2605−2608. (b) Kita, Y.; Kitagaki, S.; Yoshida, Y.; Mihara, S.; Fang, D.-F.; Kondo, M.; Okamoto, S.; Imai, R.; Akai, S.; Fujioka, H. *J. Org. Chem.* **1997**, *62*, 4991−4997. (c) Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. *Tetrahedron Lett.* **2000**, *41*, 2133−2136. (d) Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. *Tetrahedron.* **2001**, *57*, 815−825. (e) Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. *J. Org. Chem.* **2001**, *66*, 8779−8786. (f) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, K. J.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917−5924.

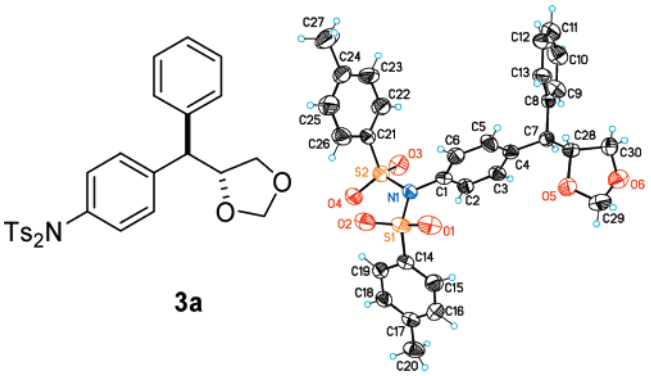


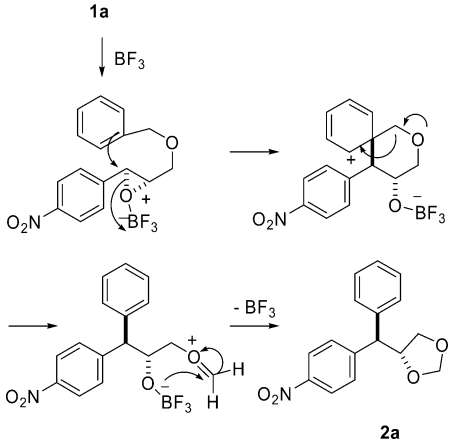
FIGURE 1. Bis(sulfonamide) **3a**, with an ORTEP plot (ellipsoids at 40% probability) of its crystal structure.

absolute configuration of **2a** could be unambiguously assigned on the basis of the X-ray analysis of the crystalline derivative **3a** (Figure 1), obtained from dioxolane **2a**[9] through reduction of the nitro group (H_2, Pd/C) and tosylation.[10]

While several examples of Lewis acid-mediated ring opening of epoxides with arenes (or Friedel−Crafts reactions with epoxides, in an alternate view) are known,[11] an intramolecular stereospecific process like the one leading to **2a** is unprecedented. A mechanistic rationale for this reaction is shown in Scheme 3. As a key feature, ipso attack to the activated epoxide by the benzyl ether moiety, followed by fragmentation, is the vehicle for the stereospecific delivery of a phenyl group to a benzylic position, ultimately leading to the formation of an enantiopure diarylmethane derivative.

For the reasons given above, extension of this method to the preparation of other enantiopure diarylmethanes was attempted among epoxy ethers bearing electron withdrawing substituents on the skeletal phenyl ring of the starting epoxide. In this context, it is important to point out that phenylglycidyl ethers, when submitted to the same reaction conditions, experience ring-opening hydrofluorination,[7] while arylglycidyl ethers with

SCHEME 3. Mechanistic Rationale for the Stereospecific Formation of Diarylmethane 2a from 1a



electron donating substituents on the aryl ring preferentially rearrange to β-alkoxyaldehydes.[7,12]

On the other hand, if the mechanistic assumption in Scheme 3 is correct, substituents on the aryl moiety of the benzyl ether that increase the electron density at the ipso carbon should also increase the ease for the rearrangement, leading to diarylmethane derivatives.

Results obtained when submitting epoxy ethers fulfilling the aforementioned structural criteria to $BF_3{\cdot}OEt_2$ under a variety of experimental conditions have been summarized in Table 1.

Starting from enantiopure epoxy ethers **1a**−**f**, prepared by alkylation with the corresponding benzyl halides (see Experimental Section) of epoxy alcohols prepared in enantiomerically pure form by the Sharpless procedure,[13] enantiopure 4-(diarylmethyl)-1,3-dioxolanes **2a**−**f** are obtained in good yields as the sole reaction products under very mild reaction conditions and, generally, in short reaction times. In only one case (entry **b**), the corresponding fluoro alcohol arising from ring opening of the starting epoxide was also obtained in 25% yield.[7]

With respect to reactivity, the anticipated trend is observed: electron withdrawing groups on the skeletal phenyl substituent and electron donating groups on the benzyl substituent favor the rearrangement leading to **2**. It is to be noted, however, that the formation of the dioxolane products responds to a combination of factors: availability of a low-energy path for the intramolecular Friedel−Crafts reaction with the epoxide and inhibition of alternative reactivities of the epoxide (ring opening by fluoride, Lewis acid-mediated rearrangement) that would lead to fluoro alcohol or carbonyl products. Probably as a combination of these two factors, the highest reactivity among the studied substrates is depicted by **1d**, which was completely converted after 5 min at −78 °C in the presence of 0.33 equiv of $BF_3{\cdot}OEt_2$. Much for the same reasons, while *p*-methoxy benzyl ethers led to dioxolane products under mild conditions (entries **c**−**g**), the *o*- and *m*-methoxy benzyl ethers of phenylglycidol yielded mainly the corresponding fluoro alcohols.[7]

As already mentioned, the reactions leading to dioxolanes **2a**−**f** are in general very clean. For instance, when the

(9) For examples of 1,3-dioxolanes with nonequivalent, yet noncoupled C-2 protons, see: (a) Gras, J. L.; Poncet, A. *Bull. Soc. Chim. Fr.* **1991**, *128*, 566. (b) McCombie, W. S.; Metz, A. W. *Tetrahedron Lett.* **1987**, *28*, 383. (c) Hojo, M.; Aihara, H.; Suginohara, Y.; Sakata, K.; Nakamura, S.; Murakami, Ch.; Hosomi, A. *J. Org. Chem.* **1997**, *62*, 8610.

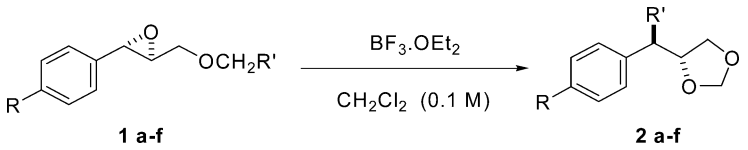
(10) (a) To a solution of **2a** (0.012 g, 0.042 mmol) in AcOEt (1 mL) and MeOH (0.100 mL), 10% Pd/C (0.020 g) was added, and the mixture was stirred under H_2 at room temperature for 3 h. The reaction mixture was filtered through a short pad of Celite, the solvent was evaporated in vacuo, and the resulting oil (0.011 g) was used for the next reaction without purification. (b) To a solution of the hydrogenation product (0.008 g, 0.031 mmol) in anhydrous CH_2Cl_2 (0.50 mL) under N_2 at room temperature DMAP (0.003 g, 0.031 mmol), *p*-toluenesulfonyl chloride (0.009 g, 0.047 mmol) and Et_3N (0.004 mL, 0.031 mmol) were added. After 3 h of stirring, a saturated solution of NH_4Cl (1 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual oil was purified by column chromatography using hexane:EtOAc (80:20) as eluent to give a sample of pure **3a** [^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 6H), 3.54 (dd, J = 6.8, 8.4 Hz, 1H), 3.84 (dd, J = 6.4, 8.4 Hz, 1H), 4.04 (d, J = 9.2 Hz, 1H), 4.70 (m, 1H), 4.96 (s, 1H), 5.06 (s, 1H), 6.96 (d, J = 8.4 Hz, 4H), 7.20−7.32 (m, 8H), 7.78 (d, J = 8.4 Hz, 5H)]. A recrystallization from dichloromethane afforded crystals suitable for X-ray diffraction.

(11) (a) Taylor, K. S.; Hockerman, H. G.; Karrick, L. G.; Lyle, B. S.; Schramm, B. S. *J. Org. Chem.* **1983**, *48*, 2449−2452. (b) Tanis, P. S.; Raggon, W. J. *J. Org. Chem.* **1987**, *52*, 819−827. (c) Broka, A. C.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584−1586. (d) Taylor, K. S.; May, A. S.; Stansby, S. E. *J. Org. Chem.* **1996**, *61*, 2075−2080. (e) For an intermolecular process leading to a racemic diarylmethane, see: Taylor, K. S.; Clark, L. D.; Heinz, L. K.; Schramm, B. S.; Westermann, D. C.; Barnell, K. K. *J. Org. Chem.* **1983**, *48*, 592−596.

(12) For a recent account on the rearrangement of silyl ethers of glycidols to β-alkoxyaldehydes catalyzed by a Cr(III) porphyrin complex, see: Suda, K.; Kikkawa, T.; Nakajima, S.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554−9555.

(13) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (b) Katsuki, T.; Martín, V. S. *Org. React.* **1996**, *48*, 1−299.

TABLE 1. Stereospecific Rearrangement of Epoxy Ethers 1a−f Leading to Diarylmethanes 2a-f

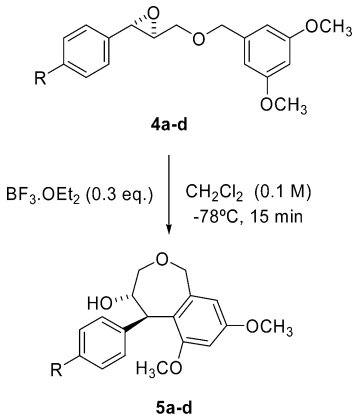


1 a-f 2 a-f

entry	R	R′	ee **1** (%)	*T* (°C)	*t* (min)	BF_3·OEt_2 (equiv)	yield (%)	ee **2** (%)
a	NO_2	Ph	95	rt	30	1.0	60	98
b	CF_3	Ph	96	rt	180	0.5	60[a]	96
c	CF_3	PMP	96	−35[b]	30	1.0	60	97
d	H	PMP	99	−35[c]	5	0.5[d]	59	>99
e	NO_2	PMP	95	rt	30	2.0	28	98
f	Cl	PMP	80	−20	5	0.3	44	85

[a] The corresponding fluoro alcohol arising from the ring opening was also obtained in this case (25% yield). [b] When the reaction was performed at 0 °C (1 h), the yield was 40%. [c] At −50 °C (5 min reaction), the yield was 46%; at −78 °C (0.3 equiv of BF_3·OEt_2, 5 min reaction), the yield was 44%. [d] With 1 equiv of BF_3·OEt_2 under the same reaction conditions, the yield was 48%.

SCHEME 4. Reaction Conditions for the Stereospecific Rearrangement of 4a Leading to 5a



rearrangement of **1c** was studied by NMR in CD_2Cl_2 at −30 °C, it was observed that the conversion of the starting material was complete after 30 min and that **2c** was the sole product arising from the reaction. Despite that, the reaction yield was limited to ca. 60%, as for other examples in Table 1. The possibility that this limit in yield could arise from product association with BF_3 leading to decomposition during hydrolysis led us to explore the use of a less oxophilic Lewis acid, such as $InBr_3$, which has been shown to promote Friedel−Crafts reactions of epoxides.[14] However, when this reagent was used with **1d** (1 equiv, 0 °C, 15 min), a mixture of **2d** and the two regioisomeric fluoro alcohols arising from the ring opening of the epoxide was obtained.

Very interestingly, the course of the electrophilic attack of the epoxide on the benzyl ether moiety can be fine-tuned by manipulation of the electronic properties of the benzyl group. We reasoned that, if a 3,5-dimethoxybenzyl substituent was used as protecting group in the starting epoxy ether, the nucleophilic reactivity of the aromatic system would shift from the ipso to the ortho/ortho′ positions and that the double activation at these sites would overcome the tendency of the simple *m*-methoxybenzyl ether (see above) to preferentially undergo ring-opening hydrofluorination. In agreement with these expectations, when epoxy ether **4a** (R = H, >99% ee) was treated with BF_3·OEt_2 in dichloromethane at −78 °C (Scheme 4), a fast reaction took

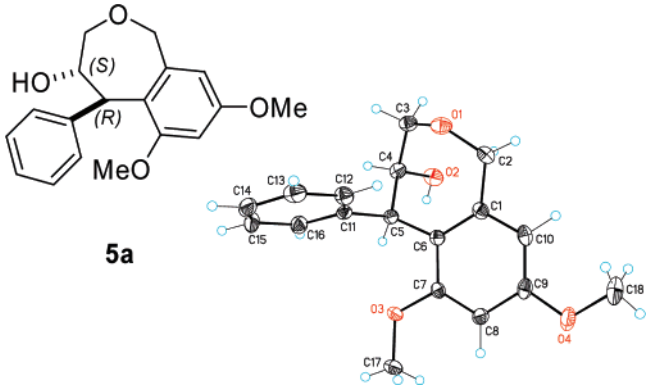
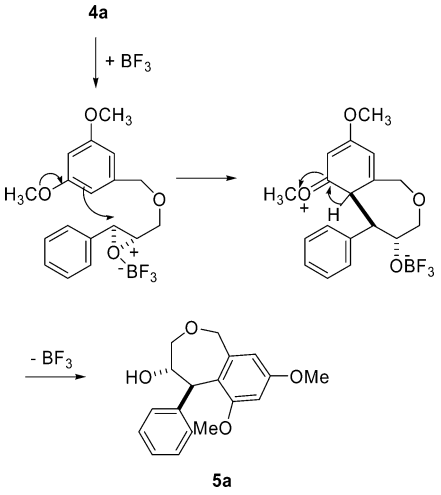


FIGURE 2. Tetrahydrobenzoxepinol **5a**, with an ORTEP plot (ellipsoids at 50% probability) of its crystal structure.

SCHEME 5. Mechanistic Rationale for the Formation of Tetrahydrobenzoxepinol 5a from 4a



place and the enantiomerically pure tetrahydrobenzoxepinol **5a** (>99% ee) could be isolated in 80% yield.

Benzo[*c*]oxepin **5a** could be crystallized, and X-ray analysis allowed its stereochemical assignment (Figure 2). A mechanistic rationale for this rearrangement is provided in Scheme 5. As in the reaction leading to diarylmethanes (Scheme 2), the aryl group in the benzyl moiety behaves as a nucleophile toward the α-aryl carbon of the epoxide, which suffers a stereospecific S_N2 type ring opening. In this case, however, the presence of a

(14) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 5386−5389.

TABLE 2. Stereospecific Rearrangement of Epoxy Ethers 4a−d Leading to Tetrahydrobenzoxepinols 5a−d

entry	R	ee **4** (%)	yield (%)	ee **5** (%)
a	H	>99	80	>99
b	CF_3	96	14 (54)[a]	96
c	Cl	80	60 (75)[a]	80
d	Ph	78	60	80

[a] Reactions did not proceed to completion. Yield according to conversion is given in parentheses.

hydrogen atom as a substituent on the nucleophilic aromatic carbon allows the process to be completed as an intramolecular Friedel−Crafts reaction.

When epoxy ethers **4b−d** were submitted to the same reaction conditions, aryl-substituted tetrahydrobenzoxepinols **5b−d** were formed stereospecifically, the enantiomeric purity of the starting materials being conserved in all cases in the cyclization products (Table 2). To get some insight into the factors controlling the reactivity of epoxy ethers **4** in this process, all reactions were performed under the same reaction conditions (−78 °C in dichloromethane, 15 min). It could be seen in this way that substrates with a more electron-rich skeletal aryl substituent (**4a** and **4d**) are those undergoing the fastest Friedel−Crafts cyclization. Even the substrates containing an electronically poor aryl substituent (**4b** and **4c**) react to a considerable extent under these very mild conditions, and, more importantly, they experience exclusively Friedel−Crafts cyclization vs ring-opening hydrofluorination. The nucleophilic power of the 3,5-dimethoxybenzyl is an important factor in reactivity control since, as mentioned above, the *m*-methoxybenzyl ether of the same substrate leads to the corresponding fluorhydrin when submitted to the same treatment.[7]

The very low temperature at which $BF_3{\cdot}OEt_2$ is able to induce the considered process in truly remarkable. In this sense, it is interesting to compare our results with those recently reported by He[15] on the formally related intramolecular cyclialkylation of aryl ethers of epoxy alcohols leading to 3-chromanols. This process, mediated by the $AuCl_3$/3AgOTf system, requires to proceed temperatures of 50 °C or higher and has been reported to fail when $BF_3{\cdot}OEt_2$ is employed as the catalyst.[16]

Although some examples of Friedel−Crafts type cyclization of epoxides leading to seven-membered rings are known,[17] the totally regioselective and stereospecific formation of tetrahydrobenzoxepinols **5** is unprecedented. Since oxygenated seven-membered rings are appealing from the pharmacological perspective[18] and, despite considerable synthetic effort,[19] methods for their enantioselective synthesis have remained practically unexplored, the stereospecific Friedel−Crafts cyclization of enantiopure epoxyethers **4** leading to **5** offers a considerable interest.

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Conclusions

In summary, the $BF_3{\cdot}OEt_2$-promoted rearrangements described here provide useful and stereospecific methods for the synthesis of enantiopure diarylmethane derivatives (4-(diarylmethyl)-1,3-dioxolanes and tetrahydrobenzoxepinols) from readily available, enantiopure *O*-benzyl-protected epoxy alcohols. Very interestingly, the regiochemical course of the underlying Friedel−Crafts process can be easily controlled by shifting the nucleophilic reactivity in the benzyl moiety of the substrate from the ipso to the ortho/ortho′ positions.

Experimental Section

(2*S*,3*S*)-3-(4-Nitrophenyl)-2-(benzyloxymethyl)oxirane (1a). A solution of (2*S*,3*S*)-2,3-epoxy-3-(4′-nitrophenyl)propan-1-ol (0.2 g, 1.025 mmol) in dimethylformamide (DMF, 2 mL) was added via cannula to a suspension of sodium hydride (0.045 g, 1.13 mmol) in DMF (2 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and benzyl bromide (0.121 mL, 1.025 mmol) was added via syringe. After 5 h of stirring at −20 °C, MeOH (1 mL) and brine (2 mL) were added, and the solution was extracted with ether (3 × 5 mL). The combined organic extracts were dried and concentrated in vacuo, and the residual oil was purified by column chromatography using hexane:EtOAc (80:20/60:40) as the eluent to give 0.20 g (68%) of **1a** as an oil: $[\alpha]_D^{20} = -24.0$ ($c = 0.485$ in $CHCl_3$); IR ($CHCl_3$) 3033, 2861, 1605, 1522, 1348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.19 (m, 1H), 3.65 (dd, $J = 4.8$, 11.6 Hz, 1H), 3.82 (dd, $J = 3.2$, 11.6 Hz, 1H), 3.92 (d, $J = 2.0$ Hz, 1H), 4.62 (s, 2H), 7.32 (m, 1H), 7.36 (d, $J = 4.4$ Hz, 4H), 7.43 (d, $J = 8.4$ Hz, 2H), 8.20 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz) δ 55.1, 62.1, 69.4, 73.8, 124.0, 126.7, 128.1, 128.2, 128.8, 137.8, 144.8, 148.1; MS (CI, NH_3) *m*/*z*: 303 $[M + NH_4]^+$. HRMS (CI). Calcd for $[M + H]^+$: 286.1079. Found: 286.1087.

(2*S*,3*S*)-3-(4-(Trifluoromethyl)phenyl)-2-(benzyloxymethyl)-oxirane (1b). A solution of (2*S*,3*S*)-2,3-epoxy-3-(4-(trifluoromethyl)phenyl)propan-1-ol (0.22 g, 1.01 mmol) in DMF (5 mL) was added via cannula to a suspension of sodium hydride (0.044 g, 1.11 mmol) in DMF (5 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and benzyl bromide (0.132 mL, 1.11 mmol) was added to the mixture. After 4 h of stirring at −20 °C, the reaction mixture was treated as described for **1a**. The residual oil was purified by column chromatography using hexane:ether (47:3/ 45:5) as eluent to give 0.258 g (83%) of **1b** as a white solid: mp = 58−60 °C; $[\alpha]_D^{20} = -24.0$ ($c = 0.96$ in $CHCl_3$); IR ($CHCl_3$) 3441, 2858, 1622, 1323, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.21 (m, 1H), 3.68 (dd, $J = 5.2$, 11.6 Hz, 1H), 3.84 (d, $J = 3.2$ Hz, 1H), 3.87 (m, 1H), 2H), 7.31 (m, 3H), 7.37 (m, 4H), 7.59 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.1, 61.5, 64.4, 73.5, 125.4 (q, $J = 3.8$ Hz), 125.9, 127.8 (d, $J = 9.0$ Hz), 128.5, 137.7, 141.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0 (s, CF_3); MS (CI, CH_4) *m*/*z*: 309 $[M + H]^+$. Anal. Calcd for $C_{17}H_{15}F_3O_2$: C, 66.23; H, 4.90. Found: C, 66.21; H, 5.07.

(2*S*,3*S*)-3-(4-(Trifluoromethyl)phenyl)-2-((4-methoxy)benzyl-oxymethyl)oxirane (1c). A solution of (2*S*,3*S*)-2,3-epoxy-3-(4-(trifluoromethyl)phenyl)propan-1-ol (0.20 g, 0.917 mmol) in DMF (5 mL) was added via cannula to a suspension of sodium hydride (0.04 g, 1.01 mmol) in DMF (5 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and 4-methoxybenzyl chloride (0.136 mL, 1.01 mmol) was added to the mixture. After 3 h of stirring at 0 °C, the reaction mixture was treated as described for **1a**. The residual oil was purified by column chromatography using hexane:ether (48:2) as eluent to give 0.22 g (71%) of **1c** as a white solid: mp = 47 °C; $[\alpha]_D^{20} = -26.0$ ($c = 1.2$ in $CHCl_3$); IR ($CHCl_3$) 2897, 1612, 1330, 1119, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (m, 1H), 3.63 (dd, $J = 5.2$, 11.6 Hz, 1H), 3.80 (d, $J = 2.8$ Hz, 1H), 3.81 (s, 3H), 3.83 (dd, $J = 2.0$, 6.6 Hz, 1H), 4.55 (d, $J = 3.2$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.37

(d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 55.3, 61.5, 69.1, 73.19, 113.9, 125.4 (c, J = 3.8 Hz), 125.9 (d, J = 2.6 Hz), 129.5, 129.8, 130.4 (d, J = 32.7 Hz), 141.2, 159.4 (d, J = 1.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0 (s, CF_3); MS (CI, CH_4) m/z: 339 $[M + H]^+$. Anal. Calcd for $C_{18}H_{17}F_3O_3$: C, 63.90; H, 5.06. Found: C, 64.06; H, 4.99.

(2*S*,3*S*)-3-Phenyl-2-((4-methoxy)benzyloxymethyl)oxirane (1d). A solution of (2*S*,3*S*)-2,3-epoxy-3-phenylpropan-1-ol (0.51 g, 3.4 mmol) in DMF (5 mL) was added via cannula to a suspension of sodium hydride (0.149 g, 3.74 mmol) in DMF (5 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and 4-methoxybenzyl chloride (0.505 mL, 3.74 mmol) was added to the mixture. After 3 h of stirring at −20 °C and 2 h at 0 °C, the reaction mixture was treated as described for **1a**. The residual oil was purified by column chromatography using hexane:ether (48:2/45:5) as eluent to give 0.78 g (85%) of **1d** as an oil: $[\alpha]_D^{20} = -35.0$ (c = 1.1 in $CHCl_3$); IR ($CHCl_3$) 2997, 2934, 2836, 1612, 1585, 1513, 1248, 1174, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (m, 1H), 3.60 (dd, J = 5.2, 11.6 Hz, 1H), 3.79 (dd, J = 2, 13 Hz, 1H), 3.81 (s, 3H), 3.83 (d, J = 2.8 Hz, 1H), 4.56 (d, J = 4.4 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.25−7.34 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 55.9, 61.2, 69.5, 73.0, 113.8, 125.7, 128.2, 128.4, 129.4, 129.9, 136.9, 159.3; MS (CI, CH_4) m/z: 271 $[M + H]^+$. HRMS (CI). Calcd for $[M + H]^+$: 271.1334. Found: 271.1336.

(2*S*,3*S*)- 3-(4′-Nitrophenyl)-2-((4-methoxy)benzyloxymethyl)-oxirane (1e). A solution of (2*S*,3*S*)-2,3-epoxy-3-(4′-nitrophenyl)-propan-1-ol (0.146 g, 0.748 mmol) in DMF (2 mL) was added via cannula to a suspension of sodium hydride (0.033 g, 0.823 mmol) in DMF (5 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and 4-methoxybenzyl chloride (0.111 mL, 0.823 mmol) was added to the mixture via syringe. After 5 h of stirring at −20 °C, the reaction mixture was treated as described for **1a**. The residual oil was purified by column chromatography using hexane: EtOAc:Tol (70:20:10) as the eluent to give 0.115 g (49%) of **1e** as an oil: $[\alpha]_D^{20} = -31.6$ (c = 1.0 in $CHCl_3$); IR ($CHCl_3$) 3417, 2935, 2837, 1611, 1514, 1248, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (m, 1H), 3.66 (dd, J = 4.8, 12.0 Hz, 1H), 3.80 (s, 3H), 3.83 (d, J = 3.2 Hz, 1H), 3.90 (d, J = 2.0 Hz, 1H), 4.55 (d, J = 1.6 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H) 8.18 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz) δ 54.8, 55.2, 61.9, 68.8, 73.2, 113.9, 123.7, 126.4, 129.5, 129.6, 144.6, 147.8, 159.4; MS (CI, CH_4) m/z: 356 $[M + C_3H_5]^+$, 344 $[M + C_2H_5]^+$, 316 $[M + H]^+$, 121. HRMS (CI). Calcd for $[M]^+$: 315.1107. Found: 315.1105.

(2*S*,3*S*)-3-(4-Chlorophenyl)-2-((4-methoxy)benzyloxymethyl)-oxirane (1f). A solution of (2*S*,3*S*)-2,3-epoxy-3-(chlorophenyl)-propan-1-ol (0.304 g, 1.65 mmol) in DMF (5 mL) was added via cannula to a suspension of sodium hydride (0.072 g, 1.82 mmol) in DMF (5 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and 4-methoxybenzyl chloride (0.245 mL, 1.82 mmol) was added to the mixture. After 5 h of stirring at −20 °C, the reaction mixture was treated as described for **1a**. The residual oil was purified by column chromatography using hexane:ether (96:4) as eluent to give 0.32 g (64%) of **1f** as a white solid: mp = 58 °C; $[\alpha]_D^{20} = -28.6$ (c = 1.0 in $CHCl_3$); IR ($CHCl_3$) 2907, 2836, 1612, 1513, 1247, 1089, 821 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 (m, 1H), 3.60 (dd, J = 5.6, 11.4 Hz, 1H), 3.75 (d, J = 2.0 Hz, 1H), 3.79 (dd, J = 3.2, 11.6 Hz, 1H), 3.80 (s, 3H), 4.54 (d, J = 4.0 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 61.3, 69.3, 73.1, 113.8, 127.0, 128.7, 129.4, 129.8, 134.0, 135.5, 159.4; MS (CI, CH_4) m/z 305 $[M + H]^+$. Anal. Calcd for $C_{17}H_{17}ClO_3$: C, 67.00; H, 5.62. Found: C, 67.28; H, 5.44.

(4*R*)-[(*R*)-(4-Nitrophenyl)phenylmethyl]-1,3-dioxolane (2a). A solution of enantiomerically pure (95% ee) (2*S*,3*S*)-**1a** (0.05 g, 0.175 mmol) in anhydrous CH_2Cl_2 (1.7 mL) and $BF_3.Et_2O$ (0.022 mL, 0.175 mmol) under N_2 was stirred for 30 min at room temperature. The reaction mixture was treated with a saturated $NaHCO_3$ solution; the aqueous solution was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried and concentrated in vacuo, and the crude product was purified by column chromatography using hexane:ether:toluene (70:20:10) as the eluent to give **2a** (0.030 g, 60%) as a white solid: mp 83−85 °C; $[\alpha]_D^{20} = +8.3$ (c = 1.0 in $CHCl_3$); IR ($CHCl_3$) 2860, 1596, 1518, 1349, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.61 (dd, J = 6, 8.6 Hz, 1H), 3.89 (dd, J = 6, 8.6 Hz, 1H), 4.15 (d, J = 9,6 Hz, 1H), 4.78 (m, 1H; CH), 4.94 (s, 1H), 5.08 (s, 1H), 7.23−7.38 (m, 5H), 7.52 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz) δ 54.9, 69.2, 77.9, 95.9, 124.0, 127.9, 128.4, 129.4, 129.6, 139.9, 149.6; MS (EI) m/z (%): 285 $[M]^+$, 213 $[M - C_3H_5O_2]^+$. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.28; H, 5.39; N, 4.86. ee = 98% (HPLC: Chiralcel AD, 10% 2-propanol in hexane, 0.5 mL/min, (*S*,*S*) isomer 32.06 min, (*R*,*R*) isomer 37.05 min).

(4*R*)-[Phenyl-(*R*)-(4-(trifluoromethyl)phenyl)methyl]-1,3-dioxolane (2b). A solution of enantiomerically pure (96% ee) (2*S*,3*S*)-**1b** (0.051 g, 0.165 mmol) in anhydrous. CH_2Cl_2 (1.65 mL) and $BF_3.Et_2O$ (0.01 mL, 0.082 mmol) under N_2 was stirred for 3 h at room temperature. The reaction mixture was treated as described for **2a**, and the crude product was purified by column chromatography using hexane:EtOAc (80:20) as the eluent to give the **2b** (0.030 g, 60%): $[\alpha]_D^{20} = -2.0$ (c = 1.4 in $CHCl_3$); IR ($CHCl_3$) 2860, 1596, 1518, 1349, 1088, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (dd, J = 6.4, 8.6 Hz, 1H), 3.89 (dd, J = 6.4, 8.4 Hz, 1H), 4.07 (d, J = 12 Hz, 1H), 4.74−4.80 (m, 1H), 4.95 (s, 1H), 5.08 (s, 1H), 7.22−7.34 (m, 5H), 7.47 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz) δ 54.6, 69.0, 77.8, 95.6, 122.8, 125.4 (q, J = 3.8 Hz), 127.4, 128.2, 128.7, 129.0, 140.3, 145.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0 (s, CF_3); MS (CI, NH_3) m/z: 326 $[M + NH_4]^+$. HRMS (CI). Calcd for $[M]^+$: 309.1102. Found: 309.1109. ee = 96% (HPLC: Chiralcel ODH, 2% 2-propanol in hexane, 0.5 mL/min, (*S*,*S*) isomer 15.91 min, (*R*,*R*) isomer 17.40 min).

(4*R*)-[(4-Methoxyphenyl)-(*R*)-(4-(trifluoromethyl)phenyl)-methyl]-1,3-dioxolane (2c). A solution of enantiomerically pure (96% ee) (2*S*,3*S*)-**1c** (0.030 g, 0.088 mmol) in anhydrous CH_2Cl_2 (0.9 mL) and $BF_3{\cdot}Et_2O$ (0.011 mL, 0.088 mmol) under N_2 was stirred for 30 min at −35 °C. The reaction mixture was treated as described for **2a**, and the crude product was purified by column chromatography using hexane:EtOAc (9:1) as the eluent to give **2c** (0.018 g, 60%) as a liquid: $[\alpha]_D^{20} = -4.2$ (c = 0.96 in $CHCl_3$); IR ($CHCl_3$) 2937, 2840, 1618, 1513, 1327, 1123, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (dd, J = 6.8, 8.4 Hz, 1H), 3.77 (s, 3H), 3.89 (dd, J = 6.4, 8.4 Hz, 1H), 4.02 (d, J = 9.6 Hz, 1H), 4.68−4.75 (m, 1H), 4.94 (s, 1H), 5.07 (s, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz) δ 53.8, 55.2, 69.1, 77.9, 95.6, 114.4, 125.4 (q, J = 3.8 Hz), 128.6, 129.2, 132.4, 146.2, 158.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.90 (s, CF_3); MS (CI, CH_4) m/z 339 $[M + H]^+$. HRMS (CI). Calcd for $[M]^+$: 338.1129. Found: 338.1131. ee = 97% (HPLC: Chiralcel OD-H, 5% 2-propanol in hexane, 0.5 mL/min, (*S*,*S*) isomer 15.52 min, (*R*,*R*) isomer 17.97 min).

(4*R*)-[(4-Methoxyphenyl)-(*R*)-(4-phenyl)methyl]-1,3-dioxolane (2d). A solution of enantiomerically pure (99% ee) (2*S*,3*S*)-**1d** (0.022 g, 0.081 mmol) in anhydrous CH_2Cl_2 (0.8 mL) and $BF_3{\cdot}Et_2O$ (0.005 mL, 0.04 mmol) under N_2 was stirred for 5 min at −35 °C. The reaction mixture was treated as described for **2a**, and the crude was purified by column chromatography using hexane: EtOAc (9:1) as the eluent to give **2d** (0.018 g, 59%) as a white solid: mp = 113 °C; $[\alpha]_D^{20} = -7.0$ (c = 0.98 in $CHCl_3$); IR ($CHCl_3$) 2954, 2901, 2851, 1610, 1513, 1255, 1081, 940 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (dd, J = 6.8, 8.4 Hz, 1H), 3.77 (s, 3H), 3.88 (dd, J = 6.4, 8.2 Hz, 1H), 3.97 (d, J = 9.6 Hz, 1H), 4.73 (m, 1H), 4.94 (s, 1H), 5.06 (s, 1H), 6.81 (dd, J = 2.0, 6.6 Hz, 2H), 7.16 (dd, J = 2.0, 6.6 Hz, 2H), 7.20−7.35 (m, 5H); ^{13}C NMR (100 MHz) δ 53.8, 55.2, 69.1, 78.2, 95.5, 114.2, 126.6, 128.2, 128.5, 129.1, 133.4, 142.1, 158.5; MS (CI, CH_4) m/z 271 $[M + H]^+$. Anal.

Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.75; H, 6.35. ee = >99% (HPLC: Chiralcel OD, 5% 2-propanol in hexane, 0.5 mL/min, (*S*,*S*) isomer 18.94 min, (*R*,*R*) isomer 20.30 min).

(4*R*)-[(*R*)-(4-Nitrophenyl)(4-methoxyphenyl)methyl]-1,3-dioxolane (2e). A solution of enantiomerically pure (95% ee) (2*S*,3*S*)-**1e** (0.050 g, 0.16 mmol) in anhydrous CH_2Cl_2 (1.6 mL) and $BF_3.Et_2O$ (0.03 mL, 0.32 mmol) under N_2 was stirred for 30 min at room temperature. The reaction mixture was treated as described for **2a**, and the crude product was purified by column chromatography using hexane:EtOAc (47:3) as the eluent to give **2e** (0.014 g, 28%) as a liquid: $[\alpha]_D^{20} = +3.0$ ($c = 0.32$ in $CHCl_3$); IR ($CHCl_3$) 2934, 2838, 1607, 1514, 1348, 1251, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (dd, $J = 6.4$, 8.4 Hz, 1H), 3.78 (s, 3H), 3.89 (dd, $J = 6.4$, 8.4 Hz, 1H), 4.06 (d, $J = 9$,6 Hz, 1H), 4.72 (m, 1H), 4.94 (s, 1H), 5.08 (s, 1H), 6.85 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 8.16 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz) δ 53.8, 55.3, 69.0, 77.8, 95.7, 114.6, 123.7, 129.2, 129.2, 131.7, 146.6, 149.8, 159.0; MS (CI, NH_3) *m*/*z*: 333 $[M + NH_4]^+$, 242 (100). HRMS (CI). Calcd for $[M + H]^+$: 316.1184. Found: 316.1179. ee = 98.0% (HPLC: Chiralcel OD, 5% 2-propanol in hexane, 0.5 mL/min, (*S*,*S*) isomer 40.91 min, (*R*,*R*) isomer 44.14 min).

(4*R*)-[(4-Methoxyphenyl)-(*R*)-(4-chlorophenyl)methyl]-1,3-dioxolane (2f). A solution of enantiomerically enriched (80% ee) (2*S*,3*S*)-**1f** (0.080 g, 0.263 mmol) in anhydrous CH_2Cl_2 (2.6 mL) and $BF_3{\cdot}Et_2O$ (0.01 mL, 0.079 mmol) under N_2 was stirred for 5 min at −20 °C. The reaction mixture was treated as described for **2a**, and the crude product was purified by column chromatography using hexane:ether (47:3) as the eluent to give **2f** (0.035 g, 44%) as an oil: $[\alpha]_D^{20} = -2.0$ ($c = 0.5$ in $CHCl_3$); IR ($CHCl_3$) 2934, 2837, 1512, 1252, 1090, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.56 (dd, $J = 6.4$, 8.4 Hz, 1H), 3.77 (s, 3H), 3.87 (dd, $J = 6.4$, 8.4 Hz, 1H), 3.94 (d, $J = 9.6$ Hz, 1H), 4.66 (m, 1H), 4.93 (s, 1H), 5.05 (s, 1H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.12 (d, $J = 8.8$ Hz, 2H), 7.27 (s, 4H); ^{13}C NMR (100 MHz) δ 53.2, 55.2, 69.0, 78.1, 95.6, 114.3, 128.6, 129.1, 129.6, 132.4, 132.9, 140.7, 158.6; MS (CI, NH_3) *m*/*z* 322 $[M + NH_4]^+$, 231 (100%). HRMS (CI). Calcd for $[M]^+$: 304.0866. Found: 304.0866. ee = 85% (HPLC: Chiralcel ODH, 5% 2-propanol in hexane, flux 0.5 mL/min, (*S*,*S*) isomer 16.71 min, (*R*,*R*) isomer 18.17 min).

(2*S*,3*S*)-3-Phenyl-2-((3,5-dimethoxy)benzyloxymethyl)oxirane (4a). A solution of (2*S*,3*S*)-2,3-epoxy-3-phenylpropan-1-ol (1.5 g, 10 mmol) in DMF (5 mL) was added via cannula to a suspension of sodium hydride (0.42 g, 10.5 mmol) in DMF (20 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and 3,5-dimethoxybenzyl bromide (2.55 g, 10.5 mmol) in DMF (10 mL) was added via cannula to the mixture. After 3 h of stirring at −20 °C and 4 h of stirring at 0 °C, the reaction mixture was treated as described for **1a**. The residual oil was purified by column chromatography using hexane:ether (96:4) as eluent to give **4a** (1.5 g, 50%): $[\alpha]_D^{20} = -27.0$ ($c = 0.98$ in $CHCl_3$); IR ($CHCl_3$) 2999, 2939, 2839, 1598, 1462, 835, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (m, 1H), 3.61 (dd, $J = 5.2$, 11.6 Hz, 1H), 3.78 (s, 6H), 3.85 (dd, $J = 2.8$, 11.6 Hz, 1H), 4.56 (d, $J = 5.2$ Hz, 1H), 6.39 (t, $J = 2.4$ Hz, 1H), 6.53 (d, $J = 2.4$ Hz, 2H), 7.25−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 55.9, 61.1, 69.9, 73.3, 99.8, 105.4, 125.7, 128.2, 128.5, 136.8, 140.2, 160.9; MS (CI, NH_3) *m*/*z* 318 $[M + NH_4]^+$, 301 $[M]^+$. HRMS (CI). Calcd for $(M)^+$: 300.1362. Found: 300.1359.

(2*S*,3*S*)-3-(4-(Trifluoromethyl)phenyl)-2-((3,5-dimethoxy)benzyloxymethyl)oxirane (4b). A solution of (2*S*,3*S*)-2,3-epoxy-3-(4-(trifluoromethyl)phenyl)propan1-ol (0.23 g, 1.09 mmol) in DMF (5 mL) was added via cannula to a suspension of sodium hydride (0.046 g, 1.15 mmol) in DMF (5 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and 3,5-dimethoxybenzyl bromide (0.28 g, 1.15 mmol) in DMF (3 mL) was added via cannula to the mixture. After 6 h of stirring at −20 °C, the reaction mixture was treated as described for **1a**. The residual oil was purified by column chromatography using hexane:ether (48:2) to give **4b** (0.319 g, 79%) as an oil: $[\alpha]_D^{20} = -19.0$ ($c = 0.6$ in $CHCl_3$); IR ($CHCl_3$) 2940, 2841, 1598, 1326, 1206, 1067, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.21 (m, 1H), 3.66 (dd, $J = 5.2$, 11.6 Hz, 1H), 3.79 (s, 6H), 3.83 (d, $J = 3.2$ Hz, 1H), 3.85 (d, $J = 2.8$ Hz, 1H), 4.56 (d, $J = 4.0$ Hz, 2H), 6.40 (t, $J = 2.0$ Hz, 1H), 6.52 (d, $J = 2.4$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H), 7.59 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 55.3, 61.5, 69.5, 73.4, 99.8, 105.5, 125.5 (q, $J = 3.8$ Hz), 125.9, 140.1, 141.1, 161.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0 (s, CF_3); MS (CI, NH_3) *m*/*z* 386 $[M + NH_4]^+$, 369 $[M + H]^+$. HRMS (CI). Calcd for $(M)^+$: 368.1235. Found: 368.1225.

(2*S*,3*S*)-3-(4-Chlorophenyl)-2-((3,5-dimethoxy)benzyloxymethyl)oxirane (4c). A solution of (2*S*,3*S*)-2,3-epoxy-3-(chlorophenyl)propan-1-ol (0.201 g, 1.09 mmol) in DMF (5 mL) was added via cannula to a suspension of sodium hydride (0.046 g, 1.15 mmol) in DMF (5 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and 3,5-dimethoxybenzyl bromide (0.28 g, 1.15 mmol) in DMF (3 mL) was added via cannula to the mixture. After 6 h of stirring at −20 °C, the reaction mixture was treated as described for **1a**. The residual oil was purified by column chromatography using hexane:ether (48:2) to give **4c** (0.25 g, 68%) as an oil: $[\alpha]_D^{20} = -26.0$ ($c = 1.25$ in $CHCl_3$); IR ($CHCl_3$) 2939, 2838, 1598, 1458, 1205, 1157, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.19 (m, 1H), 3.62 (dd, $J = 4.8$, 11.4 Hz, 1H), 3.76 (d, $J = 1.6$ Hz, 1H), 3.79 (s, 6H), 3.82 (dd, $J = 3.2$, 11.6 Hz, 1H), 4.55 (d, $J = 4.8$ Hz, 2H), 6.39 (t, $J = 2.4$ Hz, 1H), 6.52 (d, $J = 2.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 55.3, 61.2, 69.6, 73.4, 99.8, 105.4, 127.0, 128.7, 134.0, 135.4, 140.1, 160.9; MS (CI, NH_3) *m*/*z* 352 $[M + NH_4]^+$, 335 $[M + H]^+$. HRMS (CI). Calcd for $(M + H)^+$: 335.1050. Found: 335.1047.

(2*S*,3*S*)-3-Biphenyl-2-((3,5-dimethoxy)benzyloxymethyl)oxirane (4d). A solution of (2*S*,3*S*)-2,3-epoxy-3-(biphenyl)propan-1-ol (0.238 g, 1.05 mmol) in DMF (5 mL) was added via cannula to a suspension of sodium hydride (0.044 g, 1.10 mmol) in DMF (5 mL) at −20 °C under N_2. The mixture was stirred for 20 min, and 3,5-dimethoxybenzyl bromide (0.27 g, 1.10 mmol) in DMF (3 mL) was added via cannula to the mixture. After 5 h of stirring at −20 °C, the reaction mixture was treated as described for **1a**. The residual oil was purified by column chromatography using hexane: ether (48:2) to give **4d** (0.24 g, 61%) as an oil: $[\alpha]_D^{20} = -24.5$ ($c = 1.0$ in $CHCl_3$); IR ($CHCl_3$) 2938, 2838, 1598, 1458, 1205, 1156, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.29 (m, 1H), 3.64 (dd, $J = 5.2$, 11.4 Hz, 1H), 3.79 (s, 6H), 3.83 (d, $J = 2.0$ Hz, 1H), 3.86 (dd, $J = 2.8$, 11.4 Hz, 1H), 4.57 (d, $J = 4.8$ Hz, 2H), 6.40 (t, $J = 2.4$ Hz, 1H), 6.54 (d, $J = 2.0$ Hz, 2H), 7.35 (t, $J = 7.4$ Hz, 3H), 7.43 (t, $J = 8.0$ Hz, 2H), 7.56 (d, $J = 6.8$ Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 55.7, 61.2, 69.9, 73.3, 99.8, 105.4, 126.2, 127.0, 127.2, 127.4, 128.8, 135.9, 140.3, 140.6, 141.3, 160.9; MS (CI, NH_3) *m*/*z* 394 $[M + NH_4]^+$, 377 $[M + H]^+$, 359. HRMS (CI). Calcd for $[M + H]^+$: 377.1752. Found: 377.1746.

(4*R*,5*S*)-1,3,4,5-Tetrahydro-6,8-dimethoxy-5-phenylbenz[*c*]-oxepin-4-ol (5a). A solution of enantiomerically pure (ee > 99%) (2*S*,3*S*)-**4a** (0.104 g, 0.346 mmol) in anhydrous CH_2Cl_2 (3.5 mL) and $BF_3{\cdot}Et_2O$ (0.013 mL, 0.104 mmol) under N_2 was stirred for 15 min at −78 °C. The reaction mixture was treated as described for **2a**, and the crude product was purified by column chromatography using hexane:AcOEt (9:1/8:2) as the eluent to give **5a** (0.088 g, 80%) as a white solid: mp113−114 °C; $[\alpha]_D^{20} = -29.6$ ($c = 1.0$ in $CHCl_3$); IR ($CHCl_3$) 3440, 2940, 2839, 1606, 1492, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (d, $J = 10.4$ Hz, 1H), 3.65 (d, $J = 12.8$ Hz,), 3.72 (s, 3H), 3.77 (d, $J = 2.4$ Hz), 3.84 (s, 3H), 3.95 (dd, $J = 3.2$, 12.6 Hz), 4.39 (m, 1H), 4.51 (d, $J = 13.6$ Hz, 2H), 5.37 (d, $J = 6.0$ Hz, 1H), 6.40 (d, $J = 2.4$ Hz, 1H), 6.49 (d, $J = 2.4$ Hz, 1H), 7.0 (dd, $J = 1.6$, 8.2 Hz, 2H), 7.17 (t, $J = 7.2$ Hz, 1H), 7.26 (m, 2H); ^{13}C NMR (100 MHz) δ 46.1, 55.3, 56.0, 71.5, 73.2, 75.9, 98.2, 106.1, 117.4, 126.1, 127.6, 128.5, 139.9, 142.2, 159.5, 160.5; MS (CI, CH_4) *m*/*z* 318 $[M + NH_4]^+$; 301 $[M + H]^+$, 283 $[M + H - H_2O]^+$. HRMS (CI). Calcd for $[M + H]^+$:

301.1439. Found: 301.1435. ee > 99% (HPLC: Chiralcel OD-R, 30% H_2O in methanol, 0.5 mL/min, (4*R*,5*S*) isomer 37.30 min, (4*S*,5*R*) isomer 44.48 min).

(4*R*,5*S*)-5-[4-(Trifluoromethyl)phenyl]-1,3,4,5-tetrahydro-6,8-dimethoxybenz[*c*]oxepin-4-ol (5b). A solution of enantiomerically pure (ee 96%) (2*S*,3*S*)-**4b** (0.050 g, 0.136 mmol) in anhydrous CH_2Cl_2 (1.4 mL) and $BF_3{\cdot}Et_2O$ (0.005 mL, 0.040 mmol) under N_2 was stirred for 15 min at −78 °C. The reaction mixture was treated as described for **2a**, and the crude product was purified by column chromatography using hexane:AcOEt (9:1/8:2) as the eluent to give **5b** (0.007 g, 14%) as an oil: $[\alpha]_D^{20} = +19.0$ ($c = 0.1$ in $CHCl_3$); IR ($CHCl_3$) 3446, 2942, 2842, 1607, 1326, 1116, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (d, $J = 10.8$ Hz, 1H), 3.60 (d, $J = 12.8$ Hz, 1 H), 3.74 (s, 3H), 3.85 (s, 3H), 3.97 (dd, $J = 2.8$, 12.4 Hz, 1 H), 4.41 (d, $J = 14.0$ Hz, 1H), 4.43 (m, 1H), 4.59 (d, $J = 14.0$ Hz, 1H), 5.40 (d, $J = 6.0$ Hz, 1H), 6.42 (d, $J = 2.4$ Hz, 1H), 6.50 (d, $J = 2.8$ Hz, 1H), 7.13 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz) δ 46.2, 55.3, 56.0, 71.5, 73.2, 75.9, 98.3, 106.2, 116.5, 125.6 (t, $J = 3.8$ Hz), 128.1, 142.1, 144.3, 159.9, 160.5; ^{19}F NMR (376 MHz) δ −62.9; MS (CI, NH_3) *m*/*z* 386 $(M + NH_4)^+$, 369 $(M + H)^+$, 350. Anal. Calcd for $C_{19}H_{19}F_3O_4$: C, 61.95; H, 5.20. Found: C, 61.88; H, 5.33. ee 96% (HPLC: Chiralcel OD, 5% ethanol: 95% hexane: 2% TFA, 0.5 mL/min, (4*R*,5*S*) isomer 36.43 min, (4*S*,5*R*) isomer 56.29 min).

(4*R*,5*S*)-5-(4-Chlorophenyl)-1,3,4,5-tetrahydro-6,8-dimethoxybenzo[*c*]oxepin-4-ol (5c). A solution of enantiomerically enriched (ee 80%) (2*S*,3*S*)-**4c** (0.050 g, 0.149 mmol) in anhydrous CH_2Cl_2 (1.5 mL) and $BF_3{\cdot}Et_2O$ (0.006 mL, 0.045 mmol) under N_2 was stirred for 15 min at −78 °C. The reaction mixture was treated as described for **2a**, and the crude product was purified by column chromatography using hexane:AcOEt (9:1/8:2) as the eluent to give **5c** (0.030 g, 60%) as a white solid: mp = 129−130 °C; $[\alpha]_D^{20} = +12.6$ ($c = 0.5$ in $CHCl_3$); IR ($CHCl_3$) 3446, 2939, 2838, 1606, 1490, 1153, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (d, $J = 10.8$ Hz, 1H), 3.63 (d, $J = 12.8$ Hz, 1 H), 3.74 (s, 3H), 3.85 (s, 3H), 3.96 (dd, $J = 3.2$, 12.4 Hz, 1H), 4.34 (m, 1H), 4.43 (d, $J = 13.6$ Hz, 1H), 4.57 (d, $J = 13.6$ Hz, 1H), 5.31 (d, $J = 5.6$ Hz, 1H), 6.41 (d, $J = 2.4$ Hz, 1H), 6.49 (d, $J = 2.4$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 2H), 7.24 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz) δ 45.7, 55.3, 56.0, 71.5, 73.2, 75.9, 98.3, 106.1, 116.9, 128.7, 129.1, 132.0, 138.5, 142.1, 159.7, 160.5; MS (CI, NH_3) *m*/*z* 352 $(M + NH_4)^+$, 335 $(M)^+$, 317 $(M - H_2O)^+$. Anal. Calcd for $C_{18}H_{19}ClO_4$: C, 64.57; H, 5.72. Found: C, 64.31; H, 5.74. ee 80% (HPLC: Chiralcel OD, 5% ethanol: 95% hexane: 2% TFA, 0.5 mL/min, (4*R*,5*S*) isomer 35.04 min, (4*S*,5*R*) isomer 53.33 min).

(4*R*,5*S*)-5-(4-Biphenyl)-1,3,4,5-tetrahydro-6,8-dimethoxybenzo[*c*]oxepin-4-ol (5d). A solution of enantiomerically enriched (ee 78%) (2*S*,3*S*)-**4d** (0.05 g, 0.133 mmol) in anhydrous CH_2Cl_2 (1.3 mL) and $BF_3{\cdot}Et_2O$ (0.005 mL, 0.040 mmol) under N_2 was stirred for 15 min at −78 °C. The reaction mixture was treated as described for **2a**, and the crude product was purified by column chromatography using hexane:AcOEt (9:1/8:2) as the eluent to give **5d** (0.030 g, 60%) as a white solid: mp = 163−164 °C; $[\alpha]_D^{20} = -18.0$ ($c = 0.4$ in $CHCl_3$); IR ($CHCl_3$) 3446, 2937, 1606, 1487, 1201, 1153, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (d, $J = 11.2$ Hz, 1H), 3.73 (d, $J = 12.4$ Hz, 0.5 H), 3.73 (s, 3H), 3.86 (s, 3H), 3.99 (dd, $J = 2.8$, 12.4 Hz, 1H), 4.43 (m, 1H), 4.55 (d, $J = 9.2$ Hz, 2H), 5.42 (d, $J = 6.0$ Hz, 1H), 6.43 (d, $J = 2.4$ Hz, 1H), 6.52 (d, $J = 2.8$ Hz, 1H), 7.08 (d, $J = 8.0$ Hz, 2H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.42 (t, $J = 8.0$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.55 (dd, $J = 1.6$, 8.4 Hz, 2H); ^{13}C NMR (100 MHz) δ 45.9, 55.4, 56.1, 71.6, 73.3, 76.0, 98.3, 106.2, 117.4, 126.9, 127.2, 127.3, 128.1, 128.8, 139.0, 139.1, 140.7, 142.3, 159.6, 160.6; MS (CI, NH_3) *m*/*z* 394 $(M + NH_4)^+$, 377 $(M + H)^+$, 359 $(M - H_2O)^+$. Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.23; H, 6.46. ee 80% (HPLC: Chiralcel OD, 5% ethanol: 95% hexane: 2% TFA, 0.5 mL/min, (4*R*,5*S*) isomer 44.91 min, (4*S*,5*R*) isomer 57.59 min).

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Supporting Information Available: ^{13}C NMR spectra of **1a**,**d**,**e**, **2b**,**c**,**e**,**f**, **4a**−**d**, and **5a**−**d**, X-ray crystal structure of **3a** and **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data corresponding to the structural analysis of **3a** and **5a** have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 259178 and 259179. These data can be obtained online (http://www.ccdc.cam.ac.uk) free of charge (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: (+44) 1223−336−033; e-mail: deposit@ccdc.cam.ac.uk).

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