JOC Article

Suzuki Cross-Coupling on Enantiomerically Pure Epoxides: Efficient Synthesis of Diverse, Modular Amino Alcohols from Single Enantiopure Precursors

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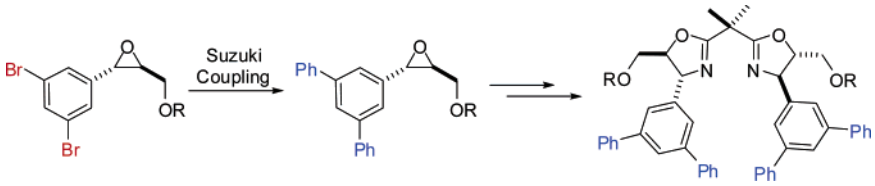

Suzuki arylation of enantiopure (4-bromophenyl)- or (3,5-dibromophenyl)glycidyl ethers has been achieved in toluene under Buchwald conditions [$ArB(OH)_2$ (1.1 equiv), Cs_2CO_3 (2 equiv), $Pd_2(dba)_3 \cdot C_6H_6$ (1 mol %), S-Phos (4 mol %), toluene, 100 °C] allowing for the formation of modular arylglycidyl ethers not directly available in enantiopure form by epoxidation routes. These bulky ethers, when submitted to regioselective and stereospecific ring opening with ammonia [aq NH_3, $LiClO_4$ (1 equiv), THF, microwave irradiation (80 W), 125 °C] in a sealed tube, provide access to novel enantiopure β-amino alcohols which, in turn, provide an easy access to structurally complex C_2 symmetrical bisoxazolines.

Introduction

β-Amino alcohols[1] play a very important role in asymmetric catalysis.[2] They can be directly used as ligands in a wide range of enantioselective reactions including transfer hydrogenation[3] and organozinc additions to aldehydes,[4] and in addition to that, they are also very useful synthons for the construction of more elaborated ligands, such as oxazolines,[5] oxazaborolidines,[6] and chiral NHCs.[7] The amino alcohols employed with these purposes have been obtained in many instances from the chiral pool, but this poses a limit to the possible structural variations in the ligands. To circumvent this limitation, we have introduced new families of β-amino alcohols derived from enantiopure epoxides such as **A**[8] and **B**[9] (Figure 1), readily available in both enantiomeric forms through well-established procedures, such as the Sharpless[10] and the Jacobsen[11] epoxidations.

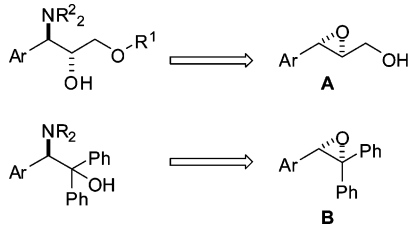

FIGURE 1. Modular amino alcohols derived from enantiopure epoxides.

The amino alcohols obtained from **A** offer three different sites for structural modification, allowing for a fine-tuning of the

[†] ICIQ.
[‡] ICIQ and UB.

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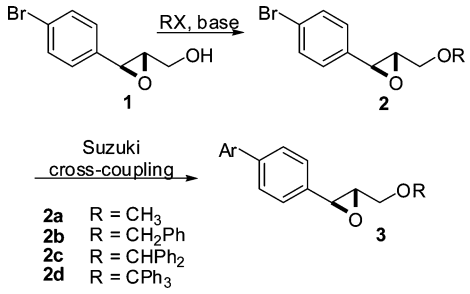
SCHEME 1. Synthesis of Structurally Complex Epoxides 3 from *p*-Bromophenylglycidol 1



electronic and steric properties of the ligand. With these tools in hand, we have succeeded in designing very efficient ligands for asymmetric diethylzinc additions on benzaldehyde,[8,12] reduction,[13] or transfer hydrogenation[14] of ketones or allylic nucleophilic substitutions.[15] However, whereas the modulations of the amino (NR^2_2) and ether (OR^1) moieties from a single phenylglycidol precursor can be readily performed, difficulties are met in varying the skeletal aryl group since it requires going back to the epoxidation step and its enantioselectivity is substrate-dependent. Here, we report the straightforward synthesis of a large variety of enantiopure epoxides featuring a modular 4-biphenyl or terphenyl (3,5-diphenylphenyl) moiety via the unprecedented Suzuki cross-coupling of enantiopure haloaryl glycidols obtained through Sharpless epoxidation and their easy derivatization into new optically pure β-amino alcohols and bis(oxazolines).

Results and Discussion

The variation of the aryl group in the family **A** of enantiopure epoxides employed as precursors for modular ligands was so far limited to the phenyl,[8] naphthyl,[15] and mesityl groups.[16] Attempts have been made to synthesize epoxides of type **A** featuring biphenyl groups, but the success of the Sharpless epoxidation was limited by low solubilities of the biaryl-containing starting and final compounds, which made scale-up difficult. To circumvent this problem, we decided to access the biaryl framework via Suzuki cross-coupling on preformed, enantiopure haloaryl glycidols. According to our plan, epoxides **3** would be obtained via a Suzuki cross-coupling on the protected Sharpless epoxides **2** (Scheme 1).

To date, Suzuki chemistry on substrates that possess epoxide functionalities has remained practically unexplored and has restricted to substrates containing unreactive epoxides.[17] The most probable reason is that these reactions are usually carried out in alcohols or water at high temperatures, conditions in which a reactive epoxide (terminal, vinyl substituted or aryl substituted) would be quickly hydrolyzed. It was thus necessary to find reaction conditions that would be compatible with this function, and the methodologies described by Fu[18] and Buchwald[19] were chosen as candidates to this end.

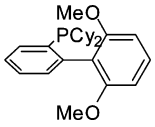
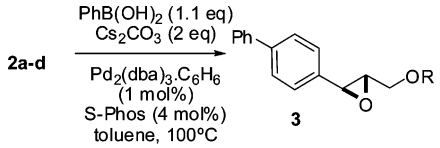


FIGURE 2. S-Phos ligand.

TABLE 1. Suzuki Phenylation of Epoxyethers 2



starting epoxide	R	product (yield, %)[a]
2a	CH_3	**3aa** (72)
2b	CH_2Ph	**3ba** (83)
2c	$CHPh_2$	**3ca** (70)
2d	CPh_3	**3da** (73)

[a] Isolated yield after flash chromatography.

Following Sharpless procedure, epoxide **1** could be obtained in fairly good yield (66%) and excellent optical purity (>99% ee) after a single recrystallization[20] and was readily converted into the protected enantiopure (4-bromophenyl)glycidols **2a**−**d**. To determine the optimal conditions for the arylations, Suzuki cross-couplings with phenylboronic acid were then carried out on epoxide **2b**, and both Fu's and Buchwald's methods yielded the epoxide **3ba**[21] with a high conversion. Notably, the diols arising from the hydrolysis of **2b** or **3ba** were not detected in the crude mixture. The best results were obtained with Buchwald's method, using 2% of palladium and 4% of S-Phos as the catalyst (Figure 2), in the presence of cesium carbonate in dry, degassed toluene at 100 °C over 3 h. The phenylation could be performed on all epoxides **2a**−**d**, affording the arylated epoxides **3aa**−**da** in good yield (70−83%) (Table 1).

The scope of the reaction was extended to various commercially available arylboronic acids displaying in their structures substituents with a variety of steric requirements as well as substituent groups with highly different electronic nature (Table 2). Interestingly, both a very electron-deficient boronic acid containing two trifluoromethyl groups (entry 1) and also electron-rich ones (entries 2 and 3) participate well in the reaction. In the same manner, *o*-monosubstituted and *o*,*o*′-

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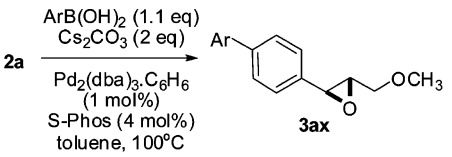
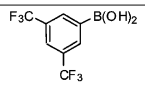
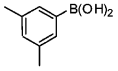
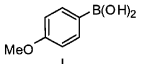
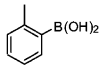
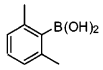
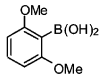
(21) The following nomenclature has been adopted: The first letter refers to the R group in the ether moiety and the second one to the aryl group in the epoxide skeleton.

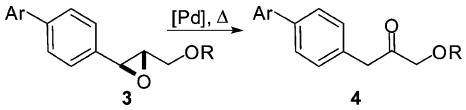
TABLE 2. Suzuki Arylation of Epoxide 2a with Different Arylboronic Acids



entry	arylboronic acid	reaction time (min)	product (yield [%][a])
1		60	**3ab** (84)
2		30	**3ac** (83)
3		100	**3ad** (80)
4		45	**3ae** (84)
5		60	**3af** (70)
6		75	**3ag** (97)

[a] Isolated yield after flash chromatography.

SCHEME 2. Palladium-Induced Rearrangement of Biaryl-Containing Epoxyethers 3



disubstituted aryl groups can also be incorporated to the epoxide molecule following this methodology (entries 4 and 5), and the reaction of the rather hindered 2,6-bis(methoxy)phenylboronic acid with **2a** yields the corresponding epoxide **3ag** in excellent yield.

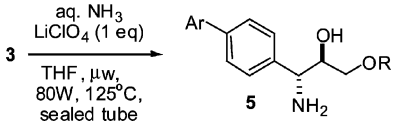
It is noteworthy that the arylation occurs cleanly, despite the relatively high reaction temperature. However, a careful monitoring of the reaction is necessary to avoid the formation of a side product arising from the isomerization of the final epoxide into the corresponding β-arylketone **4** via hydrogen migration (Scheme 2).[22] This palladium-catalyzed 1,2-H shift, which is very fast in the case of the electron-deficient biaryl-containing epoxide **3ab**, is not observed with electron-rich ones such as **3ag**.

The biaryl-containing epoxyethers **3** were next converted into the corresponding β-amino alcohols via ring opening with ammonia. This reaction was best performed with lithium perchlorate as the catalyst in a 1:1 mixture of aqueous ammonia and THF and under microwave irradiation (80 W, 125 °C, 45 min).[23] In this way, all of the epoxides could be ring-opened with good to excellent yields to afford highly pure amino alcohols **5** (Table 3).

This straightforward synthesis of biaryl-based enantiopure β-amino alcohols could then be extended to the formation of more complex and difficult to obtain structures, such as the terphenyl (3,5-diphenylphenyl)-based amino alcohols. Starting from ethyl 3,5-dibromobenzaldehyde, epoxide **6** was obtained in optically pure form (>99% ee) after olefination, reduction, Sharpless epoxidation, and recrystallizations (Scheme 3).

Following etherification of the alcohol, the Suzuki cross-coupling with arylboronic acids was carried out under Buchwald conditions as described above and provided epoxyethers **8** in good yields (Table 4). Also in this case, the phenylation occurs in high yield with the different ether groups. Either the very electron-deficient 3,5-bistrifluoromethylphenyl group (in **8ab**) or the very sterically demanding 2,6-dimethoxyphenyl group can be twice incorporated on **7a**, although the severe steric

TABLE 3. Microwave Assisted Formation of β-amino Alcohols 5 from Epoxides 3



epoxide	yield (%)[a]	epoxide	yield (%)[a]
3aa	95	**3ac**	83
3ba	76	**3ad**	91
3ca	92	**3ae**	96
3da	87	**3af**	68
3ab	93	**3ag**	97

[a] Isolated yield after flash chromatography.

SCHEME 3. Synthesis of Epoxide 6

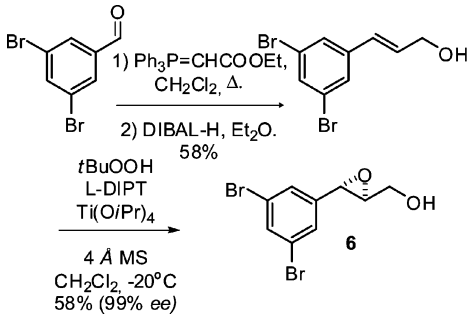
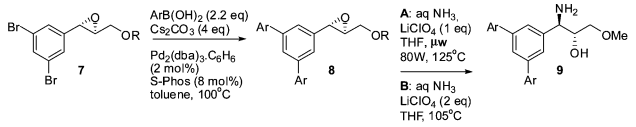
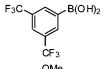


TABLE 4. Formation of β-Amino Alcohols 9 by Suzuki Arylation and Aminolysis



substrate	R	arylboronic acid	reaction time (h)	suzuki product (yield [%][a])	aminoalcohol (method, yield [%][a])
7a	CH_3		2	**8aa** (93)	**9aa** (**B**, 84)
7b	CH_2Ph		3	**8ba** (94)	**9ba** (**B**, 66)
7c	$CHPh_2$		3	**8ca** (68)	**9ca** (**B**, 71)
7d	CPh_3		3	**8da** (95)	**9da** (**A**, 37)[b]
7a	CH_3		2	**8ab** (81)	**9ab** (**A**, 96)
7a	CH_3		15	**8ag** (70)	**9ag** (**A**, 74)

[a] Isolated yield after flash chromatography. [b] The epoxide is recovered in 54% yield after flash chromatography.

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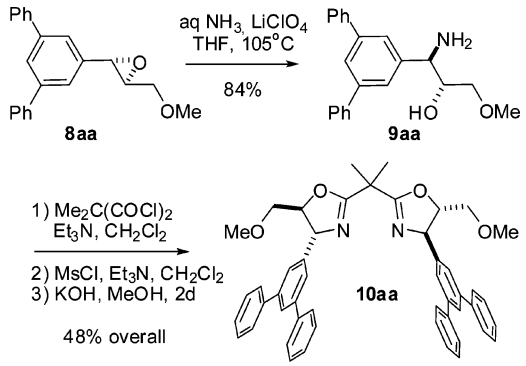
SCHEME 4. Synthesis of Bisoxazoline 10aa



hindrance provokes in the latter case the formation of significant amounts of 1,3-dimethoxybenzene, and the reaction only reaches 80% completion. The β-amino alcohols **9** were finally obtained by aminolysis of these epoxides, either under microwave irradiation or in an autoclave. It is noteworthy that the very bulky epoxide **8da** reacts much slower than the other ones, with only 40% being converted after 2.5 h at 125 °C.

As an example of the potential of this type of structures for catalytic applications, β-amino alcohol **9aa** was converted into bis(oxazoline) **10** (48% overall yield) by treatment with dimethylmalonyl chloride and subsequent cyclization using mesyl chloride and triethylamine (Scheme 4).

All the bisoxazolines derived from amino alcohols **5** and **9** might be synthesized by this way, although it is also possible to build the biaryl fragments at a later stage on preformed brominated bisoxazolines.[24] In any case, epoxides of type **A** (Scheme 1) are the precursors not only for bisoxazolines but also for a much wider range of potentially interesting enantiopure ligands obtained through ring opening of the oxirane by various nucleophiles.

Conclusion

In conclusion, we have developed conditions that allow one to carry out Suzuki cross-couplings on enantiomerically pure epoxides, allowing for the construction of highly modular bi- and teraryl moieties at a late stage in the synthesis of enantiopure β-amino alcohols. These amino alcohols can further be converted into second-generation ligands (oxazolines, oxazaborolidines, bisoxazolines, and pyridine bisoxazolines), which are difficult to obtain by other synthetic routes. These epoxides are also the ideal precursors for a wide range of chiral ligands obtained by ring opening with nucleophiles and whose catalytic applications are currently being investigated in our laboratories.

Experimental Section

General Procedure for the Synthesis of Epoxyethers 2a−c and 7a-c: Epoxide **1** or **6** (13 mmol) was dissolved in anhydrous DMF (20 mL), cooled to −20 °C, and added dropwise onto a suspension of sodium hydride (0.38 g, 15 mmol) in anhydrous DMF (20 mL). After the mixture was stirred for 1 h, the alkylating agent (15.7 mmol) dissolved in DMF (5 mL) was added dropwise. The temperature of the solution was slowly raised to rt, and the mixture was stirred overnight. Water was then carefully added, together with ether. The phases were separated, and the aqueous phase was back-extracted twice with ether. The combined organic phases were washed with water and brine and dried over magnesium sulfate. The products were purified by flash chromatography (hexanes/ethyl acetate 98/2).

Epoxyether 2a: This epoxyether was synthesized from **1** using methyl iodide as the alkylating agent. It was obtained as a colorless oil (97%). ^{1}H NMR (400 MHz): δ = 3.17 (m, 1 H), 3.46 (s, 3 H), 3.57 (dd, J = 5.0 and 11.5 Hz, 1 H), 3.77 (dd, J = 11.5 and 3.0 Hz, 2 H), 3.77 (m, 1 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.49 (d, J = 8.5 Hz, 2 H). ^{13}C NMR (100 MHz): δ = 55.2 (CH), 59.4 (CH_3), 61.1 (CH), 71.9 (CH_2), 122.1 (C), 127.4 (CH), 131.7 (CH), 136.0 (C). $[\alpha]^{20}_D$ −34.7 (*c* 1.51, $CHCl_3$). HRMS (ES+): calcd for $C_{10}H_{12}O_2Br$ (M + H), 243.0021; found, 243.0029.

Epoxyether 2d: Epoxyalcohol **1** (3.0 g, 13 mmol) was dissolved in DCM (15 mL). Triethylamine (5.5 mL, 39 mmol), DMAP (0.6 g, 5 mmol), and triphenylmethyl chloride (4.0 g, 14 mmol) were then added. The reaction mixture was stirred for 2 h at rt then refluxed for 3 h more. After cooling, the reaction mixture was taken in DCM, washed with brine, and dried over magnesium sulfate. It was recrystallized from hot hexanes to yield **2d** as a white solid (3.9 g, 63%). ^{1}H NMR (400 MHz): δ = 3.19 (m, 1 H), 3,30 (dd, J = 5.1 and 10.9 Hz, 1 H), 3.47 (dd, J = 10.9 and 3.1 Hz, 1 H), 3.78 (d, J = 2.0 Hz, 1 H), 7.16 (d, J = 8.5 Hz, 2 H), 7.27 (m, 3 H), 7.34 (m, 6 H), 7.50 (m, 8 H). ^{13}C NMR (100 MHz): δ = 55.5 (CH), 61.4 (CH), 63.9 (CH_2), 86.9 (C), 122.1 (C), 127.2 (CH), 127.4 (CH), 127.9 (CH), 128.7 (CH), 131.6 (CH), 136.3 (C), 143.7 (C). Mp 122−123 °C. $[\alpha]^{20}_D$ −32.9 (*c* 1.82, $CHCl_3$). HRMS (ES+): calcd for $C_{28}H_{23}O_2BrNa$ (M + Na), 493.0779; found, 493.0786.

General Procedure for the Suzuki Cross-Coupling on Epoxides 2: Epoxide **2** (1.0 mmol) was dissolved in anhydrous, degassed toluene (2 mL), and the resulting solution was added onto a mixture of arylboronic acid (1.1 mmol), cesium carbonate (0.67 g, 2 mmol), $Pd_2(dba)_3{\cdot}C_6H_6$ (10.2 mg, 0.01 mmol), and S-Phos (16.5 mg, 0.04 mmol) placed in a Schlenk tube under Ar. The mixture was stirred at 100 °C for 1−4 h and then cooled to rt. Ethyl acetate was added, and the mixture was filtered over a pad of Celite. After concentration, the epoxide (**3**) was purified by flash chromatography (hexanes/ethyl acetate 95/5).

Epoxyether 3aa: Reaction time: 3 h. Yield: 72%. ^{1}H NMR (400 MHz): δ = 3.28 (m, 1 H), 3.49 (s, 3 H), 3.60 (dd, J = 5.2 and 11.5 Hz, 1 H), 3.82 (dd, J = 3.2 and 11.5 Hz, 1 H), 3.86 (d, J = 2.1 Hz, 1 H), 7.37 (m, 3 H), 7.46 (m, 2 H), 7.60 (m, 4 H). ^{13}C NMR (100 MHz): δ = 55.6 (CH), 59.3 (CH_3), 61.0 (CH), 72.2 (CH_2), 126.2 (CH), 127.1 (CH), 127.3 (CH), 127.4 (CH), 128.8 (CH), 135.9 (C), 140.7 (C), 141.3 (C). Mp 56−57 °C. $[\alpha]^{20}_D$ −23.6 (*c* 0.99, $CHCl_3$). HRMS (ES+): calcd for $C_{16}H_{16}O_2Na$ (M + Na), 263.1048; found, 263.1057.

General Procedure for the Microwave Ring Opening of Epoxides with Ammonia: In a sealed microwave tube were placed epoxyether **3** (0.25 mmol), lithium perchlorate (26 mg, 0.25 mmol), ammonia (30 wt % in water, 2 mL), and THF (2 mL), and the mixture was heated to 125 °C in the microwave apparatus (maximum power = 80 W) under stirring for 45 min. After cooling, the mixture was taken in DCM and water, and the phases were separated. The aqueous phase was extracted twice with DCM, and the combined organic phases were washed with water and brine then dried over sodium sulfate. The compound was purified by flash chromatography (DCM/ethyl acetate 1/1 then DCM/MeOH 9/1).

Amino Alcohol 5aa: Yield: 95%. ^{1}H NMR (400 MHz): δ = 1.71 (br, 3 H), 3.38 (s, 3 H), 3.41 (d, J = 5.1 Hz, 2 H), 3.99 (q, J = 5.0 Hz, 1 H), 4.20 (d, J = 5.3 Hz, 1 H), 7.37 (m, 1 H), 7.45 (m, 4 H), 7.60 (m, 4 H). ^{13}C NMR (100 MHz): δ = 57.6 (CH), 59.2 (CH_3), 73.6 (CH), 73.6 (CH_2), 127.0 (CH), 127.2 (CH), 127.3 (CH), 127.5 (CH), 128.8 (CH), 140.8 (C), 141.2 (C) 1C missing. Mp 80−81 °C. $[\alpha]^{20}_D$ −36.4 (*c* 1.17, $CHCl_3$). HRMS (ES+): calcd for $C_{16}H_{20}NO_2$ (M + H), 258.1494; found, 258.1490.

(24) These results will be reported in due course.

Ethyl 3-(3,5-Dibromophenyl)propenoate: 3,5-Dibromobenzaldehyde (16 g, 60 mmol) was dissolved in DCM (50 mL) and added at 0 °C into a solution of carboethoxymethylene triphenylphosphorane (23.3 g, 67 mmol) in DCM (50 mL). The mixture was refluxed overnight then cooled to rt. After concentration, the residue was filtered over silica eluting with a 9:1 mixture of hexanes and ethyl acetate. The product was recrystallized from hot hexanes, yielding the cinnamyl ester as white needles (12.2 g, 60%). ^{1}H NMR (400 MHz): δ = 1.35 (t, J = 7.1 Hz, 3 H), 4.28 (q, J = 7.1 Hz, 2 H), 6.44 (d, J = 16.0 Hz, 1 H), 7.53 (d, J = 16.0 Hz, 1 H), 7.59 (d, J = 1.8 Hz, 1 H), 7.68 (t, J = 1.8 Hz, 2 H). ^{13}C NMR (100 MHz): δ = 14.3 (CH_3), 60.9 (CH_2), 121.2 (CH), 123.4 (C), 129.5 (CH), 135.2 (CH), 138.0 (C), 141.3 (CH), 166.1 (C).

3-(3,5-Dibromophenyl)prop-2-en-1-ol: To a solution of ethyl 3-(3,5-dibromophenyl)propenoate (12.2 g, 36.5 mmol) in anhydrous ether (50 mL) at 0 °C was added dropwise a solution of DIBALH (25 wt % in toluene, 53 mL, 80 mmol). Upon completion of the addition, the reaction mixture was allowed to warm to rt over 1 h and then carefully added to a stirred mixture of 2 N HCl and ice. Ethyl acetate was added, and the phases were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with water and brine. After drying over sodium sulfate, the solution was concentrated, yielding an off white solid which was used in the next step without purification (10.3 g, 96%). ^{1}H NMR (400 MHz): δ = 4.36 (dd, J = 1.4 and 5.1 Hz, 2 H), 6.38 (dt, J = 16.0 and 5.1 Hz, 1 H), 6.51 (dt, J = 16.0 and 1.4 Hz, 1 H), 7.45 (d, J = 1.8 Hz, 2 H), 7.54 (t, J = 1.8 Hz, 1 H). ^{13}C NMR (100 MHz): δ = 63.1 (CH_2), 123.1 (C), 127.8 (CH), 128.1 (CH), 131.7 (CH), 132.8 (CH), 140.4 (C).

(3,5-Dibromophenyl)glycidol 6: A dry flask equipped with an addition funnel was charged with 0.12 mL of L-DIPT and 40 mL of DCM. After the mixture was cooled to −20 °C, 1 g of activated 4 Å molecular sieves, 0.11 mL of Ti(O*i*Pr)$_4$, and 5.2 mL of *tert*-butylhydroperoxide in isooctane (3 M) were added sequentially. The mixture was stirred at −20 °C for 1 h. Freshly activated 3 Å molecular sieves (powder) were stirred with the cinnamyl alcohol in 8 mL of DCM for 1 h. The solution was then added dropwise over 1 h onto the previous mixture, and the sieves were rinsed with DCM (5 mL). After 3 h at −20 °C, the reaction was quenched by addition at −20 °C of a 10% NaOH solution saturated with sodium chloride (1 mL). Ether was added, and the mixture was allowed to warm to 10 °C. Then, $MgSO_4$ (0.8 g) and Celite (0.1 g) were added. After an additional 15 min of stirring, the mixture was allowed to settle, and the clear solution was filtered through a pad of Celite, washing with ethyl ether. Concentration yielded a white solid. It was dissolved in a minimum amount of ethyl acetate, filtered through a short pad of silica gel with ethyl acetate, and recrystallized from hexane (insoluble, ca. 30 mL)/ethyl acetate (soluble, ca. 6 mL), to give a white solid. The epoxide was recrystallized once again from hexanes (20 mL)/ethyl acetate (5 mL), yielding pure white crystals (58% yield, 99% ee). ^{1}H NMR (400 MHz): δ = 1.82 (dd, J = 8.0 and 5.3 Hz, 1 H), 3.16 (m, 1 H), 3.84 (ddd, J = 3.5, 8.0, and 13.0 Hz, 1 H), 3.91 (d, J = 2.1 Hz, 1 H), 4.06 (ddd, J = 2.3, 5.3, and 13.0 Hz, 1 H), 7.39 (d, J = 2.0 Hz, 2 H), 7.62 (t, J = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz): δ = 53.9 (CH), 60.7 (CH_2), 62.6 (CH), 123.2 (C), 127.5 (CH), 133.9 (CH), 141.0 (C). Mp 88−89 °C. $[\alpha]^{20}_D$ −34.7 (c 1.51, $CHCl_3$). HRMS: calcd for $C_9H_7O_2Br_2$, 304.8813; found, 304.8808. The enantiomeric excess was determined by HPLC: Chiralcel OD-H column, hexane/IPA 98/2, 1 mL/min, detection at 215 nm, t_R (minor) = 27.3 min (*R*,*R*), t_R (major) = 29.9 min (*S*,*S*), ee = 99%.

General Procedure for the Suzuki Cross-Coupling on Epoxides 7: Epoxide **7** (1.0 mmol) was dissolved in anhydrous, degassed toluene (2 mL), and the resulting solution was added onto a mixture of arylboronic acid (2.2 mmol), cesium carbonate (1.34 g, 4 mmol), $Pd_2(dba)_3{\cdot}C_6H_6$ (20.4 mg, 0.02 mmol), and S-Phos (33.0 mg, 0.08 mmol) placed in a Schlenk tube under Ar. The mixture was stirred at 100 °C for 2−15 h and then cooled to rt. Ethyl acetate was added, and the mixture was filtered over a pad of Celite. After concentration, the epoxide (**3**) was purified by flash chromatography (hexanes/ethyl acetate 95/5).

Epoxyether 8aa: Reaction time: 2 h. Yield: 93%. ^{1}H NMR (400 MHz): δ = 3.33 (m, 1 H), 3.50 (s, 3 H), 3.62 (dd, J = 5.1 and 11.5 Hz, 1 H), 3.85 (dd, J = 3.0 and 11.5 Hz, 1 H), 3.97 (d, J = 2.1 Hz, 1 H), 7.41 (m, 2 H), 7.50 (m, 4 H), 7.51 (d, J = 1.7 Hz, 2 H), 7.66 (m, 4 H), 7.77 (t, J = 1.7 Hz, 1 H). ^{13}C NMR (100 MHz): δ = 55.8 (CH), 59.4 (CH_3), 61.1 (CH), 72.1 (CH_2), 123.4 (CH), 126.1 (CH), 127.3 (CH), 127.6 (CH), 128.9 (CH), 138.1 (C), 140.7 (C), 142.2 (C). Mp 80−81 °C. $[\alpha]^{20}_D$ −38.9 (c 0.90, $CHCl_3$). HRMS: calcd for $C_{22}H_{20}O_2Na$, 339.1361; found, 339.1361.

General Procedure for the Ring Opening of Epoxides with Ammonia (Method B): In a 25 mL autoclave were placed epoxyether **3** (2.3 mmol), lithium perchlorate (0.50 g, 4.7 mmol), ammonia (30 wt % in water, 10 mL), and THF (5 mL), and the mixture was heated to 125 °C under stirring for 16 h. After cooling, the mixture was taken in DCM and water, and the phases were separated. The aqueous phase was extracted twice with DCM, and the combined organic phases were washed with water and brine and then dried over sodium sulfate. The compound was purified by flash chromatography (DCM/ethyl acetate 1/1 then DCM/MeOH 9/1).

Amino Alcohol 9aa: Method B. Yield: 84%. ^{1}H NMR (400 MHz): δ = 1.97 (br, 3 H), 3.38 (s, 3 H), 3.46 (m, 2 H), 4.06 (q, J = 5.1 Hz, 1 H), 4.31 (d, J = 5.1 Hz, 1 H), 7.39 (m, 2 H), 7.49 (m, 4 H), 7.61 (d, J = 1.7 Hz, 2 H), 7.68 (m, 4 H), 7.76 (t, J = 1.7 Hz, 1 H). ^{13}C NMR (100 MHz): δ = 58.1 (CH), 59.2 (CH_3), 73.6 (CH_2), 73.7 (CH), 125.0 (CH), 125.3 (CH), 127.3 (CH), 127.5 (CH), 128.8 (CH), 140.98 (C), 141.01 (C), 142.0 (C). Mp 120−121 °C. $[\alpha]^{20}_D$ −18.4 (c 0.83, $CHCl_3$). HRMS: calcd for $C_{22}H_{24}O_2N$, 334.1807; found, 334.1817.

Bisoxazoline 10: Amino alcohol **9aa** (0.764 g, 2.3 mmol) was dissolved in DCM (2 mL) and cooled to 0 °C. Triethylamine (0.36 mL, 2.5 mmol) and then a solution of dimethylmalonyl dichloride (0.15 mL, 1.15 mmol) in DCM (2 mL) were added. The mixture was stirred for 20 h at rt. The reaction mixture was diluted with DCM, then washed with 10% HCl (twice), saturated $NaHCO_3$, and brine. The solution was dried over sodium sulfate and concentrated, yielding a yellow foam, which was used in the next step without further purification. Methanesulfonyl chloride (0.20 mL, 2.5 mmol) was added dropwise onto a solution of the crude bis(amide) and triethylamine (0.71 mL, 5.0 mmol) in DCM (5 mL) at 0 °C. The solution was stirred for 2 h at rt, then the reaction mixture was poured into a saturated NH_4Cl solution. The phases were separated, and the aqueous layer was extracted with DCM. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated. The crude bis(mesylate) was then treated over 70 h with a 5 wt % solution of potassium hydroxide in methanol (25 mL). DCM and water were added, and the phases were separated. The aqueous layer was extracted twice with DCM, and the combined organic phases were washed with brine and dried over sodium sulfate. After concentration, it was purified by flash chromatography (hexane/AcOEt 100/0 to 70/30), yielding an oil. A white foam was obtained after addition of toluene and concentration. ^{1}H NMR (400 MHz): δ = 1.77 (s, 6 H), 3.41 (s, 6 H), 3.55 (m, 4 H), 4.59 (q, J = 5.4 Hz, 2 H), 5.10 (d, J = 5.9 Hz, 2 H), 7.35 (m, 4 H), 7.42 (m, 8 H), 7.49 (d, J = 1.7 Hz, 4 H), 7.62 (m, 8 H), 7.72 (t, J = 1.7 Hz, 2 H). ^{13}C NMR (100 MHz): δ = 24.3 (CH_3), 39.0 (C), 59.5 (CH_3), 72.0 (CH), 73.4 (CH_2), 86.2 (CH), 124.5 (CH), 125.5 (CH), 127.3 (CH), 127.4 (CH), 128.8 (CH), 141.1 (C), 142.2 (C), 143.3 (C), 169.9 (C). Mp 71−72 °C. $[\alpha]^{20}_D$ 173.5 (c 2.31, $CHCl_3$). HRMS: calcd for $C_{49}H_{47}O_4N_2$, 727.3536; found, 727.3522.

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Supporting Information Available: Experimental procedures for the synthesis of **2b,c**, **3ba**−**3ag**, **5ba**−**5ag**, **7a**−**d**, **8ba**−**8ag**, and **9ba**−**9ag**. Spectroscopic data and copies of ^{1}H, ^{13}C, and IR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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