Integrated Chemical Process: Convenient Synthesis of Enantiopure 2-Hydroxymethyl-1,4-benzodioxane Derivatives Under Iterative Catalysis of CsF

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Abstract: One-pot processes to enantiopure 2-hydroxymethyl-1,4-benzodioxane derivatives have been established under catalysis of CsF. A sequence of *O*-alkylation of catechols with enantiopure 3-chloro-1,2-propanediol, tosylation of the alcohol, deprotection of the benzyl ether, and intramolecular etherification can be integrated. The *O*-alkylation is also feasible with enantiopure oxiranes. All reactions, except debenzylation, are catalyzed by a single catalyst, CsF. The hydrogenative deprotection of the benzyl ether with Pd-C is compatible with the CsF-catalyzed reactions. The integrated protocols give rise not only to compaction of the whole processes but also to increases in overall yields.

Introduction

"Integrated chemical process" is a concept for the one-pot realization of sequential reactions.[1] According to this concept, reaction conditions that are compatible with all relevant reactions are determined first of all, and the respective reactions are then optimized within the framework of these conditions. We have already proved the versatility of this concept with various examples. However, besides the connectivity of different reactions, the utility would be further heightened if the consecutive reactions could be driven by the iterative use of a single catalyst. This is indeed the case as disclosed here for the synthesis of 2-hydroxymethyl-1,4-benzodioxane derivatives by use of CsF.

The 2-substituted 1,4-benzodioxane skeleton plays an important role in adrenoreceptor antagonists.[2] Constructions of this skeleton mostly have recourse to 2-hydroxymethyl-1,4-benzodioxane as a key building block. Of more significance is the dependence of the pharmacological activities on the chirality of the 2-substituted 1,4-benzodioxane unit.[3] The first enantiomerically enriched compounds in this category were prepared by the coupling of catechol with (*R*)-glyceraldehyde.[4] It was revealed that the *S*-enantiomers of 2-alkylaminomethyl-1,4-benzodioxanes were more potent than the *R*-counterparts as antagonists.[5] Later, glycidol,[6] epichlorohydrin,[7] and glycidyl tosylate[8] were used as chiral sources. These procedures, however, are rather lengthy and strong basic conditions are employed for reaction of the chiral units with catechol and the subsequent intramolecular etherification. As a result, the yields are not always satisfactory and the enantiopurity decreases to some extent (vide infra).

In the above protocols, catechol itself was coupled with chiral C_3 building blocks. More recently, it was found that incorporation of a methyl[9] or allyl[10] group at the 8-position of the 1,4-benzodioxane moiety provides the intermediates for better adrenoreceptor antagonists. Previously, we had disclosed that the regioselectivity of the nucleophilic attack of phenols toward C_3 oxirane derivatives is efficiently controlled by CsF.[11] In this context, we now present a concise route to 8-substituted 2-hydroxymethyl-1,4-benzodioxane derivatives in enantiopure form starting from the 3-substituted catechols under iterative catalysis by CsF.

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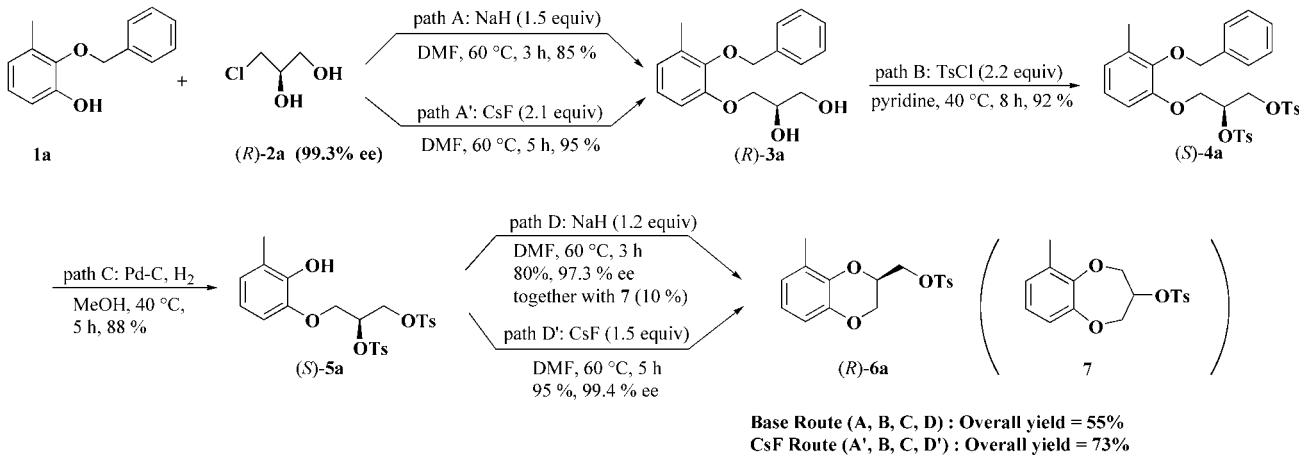
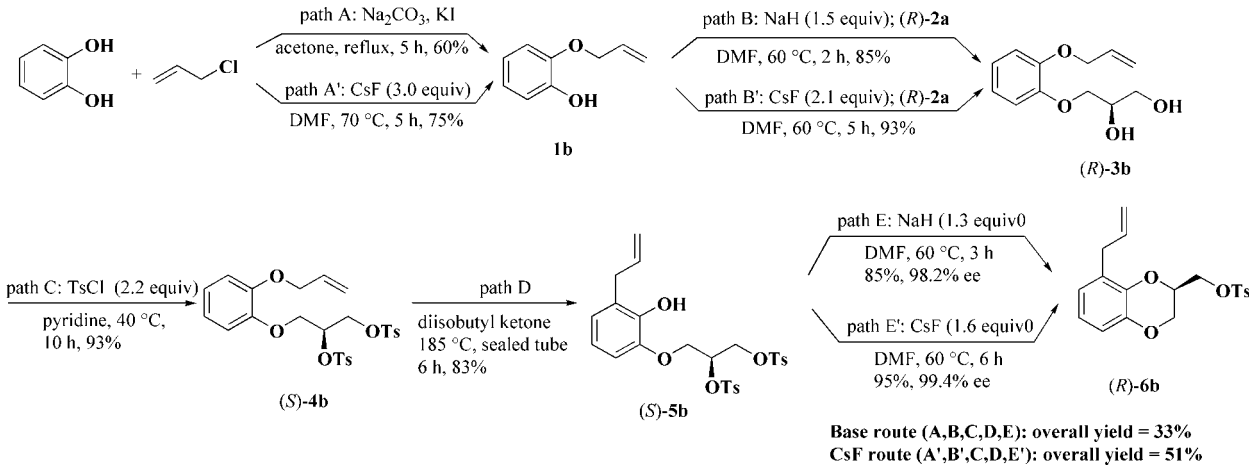


Scheme 1. A stepwise route for (*R*)-**6 a**



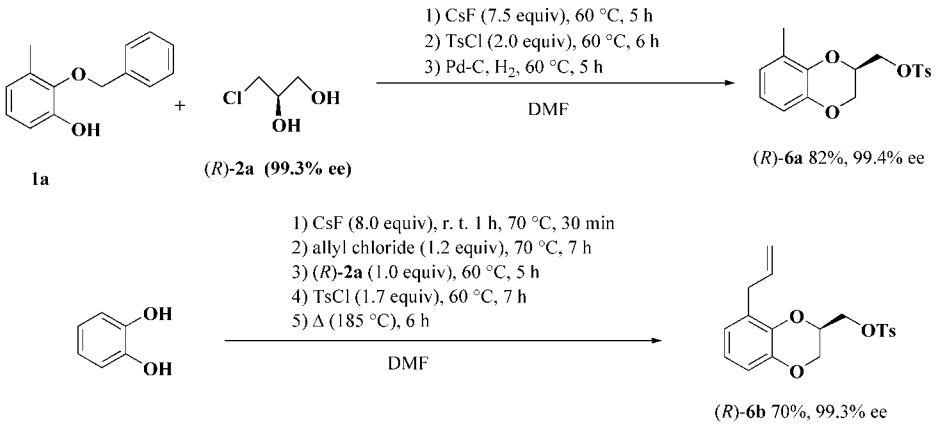
Scheme 2. A stepwise route for (*R*)-**6 b**

Results and Discussion

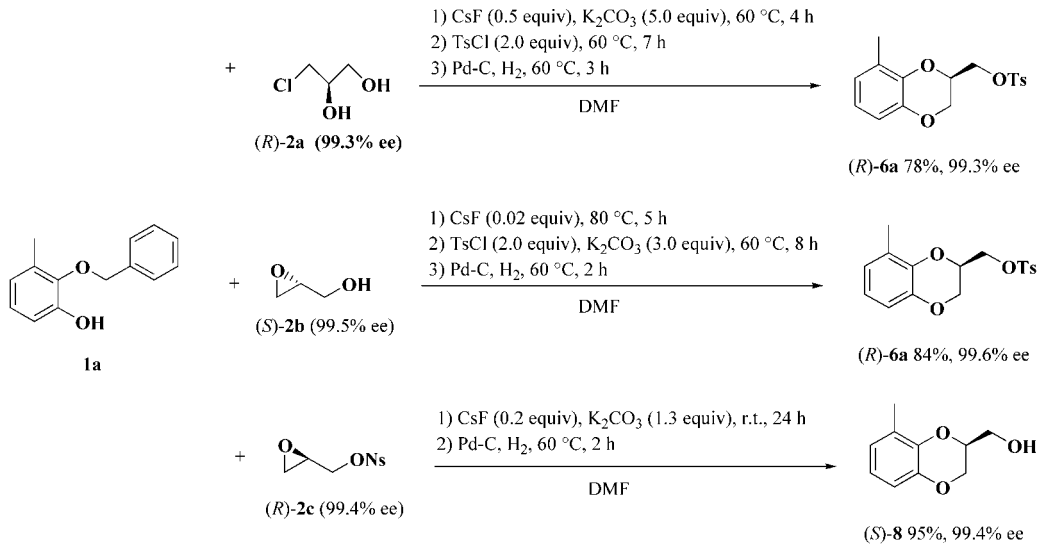
Stepwise Process

The synthetic routes were established by use of enantiopure (*R*)-3-chloro-1,2-propanediol (**2 a**) in a stepwise manner. Scheme 1 shows a route to the 8-methyl derivative (*R*)-**6 a**. A sodium salt of mono-protected 3-methylcatechol **1 a** was exposed to an equimolar amount of (*R*)-**2 a** (99.3% ee) to give the diol (*R*)-**3 a** in 85% yield (path A). Alternatively, we found that the aromatic etherification was effected more efficiently by use of CsF (path A′). Tosylation of (*R*)-**3 a** (path B) followed by deprotection of the benzyl ether (path C) provided (*S*)-**5 a**. Intramolecular etherification of this compound by use of NaH afforded the desired compound (*R*)-**6 a** in 80% yield, while the seven-membered ring compound **7** was also formed in 10% yield (path D). More seriously, the enantiopurity of (*R*)-**6 a** had decreased to 97.3% ee. These drawbacks were overcome by employing CsF which afforded a quantitative yield of (*R*)-**6a** regioselectively without formation of **7** (path D′). More importantly, no decrease of the % ee was observed. Apparently, complete inversion occurred on the secondary tosylate.[12] The overall yield was improved from 55% in the NaH protocol to 73% in the CsF version.

The Claisen rearrangement was invoked for the synthesis of the allyl analogue (*R*)-**6 b** (Scheme 2). Catechol was treated with allyl chloride (1.8 equiv.) in the presence of Na_2CO_3 and KI in refluxing acetone (path A). The resulting allyl ether **1 b** was treated with (*R*)-**2 a** (1.0 equiv.) (path B) under basic conditions to give (*R*)-**3 b**, which was then converted to the ditosylate (*S*)-**4 b** by a conventional method (path C). Heating (*S*)-**4 b** at 185 °C induced the Claisen rearrangement to furnish (*S*)-**5 b** (path D), which was converted to (*R*)-**6 b** upon treatment with NaH (path E). The overall yield was 33% based on catechol. Formation of the seven-membered byproduct as well as racemization occurred to a slight degree in the final step. Notably, replacement of the basic reagents in paths A, B, and E with CsF (paths A′, B′, and E′) gave rise to better yields in all cases resulting in a 51% overall yield and no decrease of % ee was observed.



Scheme 3. Integrated routes for (*R*)-**6 a** and (*R*)-**6 b**



Scheme 4. Catalytic protocols of the integrated process

As a whole, the CsF protocols turned out to be more promising and thus were brought under integration.

Integrated Chemical Process

According to the "integrated chemical process"concept, the one-pot process for (*R*)-**6 a** would be feasible if the steps of both tosylation and benzyl ether cleavage were made compatible with the other CsF-promoted reactions. It has now been proved that the tosylation is feasible by use of CsF because it is an effective acid captor.[13] Furthermore, we have found that the hydrogenation with Pd-C can be incorporated under the relevant conditions and, thus, an integrated process has been realized as shown in Scheme 3. The sequence of aromatic etherification, tosylation of the diol unit, and hydrogenative cleavage of the benzyl ether concomitant with intramolecular etherification could be integrated successfully. Three of these four steps were promoted by CsF and the hydrogenation with Pd–C suffered no retardation. Notably, deprotection of the benzyl ether at 60 °C in the presence of CsF was immediately followed by intramolecular etherification. As a result, the reaction times for these two steps (5 h) were shortened as compared with that in the stepwise process (10 h). Moreover, the overall yield (82%) was better than that by the stepwise process and no decrease of % ee was detected.

The allyl derivative (*R*)-**6 b** was also obtained through integration of allylation of catechol, reaction of the resulting allyl ether with (*R*)-**2 a**, tosylation, and the Claisen rearrangement followed by the intramolecular etherification. All these steps except the Claisen rearrangement were promoted by CsF. In this process, the reaction time for the last two reactions was again reduced through rapid intramolecular etherification after the Claisen rearrangement. The reactions proceeded smoothly to give the desired (*R*)-**6 b**. Remarkably, the overall yield (70%) attained a sharp increase without decrease of % ee as compared with that of the stepwise process (51%).

Catalytic Version

Since we had already disclosed that nucleophilic attack of phenol was promoted by use of a catalytic

amount of CsF together with K_2CO_3, we next addressed ourselves to the catalytic versions to arrive at (*R*)-**6a** (Scheme 4). The procedure illustrated in Scheme 3 was modified by reducing the amount of CsF to 0.5 equiv. while 5.0 equiv. of K_2CO_3 were added instead. The desired product was obtained in 78% yield with 99.3 % ee, and the overall reaction time was also shortened. It should be noted that none of the relevant reactions took place with K_2CO_3 alone. The reaction was apparently promoted by CsF and K_2CO_3 worked as a captor of the acids formed.

Much more efficient catalysis was realized with oxiranes. The use of only 0.02 equiv. of CsF was enough for reaction with (*S*)-glycidol (**2b**). Exclusive ring-opening occurred upon treatment of **1a** with (*S*)-**2b** (99.5% ee) in the presence of CsF. The resulting diol was *in situ* tosylated with TsCl (2.0 equiv.) while K_2CO_3 (3.0 equiv.) was added at this stage. Finally, hydrogenative deprotection of the benzyl ether with Pd–C delivered the phenol which spontaneously underwent intramolecular etherification with the secondary tosylate to furnished (*R*)-**6a** (99.6% ee) in 84% overall yield.

Another integrated process was established by use of (*R*)-gylcidyl nosylate (**2c**). Upon exposure of this compound to **1a**, nucleophilic substitution of the nosyl group took place exclusively. Deprotection of the benzyloxy group in the resulting diol provided (*S*)-**8** (99.4% ee) in almost quantitative yield.

In conclusion, we have established a very practical access to 2-hydroxymethyl-1,4-benzodioxane derivatives on the basis of "integrated chemical process" concept. A single promoter (or catalyst), CsF, activates various kinds of reactions: etherification of phenol with alkyl or allyl chloride, ring-opening of gylcidol, nucleophilic substitution of glycidyl nosylate, tosylation of alcohol, and intramolecular substitution of the secondary tosylate with complete inversion. All these reaction are feasible in one-pot and of more practical significance is the compatibility of these CsF-promoted reactions with hydrogenation with Pd–C, thus allowing integration of different types of reactions sequentially. It is further noted that the integration gives rise to not only the compaction of the processes but also to increases in the overall yields.

Experimental Section

General Methods

Melting points were determined with a Mettler FP-61 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-GSX-270 NMR spectrometer with tetramethylsilane as an internal standard. HRMS were recorded on a JEOL JMS-AX505W. Optical rotations were measured on a JASCO DIP-370 at 21 °C. All reactions were monitored by HPLC. HPLC analyses were performed on a DAISO PACK SP-120-5-ODS-AP column (4.6 mm i.d.×150 mm) using a Shimadzu LC-10A system equipped with an SPD-10A UV detector (eluent, MeOH-H_2O, 8:2, v/v; flow rate, 1.0 mL/min; detection, UV at 254 nm; temperature, 40 °C). Enantiomeric excesses were determined by HPLC on a Chiralcel OD column (4.6 mm i. d.×250 mm, eluent, hexane-EtOH-Et_2NH, 90:10:0.1 v/v; flow rate, 1.0 mL/min; UV at 254 nm; temperature, 40 °C).

(*R*)-2-Benzyloxy-3-(2,3-dihydroxypropoxy)toluene (3a)
NaH route: A solution of **1a** (5.36 g, 25.0 mmol) in DMF (30 mL) was added dropwise to a suspension of NaH (1.50 g, 60% in oil dispersion, 37.5 mmol) in DMF (5 mL). After the suspension had been stirred for 30 min at room temperature, a solution of *(R)*-3-chloro-1,2-propanediol **(2a)** (2.77 g, 25.0 mmol, 99.3% ee) in DMF (5 mL) was added dropwise. The reaction mixture was stirred at 60 °C for 3 h. The reaction mixture was poured into ice water (150 mL) and extracted with EtOAc (150 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc) to give (*R*)-**3a** as a colorless oil; yield: 6.13 g (85%); ^{1}H NMR ($CDCl_3$) δ = 2.33 (m, 3H), 3.71 (m, 2H), 4.06 (m, 3H), 4.96 (s, 2H), 6.88 (m, 3H), 7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ = 16.1, 63.5, 70.3, 70.7, 74.8, 112.0, 123.7, 124.1, 128.0, 128.1, 128.4, 132.6, 146.5, 151.7; HR-MS *m/z*: 288.1363 (calcd. for $C_{17}H_{20}O_4$ 288.1631).

CsF route: To a solution of **1a** (4.38 g, 20.4 mmol) in DMF (25 mL) was added CsF (6.52 g, 42.9 mmol). The reaction mixture was stirred for 1 h and *(R)*-**2a** (2.26 g, 20.4 mmol, 99.3% ee) was added. The reaction mixture was stirred at 60 °C for 5 h. After water (200 mL) had been added, the solution was extracted with EtOAc (150 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc) to give (*R*)-**3a**; yield: 5.60 g (95%).

(*S*)-2-Benzyloxy-3-(2,3-ditosyloxypropoxy)toluene (4a)
To an ice-cold solution of (*R*)-**3a** (2.35 g, 8.2 mmol) in dry pyridine (30 mL) was added *p*-toluenesulfonyl chloride (TsCl) (3.42 g,17.9 mmol). After being stirred for 8 h at 40 °C, the reaction mixture was poured into 1 N HCl (300 mL) and extracted with EtOAc (200 mL×3). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (3:1 hexane/EtOAc) to give (*S*)-**4a** as a colorless prisms; yield: 4.47 g (92%); mp 102.3–103.5 °C; ^{1}H NMR ($CDCl_3$) δ = 2.18 (s, 3H), 2.37 (s, 3H), 2.41 (s, 3H), 4.19 (m, 4H), 4.73 (m, 3H), 6.76 (m, 3H), 7.32 (m, 9H), 7.64 (d, 2H, *J* = 8.5 Hz), 7.73 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ = 16.1, 21.6, 66.3, 66.9, 74.5, 75.7, 111.9, 123.8, 124.2 127.8, 127.9, 128.3, 129.9, 132.7, 137.8, 145.1, 145.3, 146.6, 150.9; HR-MS *m/z*: 596.1539 (calcd. for $C_{31}H_{32}O_8S_2$ 596.1538).

(*S*)-3-(2,3-Ditosyloxypropoxy)-2-hydroxytoluene (5a)
To a solution of (*S*)-**4a** (2.89 g, 4.8 mmol) in methanol (100 mL) was added 10% Pd–C (936 mg). After being stirred for 5 h at 40 °C under a hydrogen atmosphere, the reaction mixture was filtered through a Celite pad and washed thoroughly with methanol. The filtrate was concentrated and the residue thus obtained was purified by column chromatogra-

phy on silica gel (2:1 hexane/EtOAc) to give (*S*)-**5a** as a colorless solid; yield: 2.16 g (88%); ^{1}H NMR ($CDCl_3$) δ = 2.23 (s, 3H), 2.45 (s, 6H), 4.15 (m, 4H), 4.99 (m, 3H), 6.76 (m, 1H), 6.29 (m, 3H), 7.31 (d, 4H, J = 8.5 Hz), 7.74 (d, 4H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ = 16.2, 21.3, 66.2, 66.8, 75.5, 111.9, 123.6, 124.2 127.6, 128.0, 132.5, 134.1, 137.8, 146.9, 150.9; HRMS *m/z*: 506.1070 (calcd. for $C_{24}H_{26}O_8S_2$ 506.1069).

(*R*)-8-Methyl-2-tosyloxymethyl-1,4-benzodioxane (6a)

NaH route: A solution of (*S*)-**5a** (2.06 g, 4.1 mmol) in DMF (10 mL) was added dropwise to a suspension of NaH (0.20 g, 60% in oil dispersion, 4.9 mmol) in anhydrous DMF (1 mL). The suspension was stirred for 30 min at room temperature, and then at 60 °C for 3 h. The reaction mixture was poured into ice water (150 mL) and extracted with EtOAc (150 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*R*)-**6a** as colorless prisms; yield: 1.09 g (80%; 97.3% ee based on chiral HPLC with Chiralcel OD); mp 60.6–62.0 °C; ^{1}H NMR ($CDCl_3$) δ = 2.10 (s, 3H), 2.37 (s, 3H), 2.45 (s, 3H), 4.02 (m, 1H), 4.22 (m, 2H), 4.42 (m, 1H), 6.69 (m, 3H), 7.35 (d, 2H, J = 8.2 Hz), 7.80 (d, 2H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ = 15.2, 21.6, 64.2, 67.2, 70.2, 114.8, 120.7, 123.2, 126.9, 127.9. 129.9, 132.4, 140.3, 142.4, 145.2; HRMS *m/z*: 334.0875 (calcd. for $C_{17}H_{18}O_5S$ 334.0875).

CsF route: To a solution of (*S*)-**5a** (1.22 g, 2.4 mmol) in DMF (5 mL) was added CsF (0.73 g, 2.9 mmol). The reaction mixture was stirred for 1 h, and then at 60 °C for 5 h. After water (200 mL) had been added, the solution was extracted with EtOAc (100 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*R*)-**6a** ; yield: 0.77 g (95%; 99.4% ee based on chiral HPLC with Chiralcel OD).

2-Allyloxyphenol (1b)

Na_2CO_3 route: An acetone solution (300 mL) of catechol (15.33 g, 139.2 mmol), Na_2CO_3 (16.23 g, 153.1 mmol) and KI (2.31 g, 13.9 mmol) was heated under reflux for 30 min. Allyl chloride (19.18 g, 250.6 mmol) was added dropwise and the reaction mixture was stirred at the same temperature. After 7 h, the reaction mixture was cooled to room temperature, filtered and concentrated to give crude **1b**. The residue thus obtained was purified by column chromatography on silica gel (3:1 hexane/EtOAc) to give pure **1b** as a colorless oil; yield: 12.54 g (60%).

CsF route: To a solution of catechol (10.2 g, 92.6 mmol) in DMF (200 mL) was added CsF (42.2 g, 277.9 mmol). The reaction mixture was stirred for 1 h at room temperature and heated at 70 °C for 30 min. Allyl chloride (12.76 g, 166.7 mmol) was added dropwise and the reaction mixture was stirred at the same temperature. After 7 h, water (300 mL) was added and the reaction mixture was extracted with EtOAc (350 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (3:1 hexane/EtOAc) to give **1b**; yield: 10.43 g (75%).

(*R*)-2-Allyloxy-1-(2,3-dihydroxypropoxy)benzene (3b)

NaH route: A solution of **1b** (3.68 g, 24.5 mmol) in DMF (15 mL) was added dropwise to a suspension of NaH (1.47 g, 60% in oil dispersion, 36.8 mmol) in DMF (2 mL). After the suspension had been stirred for 30 min at room temperature, a solution of *(R)*-**2a** (2.71 g, 24.5 mmol, 99.3% ee) in anhydrous DMF (3 mL) was added dropwise. The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was poured into ice water (150 mL) and extracted with EtOAc (100 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*R*)-**3b** as a colorless prisms; yield: 4.67 g (85%); mp 85.3–86.5 °C; $[\alpha]_D^{25}$ = –6.2° (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ = 3.46 (m, 2H), 3.88 (m, 3H), 4.55 (t, 1H, J = 5.2 Hz), 4.62 (t, 2H, J = 5.4 Hz), 4.89 (d, 1H, J = 4.0 Hz), 5.23 (d, 1H, J = 10.7 Hz), 5.40 (dd, 1H, J = 17.3, 1.5 Hz), 6.92 (m, 4H); ^{13}C NMR (DMSO-d_6) δ = 62.9, 69.0, 70.0, 70.4, 113.9, 114.4, 117.1, 120.9, 121.2, 134.0, 147.9, 148.8; HR-MS *m/z*: 224.1047 (calcd. for $C_{12}H_{16}O_4$ 224.1048).

CsF route: To a solution of **1b** (1.08 g, 7.2 mmol) in DMF (10 mL) was added CsF (2.29 g, 15.1 mmol). The reaction mixture was stirred for 1 h and *(R)*-**2a** (0.79 g, 7.2 mmol, 99.3% ee) was added. The reaction mixture was stirred at 60 °C for 5 h. After water (150 mL) had been added, the reaction mixture was extracted with EtOAc (100 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc) to give (*R*)-**3b**; yield: 1.50 g (93%).

(S)-2-Allyoxy-1-(2,3-ditosyloxypropoxy)benzene (4b)

To an ice-cold solution of **3b** (5.36 g, 23.9 mmol) in dry pyridine (100 mL) was added TsCl (10.02 g, 52.6 mmol). After being stirred for 10 h at 40 °C, the reaction mixture was poured into 1N HCl (200 mL) and extracted with EtOAc (100 mL×3). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (3:1 hexane/EtOAc) to give (*S*)-**4b** as colorless prisms; yield: 11.84 g (93%); mp 95.3–97.6 °C; ^{1}H NMR ($CDCl_3$) δ = 2.41 (s, 3H), 2.43 (s, 3H), 4.11 (m, 2H), 4.30 (m, 2H), 4.48 (m, 2H), 4.88 (m, 1H), 5.30 (m, 2H), 6.00 (m, 1H), 6.85 (m, 4H), 7.28 (m, 4H), 7.72 (m, 4H); HR-MS *m/z*: 532.1226 (calcd. for $C_{26}H_{28}O_8S_2$ 532.1225).

(S)-6-Allyl-1-(2,3-ditosyloxypropoxy)phenol (5b)

A mixture of (*S*)-**4b** (2.61 g, 4.9 mmol) and diisobutyl ketone (50 mL) was sealed under vacuum in a glass tube and heated for 6 h in an oven at 185 °C. The reaction mixture was cooled and transferred to a flask and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*S*)-**5b** as colorless prisms; yield: 2.17 g (83%); mp 78.6–79.9 °C; ^{1}H NMR ($CDCl_3$) δ = 2.42 (s, 3H), 2.44 (s, 3H), 2.80 (d, 1H, d, J = 6.6 Hz), 4.18 (m, 2H), 4.37 (m, 2H), 5.03 (m, 2H), 5.99 (m, 1H), 6.73 (m, 3H), 7.43 (m, 4H), 7.76 (m, 4H); HR-MS *m/z*: 532.1225 (calcd. for $C_{26}H_{28}O_8S_2$ 532.1225).

(R)-8-Allyl-2-tosyloxymethyl-1,4-benzodioxane (6b)

NaH route: A solution of (*S*)-**5b** (2.33 g, 4.4 mmol) in DMF (10 mL) was added dropwise to a suspension of NaH (0.227 g, 60% in oil dispersion, 5.7 mmol) in DMF (1 mL). The suspension was stirred for 30 min at room temperature, and then at 60 °C for 3 h. The reaction mixture was poured into ice water (150 mL) and extracted with EtOAc (100 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*R*)-**6b** as a col-

orless oil; yield: 1.34 g (85%; 98.2% ee based on chiral HPLC with Chiralcel OD); ^{1}H NMR ($CDCl_3$) δ = 2.44 (s, 3H), 3.23 (m, 2H), 4.02 (dd, 1H, J = 6.3, 5.3 Hz), 4.21 (m, 3H), 4.42(m, 1H), 5.00 (m, 1H), 5.17 (m, 1H), 5.90 (m, 1H), 6.74 (m, 3H), 7.33 (m, 2H), 7.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 21.6, 33.4, 64.1, 67.1, 70.2, 115.2, 115.6, 121.0, 122.3, 127.9, 128.9, 130.0, 132.4, 136.3, 139.9, 143.0, 145.2; HRMS *m/z*: 360.1031 (calcd. for $C_{19}H_{20}O_5S_2$ 360.1031).

CsF route: To a solution of (*S*)-**5b** (1.06 g, mmol) in anhydrous DMF (5 mL) was added CsF (0.484 g, 3.2 mmol). The reaction mixture was stirred for 1 h, and then at 60 °C for 6 h. Water (150 mL) was added and the solution was extracted with EtOAc (100 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*R*)-**6b**; yield: 0.68 g (95%; 99.4% ee based on chiral HPLC with Chiralcel OD).

One-pot Method

Preparation of (R)-6a by use of (R)-2a

A DMF solution (100 mL) of **1a** (5.08 g, 23.7 mmol) and CsF (27.01 g, 177.8 mmol) was stirred for 1 h, and then (*R*)-**2a** (2.62 g, 23.7 mmol, 99.3% ee) was added. After the reaction mixture had been stirred at 60 °C for 5 h, TsCl (9.04 g, 47.4 mmol) was added dropwise at the same temperature. The reaction mixture was heated at 60 °C for 6 h. To the reaction mixture was added 10% Pd-C (1.53 g). After being stirred for 5 h at 60 °C under a hydrogen atmosphere, the reaction mixture was filtered through a Celite pad and washed thoroughly with DMF. The filtrate was concentrated, water (350 mL) was added, and the solution was extracted with EtOAc (250 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*R*)-**6a**; yield: 6.50 g (82% overall, 99.4% ee based on chiral HPLC with Chiralcel OD).

Preparation of (R)-6b by use of (R)-2a

To a solution of catechol (5.02 g, 45.6 mmol) in DMF (300 mL) was added CsF (55.40 g, 364.7 mmol). After the mixture had been stirred for 1 h at room temperature and heated at 70 °C for 30 min, allyl chloride (4.19 g, 54.7 mmol) was added dropwise. The reaction mixture was stirred at the same temperature. After 7 h, (*R*)-**2a** (4.54 g, 41.0 mmol, 99.3% ee) was added. The reaction mixture was stirred at 60 °C for 5 h, and TsCl was added (14.8 g, 77.5 mmol) at the same temperature. The reaction mixture was heated at 60 °C for 7 h and, then, sealed under vacuum in a glass tube. The glass tube was heated in an oven at 185 °C for 6 h. The reaction mixture was cooled and transferred to a flask and the solvent was removed under reduced pressure. After water (400 mL) had been added, the solution was extracted with EtOAc (300 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*R*)-**6b**; yield: 11.50 g (70% overall; 99.3% ee based on chiral HPLC with Chiralcel OD).

Catalytic One-pot Protocols

Preparation of (R)-6a by use of (R)-2a

A DMF solution (150 mL) of **1a** (0.52 g, 2.4 mmol), K_2CO_3 (1.66 g, 12.0 mmol) and CsF (182 mg, 1.2 mmol) was stirred for 1 h, and then (*R*)-**2a** (265 mg, 2.4 mmol, 99.3% ee) was added. After the reaction mixture had been stirred at 60 °C for 4 h, TsCl (778 mg, 4.1 mmol) was added dropwsie at the same temperature. The reaction mixture was heated at 60 °C for 7 h. To the reaction mixture was added 10% Pd–C (180 mg). After being stirred for 3 h at 60 °C under a hydrogen atmosphere, the reaction mixture was filtered through a Celite pad and washed thoroughly with DMF. The filtrate was concentrated, water (50 mL) was added, and the solution was extracted with EtOAc (50 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*R*)-**6a**; yield: 640 mg (78% overall; 99.3% ee based on chiral HPLC with Chiralcel OD).

Preparation of (R)-6a by use of (S)-glycidol (2b)

To a solution of **1a** (5.02 g, 23.4 mmol) in DMF (100 mL) was added CsF (70 mg, 0.47 mmol). The reaction mixture was stirred for 1 h and (*S*)-**2b** (1.74 g, 23.4 mmol, 99.5% ee) was added. The reaction mixture was stirred at 80 °C for 8 h. Then, TsCl (8.93 g, 46.9 mmol) was added dropwise. The reaction mixture was heated at 60 °C for 8 h. To the reaction mixture was added 10% Pd–C (1.51 g). After being stirred for 2 h at 60 °C under a hydrogen atmosphere, the reaction mixture was filtered through a Celite pad and washed thoroughly with DMF. The filtrate was concentrated, water (350 mL) was added, and the solution was extracted with EtOAc (250 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*R*)-**6a**; yield: 6.58 g (84% overall; 99.6% ee based on chiral HPLC with Chiralcel OD).

Preparation of (S)-2-hydroxymethyl-8-methyl-1,4-benzodioxane (8) by use of (R)-glycidyl nosylate (2c)

To a solution of **1a** (5.02 g, 23.4 mmol) in DMF (150 mL) was added CsF (0.71g, 4.7 mmol) and dried K_2CO_3 (4.2 g, 30.5 mmol). After the mixture had been stirred for 1 h, (*R*)-**2c** (6.07 g, 23.4 mmol, 99.4% ee) was added. The reaction mixture was stirred at 25 °C for 24 h. To the reaction mixture was added 10% Pd–C (0.51 g). After being stirred for 4 h at 60 °C under a hydrogen atmosphere, the reaction mixture was filtered through a Celite pad and washed thoroughly with DMF. The filtrate was concentrated, water (350 mL) was added, and the solution was extracted with EtOAc (250 mL×2). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to give (*S*)-**8** as colorless prisms; yield: 4.01 g (95% overall; 99.4% ee based on chiral HPLC with Chiralcel OD); mp 80.6–81.4 °C; ^{1}H NMR ($CDCl_3$) δ = 2.20 (s, 3H), 2.43 (br–s, 1H), 3.72-4.53 (m, 5H), 6.67 (br–s, 3H); ^{13}C NMR ($CDCl_3$) δ 15.3, 63.8, 67.0, 70.2, 114.8, 117.1, 120.8, 148.3, 149.3; HR-MS *m/z*: 180.0787 (calcd. for $C_{10}H_{12}O_3$ 180.0786).

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