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N,N′-Dioxide–Scandium(III)-Catalyzed Asymmetric Aza-Friedel–Crafts Reaction of Sesamol with Aldimines

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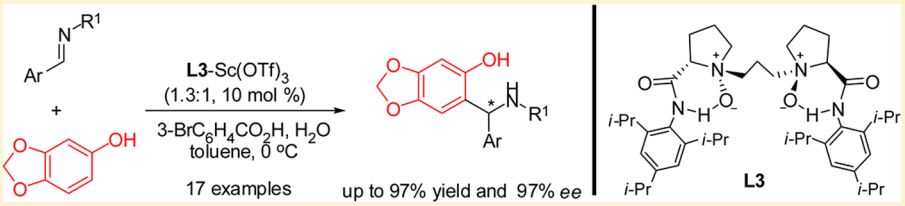
Supporting Information



ABSTRACT: A highly efficient aza-Friedel–Crafts reaction of sesamol with aldimines has been realized by using a chiral *N,N′*-dioxide–scandium(III) complex as the catalyst. A series of corresponding bioactive chiral *α*-amino-sesamols were obtained in moderate to good yields (up to 97%) with excellent enantioselectivities (up to 97% *ee*). Furthermore, the control experiments were conducted to provide fundamental insights into the mechanism of the reaction.

Sesamol, a natural organic compound derived from sesame oil, is a crucial fragment found in a number of biologically active molecules and natural products.[1] Meanwhile, chiral *α*-amino-substituted sesamol derivatives have emerged as ubiquitous antibacterial and antitumor pharmaceuticals, such as (−)-fumimycin, (+)-FRDA drug, cyanocycline, and oxaazapodophyllotoxin I (Figure 1).[2] A facile way to construct

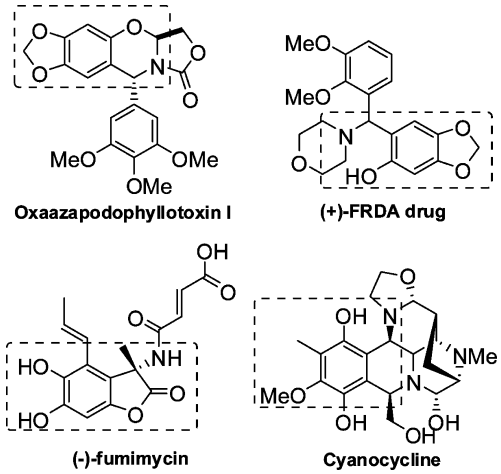


Figure 1. Examples of amino-sesamol derivatives.

these *α*-amino-sesamols in enantiomerically enriched form is the asymmetric aza-Friedel–Crafts (F–C) reaction[3] of sesamol with imines. Notably, the nucleophiles[4] toward the asymmetric aza-Friedel–Crafts reaction with imines mainly focused on indoles,[5] pyrroles,[6] and naphthols,[7] but limited research has been conducted in sesamols.

Very recently, Chimni[8] et al. reported the asymmetric aza-Friedel–Crafts reaction of sesamol with aldimines using 6′-OH *Cinchona* alkaloids[7,8] as the organocatalyst, yet moderate to high enantioselectivities were obtained (62–95% *ee*). For the importance of chiral *α*-amino-substituted sesamol derivatives, the development of new catalyst systems for the asymmetric aza-Friedel–Crafts reaction[3] of sesamol with imines with higher reactivity and enantioselectivity is desirable. We envisioned that the chiral *N,N′*-dioxide/metal complex catalysts developed by our group might be competent, because both of the oxygen atoms on sesamol and imines could coordinate with the metal center strongly to ensure a better chiral environment (Scheme 1). Herein, we made our efforts to develop a highly efficient chiral *N,N′*-dioxide–scandium(III) catalyst[9] system for the asymmetric aza-Friedel–Crafts reaction of sesamol with aldimines.

Our initial investigation began with the aza-Friedel–Crafts reaction of *N*-Ts phenyl imine (**1a**) with sesamol (**2**) as a model reaction. First, several chiral Lewis acid catalysts generated in situ from metal salts and *L*-proline derived *N,N′*-dioxide **L1** were evaluated in CH_2Cl_2 at 0 °C for 30 h (Table 1). The reaction proceeded sluggishly in the presence of most of the metal sources evaluated (for more details, see the Supporting Information). For example, the complex of $Cu(OTf)_2$ or $Fe(ClO_4)_2{\cdot}6H_2O$ gave only less than 10% yield with 13% *ee* and 9% *ee*, respectively, while the complex of $La(OTf)_3$ gave a racemic product in 20% yield (Table 1, entries 1, 2, and 3). Pleasingly, the **L1**–$Sc(OTf)_3$ complex promoted the reaction with moderate enantioselectivity (50% *ee*), though the yield was still low (27% yield, Table 1, entry 4). In order to

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Scheme 1. Catalytic Asymmetric Aza-Friedel–Crafts Reaction of Sesamol with Imines

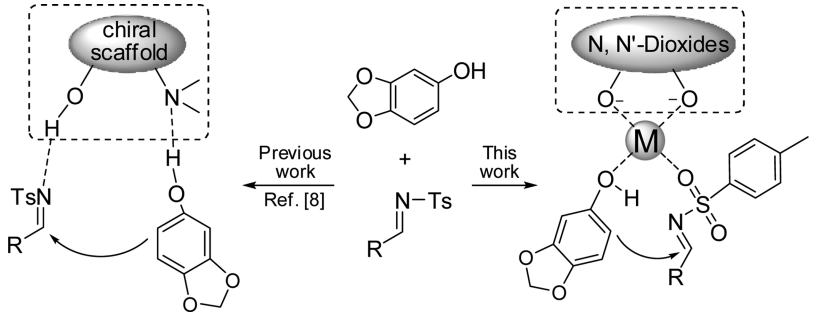
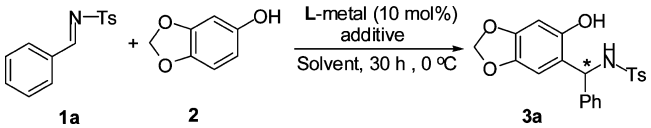


Table 1. Evaluation of the Reaction Conditions



1a 2 3a

entry[a]	L	metal	solvent	yield[b] (%)	ee[c] (%)
1	**L1**	$Cu(OTf)_2$	CH_2Cl_2	8	13
2	**L1**	$Fe(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	7	9
3	**L1**	$La(OTf)_3$	CH_2Cl_2	20	0
4	**L1**	$Sc(OTf)_3$	CH_2Cl_2	27	50
5	**L2**	$Sc(OTf)_3$	CH_2Cl_2	16	25
6	**L3**	$Sc(OTf)_3$	CH_2Cl_2	35	67
7	**L4**	$Sc(OTf)_3$	CH_2Cl_2	21	55
8	**L5**	$Sc(OTf)_3$	CH_2Cl_2	16	47
9	**L3**	$Sc(OTf)_3$	$PhCH_3$	37	77
10[d]	**L3**	$Sc(OTf)_3$	$PhCH_3$	36	91
11[d,e]	**L3**	$Sc(OTf)_3$	$PhCH_3$	58	93
12[d,e,f,g]	**L3**	$Sc(OTf)_3$	$PhCH_3$	93	94
13[d,e,f,g]	**L6**	$Sc(OTf)_3$	$PhCH_3$	90	−94

[a]Unless otherwise noted, the reactions were performed with **L3**/$Sc(OTf)_3$ (1:1, 10 mol %), aldimine **1a** (0.10 mmol), and sesamol **2** (0.10 mmol) in solvent (0.5 mL) at 0 °C for 30 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis (Chiralcel ID). [d]3-$BrC_6H_4CO_2H$ (10 mol %) was used. [e]3 μL of water was added. [f]In 0.1 mL of toluene. [g]Reaction was carried out with **L**/$Sc(OTf)_3$ (1.3/1), and the reaction time was 48 h.

further improve the reactivity and enantioselectivity of the reaction, various chiral *N*,*N*′-dioxide ligands in coordination with $Sc(OTf)_3$ were surveyed (Figure 2). Both the chiral backbone and the amide moiety of the ligand played a key role in the enantioselectivity. When the amide moiety was replaced by an aliphatic 1-adamantyl group, the enantioselectivity as well

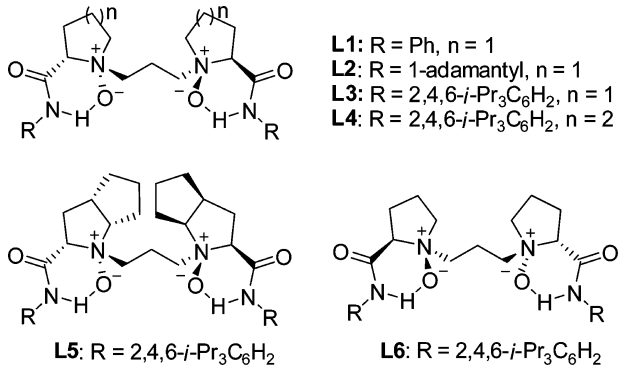


Figure 2. Chiral ligands used in this study.

as the reactivity obviously dropped (16% yield and 25% *ee*; Table1, entry 5 vs entry 4). In addition, steric hindrance of the amide moiety on the ligand was crucial for the enantioselectivity, and more hindered ligand **L3** improved the yield to 35% and the *ee* to 67% (Table1, entry 6). As for the amino acid backbone, *L*-proline derived *N*,*N*′-dioxide **L3** was superior to (*S*)-pipecolic acid derived **L4** and *L*-ramipril derived **L5** (Table1, entry 6 vs entries 7 and 8). Solvent investigation revealed that the reaction underwent smoothly in toluene with the increased *ee* to 77% (Table1, entry 9). To our delight, the addition of a catalytic amount of 3-bromobenzoic acid to the system could further improve the enantioselectivity to 91% *ee* (Table 1, entry 10), which implied that the acid might participate in the chiral control step. Interestingly, when a small amount of water[10] existed, the yield was improved significantly to 58% with the *ee* increased slightly to 93% (Table1, entry 11). Eventually, the optimized conditions were established with the outcomes of 93% yield with 94% *ee* when the concentration of substrates was increased to 1×10^{-3} mol/mL and the ratio of **L3**/$Sc(OTf)_3$ was adjusted to 1.3/1 along with the prolonged reaction time to 48 h (Table 1, entry 12). In addition, the opposite enantiomer was directly obtained by using the *D*-proline derived **L6**–$Sc(OTf)_3$ (Table 1, entry 13). Furthermore, it was noteworthy that the overall operation was easily accessible including air and moisture tolerant.

With the optimized conditions in hand, various *N*-Ts phenyl imines were examined. As summarized in Table 2, regardless of the electron-donating or electron-withdrawing substituents on the aromatic ring of **1**, high enantioselectivities (89–97% *ee*) were obtained. The yields of the products were dependent on the position of the substituents. Generally, substituents on the *meta*-position of the aromatic ring of **1** presented better yields than the *ortho*- or *para*-substituted ones (Table 2, entry 3 vs entries 2 and 4; entry 6 vs entries 5 and 7). Remarkably, heteroaromatic 2-furyl aldimine **1m** was tolerated, generating the desired product in 80% yield and 86% *ee* (Table 2, entry 13). The 2-thienyl aldimine **1n** transformed to **3n** in reduced yield (32%) and 83% *ee* (Table 2, entry 14). Ring-fused 2-naphthyl aldimine **1o** was also a suitable substrate to generate the **3o** in 53% yield and 86% *ee* (Table 2, entry 15). When the protected group was changed to Bs or a more electron-withdrawing 4-chloro-phenylsulfonyl group, the reactivity as well as the enantioselectivity maintained (Table 2, entries 16 and 17). Unfortunately, the reaction of aliphatic aldimines performed sluggishly.

The absolute configuration of the α-amino-substituted sesamol **3f** was unambiguously determined to be *R* by single-crystal X-ray diffraction analysis of the corresponding *t*-butoxycarbonyl-protected derivative **4**.[11]

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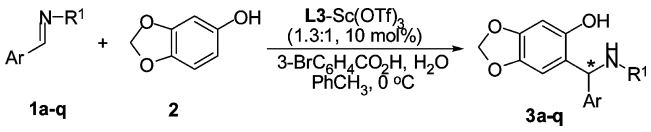
Table 2. Substrate Scope of the Asymmetric Aza-Friedel–Crafts Reaction of Aldimines

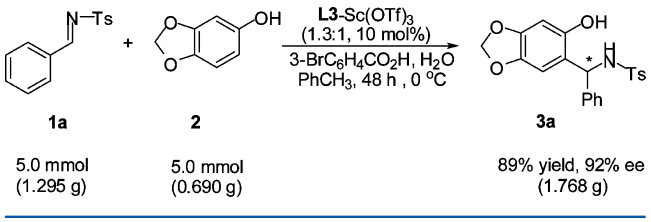


entry[a]	Ar	R^1	yield[b] (%)	ee[c] (%)
1[d]	Ph	Ts	**3a**: 93	94
2	2-MeC_6H_4	Ts	**3b**: 63	97
3	3-MeC_6H_4	Ts	**3c**: 80	93
4	4-MeC_6H_4	Ts	**3d**: 72	91
5[d]	2-FC_6H_4	Ts	**3e**: 83	96
6[d]	3-FC_6H_4	Ts	**3f**: 97	95
7[d]	4-FC_6H_4	Ts	**3g**: 90	95
8[d]	3-ClC_6H_4	Ts	**3h**: 91	96
9	4-ClC_6H_4	Ts	**3i**: 75	94
10	3-BrC_6H_4	Ts	**3j**: 64	92
11	3-$F_3CC_6H_4$	Ts	**3k**: 90	96
12	4-$F_3CC_6H_4$	Ts	**3l**: 71	89
13[e]	2-furyl	Ts	**3m**: 80	86
14	2-thienyl	Ts	**3n**: 32	83
15	2-naphthyl	Ts	**3o**: 53	86
16	C_6H_5	Bs	**3p**: 85	92
17	C_6H_5	4-$ClC_6H_4SO_2$	**3q**: 80	95

[a]Unless otherwise noted, the reactions were performed with **1** (0.20 mmol), **2** (0.20 mmol), **L3**/$Sc(OTf)_3$ (1.3:1, 10 mol %), $PhCH_3$ (0.2 mL), 3-$BrC_6H_4CO_2H$ (0.02 mmol), and H_2O (3 μL) at 0 °C for 72 h. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase. [d]The reaction time was 48 h. [e]Determined by chiral HPLC analysis of the *N*-Boc-protected product **3m**.

To evaluate the synthetic potential of the catalyst system, a gram-scale synthesis of α-amino-sesamol **3a** was carried out. In the presence of 10 mol % of **L3**–$Sc(OTf)_3$, 5.0 mmol of *N*-Ts phenyl imine **1a** (1.295 g) reacted with 1.0 equiv of sesamol **2** (0.690 g), generating the desired product **3a** in 89% yield (1.768 g) and 92% *ee* (Scheme 2).

Scheme 2. Scaled-Up Version of the Reaction



In order to gain an insight into the reaction mechanism, the relationship between the *ee* of the ligand **L3** and that of the product **3a** was investigated (see the Supporting Information for details). A linear effect was observed, which suggested that the monomeric complex might function as the most active and effective catalytic species.[12]

Then, ^{1}H NMR analysis was carried out to provide a further insight on the catalytic process. As shown by the ^{1}H NMR spectra (Figure 3), the proton signal of the hydroxyl group on sesamol **2** was obviously shifted downfield from 4.77 to 5.30 ppm, which corresponded to the coordination of the hydroxyl group on the sesamol to the Sc^{3+}. To supplement, the catalytic compositions were investigated by using ESI-MS (Figure 4). The spectra of the sample obtained from the mixture of **L3**–

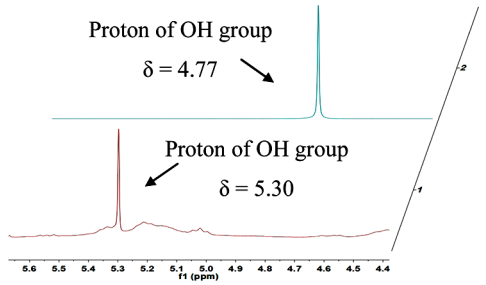


Figure 3. ^{1}H NMR spectra of the OH group of sesamol **2** in diverse conditions: (**1**) **2** in $CDCl_3$; (**2**) $Sc(OTf)_3$/**L3**/**2** (1/1.3/1) in $CDCl_3$.

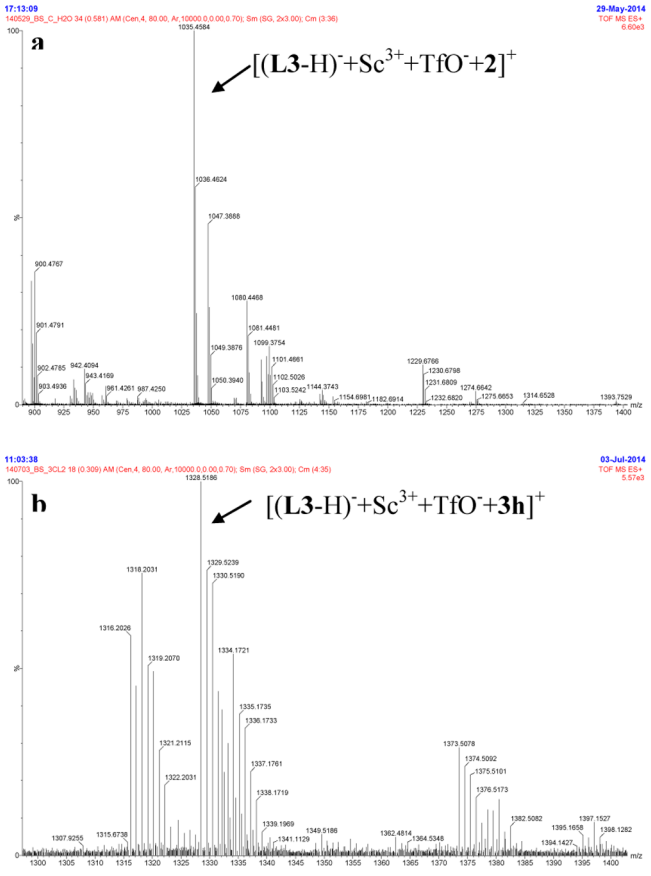


Figure 4. ESI-MS spectra of solutions of the catalyst-substrate: (a) **L3**–Sc^{3+}-**2**; (b) **L3**–Sc^{3+}-**2**-**1h**-additives.

$Sc(OTf)_3$ and sesamol **2** revealed an ion at *m*/*z* 1035.4584, which was assigned to the intermediate $[(\mathbf{L3}\text{-H})^- + Sc^{3+} + TfO^- + \mathbf{2}]^+$. Upon addition of aldimine **2h** and additives for 48 h, the ion at *m*/*z* 1328.5186 was gained, which corresponded to the intermediate $[(\mathbf{L3}\text{-H})^- + Sc^{3+} + TfO^- + \mathbf{3h}]^+$.

On the basis of the experiments and previous reports,[9d,f] a catalytic cycle with a transition-state model was proposed in Figure 5. First, the catalyst[13] generated in situ from **L3** and $Sc(OTf)_3$ coordinated with the hydroxyl group of **2**[14] to give intermediate **T1**. Then, **T1** coordinated with the oxygen atom of the sulfonyl group because of the oxygen affinity characteristic of scandium,[15] accompanying with the hydrogen bonding[16] between the nitrogen atom of aldimine **1** and the hydrogen atom of 3-bromobenzoic acid (**T2**). The *Re* face of aldimine **1** was shielded by the neighboring 2,4,6-triisopropylphenyl group. Therefore, the nucleophile **2** preferably attacked electrophile **1** from the *Si*-face to generate the corresponding *R*-

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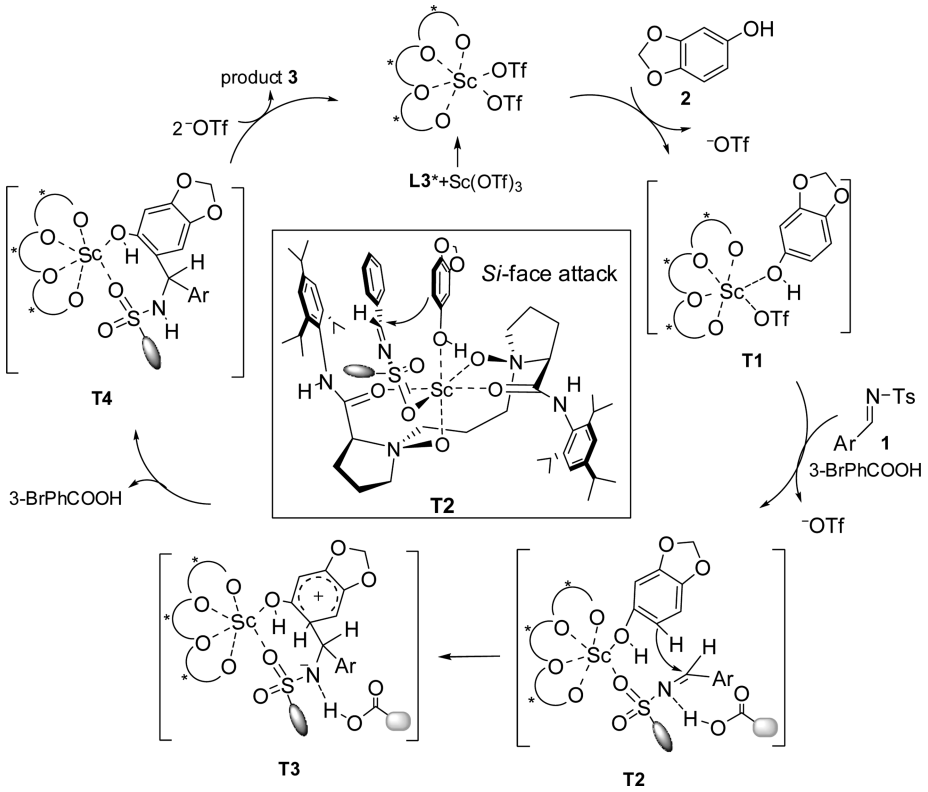

Figure 5. Proposed catalytic cycle.

configured product. Additionally, the C−C bond formation disrupted the aromaticity of the sesamol (**T3**). After attracting a proton to form 3-bromobenzoic acid, the aromaticity was reestablished (**T4**). In the last step, the desired product **3** was dissociated and the catalyst was regenerated.

In summary, we have developed an efficient asymmetric aza-Friedel−Crafts reaction of aldimines with sesamol catalyzed by a chiral *N,N′*-dioxide−Sc(III) complex. A wide range of *α*-amino-sesamols were obtained in good yields (up to 97%) with good to excellent enantioselectivities (up to 97% *ee*) under mild reaction conditions. On the basis of the experiments and the previous work, a possible catalytic cycle was proposed.

EXPERIMENTAL SECTION

General Remarks. Reactions were carried out using commercially available reagents in oven-dried apparatus. Toluene was directly distilled before use. Enantiomeric excesses (*ee*) were determined by HPLC analysis using the corresponding commercial chiral column as stated in the experimental procedures at 23 °C with a UV detector at 254 nm. Optical rotations were reported as follows: $[\alpha]_D^{25}$ (*c* g/100 mL, in solvent). ^{1}H NMR spectra were recorded on commercial instruments (400 MHz). ^{13}C NMR spectra was collected on commercial instruments (100 MHz) with complete proton decoupling. HRMS was recorded on a commercial apparatus (ESI Source).

General Procedure for the Catalytic Asymmetric Aza-Friedel−Crafts Reaction. A solution of *N,N′*-dioxide **L3** (18.2 mg, 0.026 mmol), $Sc(OTf)_3$ (10.0 mg, 0.020 mmol), and 3-$BrC_6H_4CO_2H$ (4.0 mg, 0.020 mmol) in 0.2 mL of $PhCH_3$ was stirred at 30 °C for 0.5 h. Then, sesamol **2** (0.20 mmol), H_2O (3 μL), and aldimine **1** (0.20 mmol) were added. The mixture was stirred at 0 °C for 48 or 72 h. The reaction mixture was purified via flash chromatography (CH_2Cl_2/EtOAc = 20/1) on silica gel to afford the desired product. The enantiomeric excess (*ee*) was determined by high-performance liquid chromatography (HPLC).

N-((6-Hydroxybenzo[d][1,3]dioxol-5-yl)(phenyl)methyl)-4-methylbenzenesulfonamide ***3a***. Yield: 36.9 mg, 93%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 75/25, flow rate = 1.0 mL/min, *λ* = 254 nm), t_r(major) = 13.94 min, t_r(minor) = 19.47 min, *ee* = 94%. $[\alpha]_D^{16.3}$ = 40.0 (*c* = 0.80, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* = 7.54 (d, *J* = 8.3 Hz, 2H), 7.23−7.12 (m, 5H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.26 (d, *J* = 6.4 Hz, 3H), 6.00 (d, *J* = 8.7 Hz, 1H), 5.78 (s, 2H), 5.54 (d, *J* = 8.7 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* = 148.2, 147.5, 143.3, 141.1, 139.8, 136.7, 129.3, 128.4, 127.4, 127.1, 126.9, 118.1, 108.6, 101.2, 99.1, 58.4, 21.4. HRMS (ESI-TOF): Calcd for $C_{21}H_{19}NO_5S$ [M + Na]$^+$ 420.0876, Found: 420.0880.

N-((6-Hydroxybenzo[d][1,3]dioxol-5-yl)(o-tolyl)methyl)-4-methylbenzenesulfonamide ***3b***. Yield: 25.9 mg, 63%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, *λ* = 254 nm), t_r(major) = 10.52 min, t_r(minor) = 19.05 min, *ee* = 97%. $[\alpha]_D^{24.5}$ = 15.0 (*c* = 0.99, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* = 7.55 (d, *J* = 7.9 Hz, 2H), 7.20−6.94 (m, 6H), 6.38 (s, 1H), 6.22 (s, 1H), 6.13 (s, 1H), 5.86 (d, *J* = 7.7 Hz, 1H), 5.79 (d, *J* = 6.2 Hz, 2H), 5.36 (d, *J* = 7.6 Hz, 1H), 2.33 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* = 149.0, 147.8, 143.5, 141.4, 136.8, 136.4, 135.7, 130.7, 129.3, 127.6, 127.2, 126.5, 126.0, 117.6, 107.8, 101.2, 99.4, 54.0, 21.5, 19.1. HRMS (ESI-TOF): Calcd for $C_{22}H_{21}NO_5S$ [M + Na]$^+$ 434.1033, Found: 434.1034.

N-((6-Hydroxybenzo[d][1,3]dioxol-5-yl)(m-tolyl)methyl)-4-methylbenzenesulfonamide ***3c***. Yield: 32.9 mg, 80%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 75:25, flow rate = 1.0 mL/min, *λ* = 254 nm), t_r(major) = 11.78 min, t_r(minor) = 15.66 min, *ee* = 93%. $[\alpha]_D^{24.5}$ = 14.8 (*c* = 0.85, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* = 7.55 (d, *J* = 8.0 Hz, 2H), 7.08 (dd, *J* = 7.3, 4.7 Hz, 3H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.93 (s, 2H), 6.28 (d, *J* = 6.8 Hz, 2H), 6.23−5.98 (m, 1H), 5.94−5.72 (m, 3H), 5.53 (d, *J* = 8.5 Hz, 1H), 2.33 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* = 148.3, 147.5, 143.3, 141.2, 139.5, 138.1, 136.8, 129.3, 128.3, 128.2, 127.6, 127.2, 123.9, 118.3, 108.6, 101.2, 99.2, 58.2, 21.4, 21.4. HRMS (ESI-TOF): Calcd for $C_{22}H_{21}NO_5S$ [M + Na]$^+$ 434.1033, Found: 434.1033.

N-((6-Hydroxybenzo[d][1,3]dioxol-5-yl)(p-tolyl)methyl)-4-methylbenzenesulfonamide ***3d***. Yield: 29.6 mg, 72%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, *λ* = 254 nm), t_r(major) = 10.41 min, t_r(minor) = 13.81 min, *ee* = 91%.

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$[\alpha]_D^{26.0}$ = 20.2 (c = 0.70, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.2 Hz, 2H), 7.12−6.96 (m, 6H), 6.33−6.16 (m, 3H), 5.94 (d, J = 8.0 Hz, 1H), 5.78 (s, 2H), 5.50 (d, J = 8.5 Hz, 1H), 2.32 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.2, 147.5, 143.3, 141.1, 137.1, 136.8, 129.3, 129.1, 127.2, 126.8, 118.3, 108.6, 101.1, 99.1, 58.2, 21.4, 21.0. HRMS (ESI-TOF): Calcd for $C_{22}H_{21}NO_5S$ $[M + Na]^+$ 434.1033, Found: 434.1044.

N-((2-Fluorophenyl)(6-hydroxybenzo[d][1,3]dioxol-5-yl)methyl)-4-methylbenzenesulfonamide ***3e***. Yield: 34.5 mg, 83%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 75/25, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 17.23 min, t_r(minor) = 25.53 min, *ee* = 96%. $[\alpha]_D^{16.3}$ = 23.5 (c = 0.60, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.19−7.11 (m, 1H), 7.08 (d, J = 8.0 Hz, 2H), 6.96 (t, J = 7.2 Hz, 1H), 6.87 (dd, J = 10.0, 8.8 Hz,1H), 6.39 (s, 1H), 6.34 (s, 1H), 6.30 (s, 1H), 5.93 (d, J = 8.8 Hz, 1H), 5.81 (d, J = 10.3 Hz, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.78 (d, J = 247.4 Hz), 148.66, 147.82, 143.53, 141.20, 136.30, 129.33, 129.24, 128.85 (d, J = 4.0 Hz), 127.2, 126.4 (d, J = 12.1 Hz), 124.1 (d, J = 4.0 Hz), 117.0, 115.5 (d, J = 22.2 Hz), 107.9, 101.2, 99.2, 53.2, 21.4. HRMS (ESI-TOF): Calcd for $C_{21}H_{18}FNO_5S$ $[M + Na]^+$ 438.0782, Found: 438.0783.

N-((3-Fluorophenyl)(6-hydroxybenzo[d][1,3]dioxol-5-yl)methyl)-4-methylbenzenesulfonamide ***3f***. Yield: 40.3 mg, 97%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 8.37 min, t_r(minor) = 10.01 min, *ee* = 95%. $[\alpha]_D^{24.5}$ = 24.7 (c = 1.03, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (d, J = 8.2 Hz, 2H), 7.17 (td, J = 8.3, 4.0 Hz, 1H), 7.10 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 7.7 Hz, 1H), 6.92−6.79 (m, 2H), 6.26 (d, J = 17.3 Hz, 2H), 6.19 (s, 1H), 6.03 (d, J = 8.9 Hz, 1H), 5.81 (s, 2H), 5.50 (d, J = 8.9 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.7 (d, J = 247.4 Hz), 148.0, 147.7, 143.5, 142.6 (d, J = 7.1 Hz), 141.2, 136.6, 129.8 (d, J = 9.1 Hz), 129.4, 127.1, 122.5 (d, J = 3.0 Hz), 117.6, 114.2 (d, J = 21.2 Hz), 114.0 (d, J = 23.2 Hz), 108.6, 101.3, 99.0, 58.0, 21.4. HRMS (ESI-TOF): Calcd for $C_{21}H_{18}FNO_5S$ $[M + Na]^+$ 438.0782, Found: 438.0793.

N-((4-Fluorophenyl)(6-hydroxybenzo[d][1,3]dioxol-5-yl)methyl)-4-methylbenzenesulfonamide ***3g***. Yield: 37.4 mg, 90%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 8.32 min, t_r(minor) = 10.91 min, *ee* = 95%. $[\alpha]_D^{16.3}$ = 27.4 (c = 0.68, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.3 Hz, 2H), 7.17−7.07 (m, 4H), 6.88 (t, J = 8.7 Hz, 2H), 6.28 (s, 1H), 6.24 (s, 1H), 6.12 (s, 1H), 5.95 (d, J = 8.8 Hz, 1H), 5.82 (s, 2H), 5.51 (d, J = 8.6 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.0 (d, J = 247.4 Hz), 148.0, 147.7, 143.5, 141.3, 136.6, 135.6 (d, J = 3.0 Hz), 129.3, 128.6 (d, J = 8.1 Hz), 127.1, 117.8, 115.2 (d, J = 21.2 Hz), 108.6, 101.3, 99.1, 57.9, 21.5. HRMS (ESI-TOF): Calcd for $C_{21}H_{18}FNO_5S$ $[M + Na]^+$ 438.0786, Found: 438.0782.

N-((3-Chlorophenyl)(6-hydroxybenzo[d][1,3]dioxol-5-yl)methyl)-4-methylbenzenesulfonamide ***3h***. Yield: 39.3 mg, 91%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 75/25, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 10.47 min, t_r(minor) = 13.27 min, *ee* = 96%. $[\alpha]_D^{19.3}$ = 30.7 (c = 0.84, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, J = 8.2 Hz, 2H), 7.20−6.95 (m, 6H), 6.38−6.16 (m, 3H), 6.06 (dd, J = 13.8, 8.7 Hz,1H), 5.80 (s, 2H), 5.50 (d, J = 8.9 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.1, 147.7, 143.6, 142.0, 141.2, 136.6, 134.2, 129.6, 129.4, 127.4, 127.1, 127.0, 125.1, 117.4, 108.6, 101.3, 99.0, 58.0, 21.4. HRMS (ESI-TOF): Calcd for $C_{21}H_{18}{}^{34.9689}ClNO_5S$ $[M + Na]^+$ 454.0486, Found: 454.0488. HRMS (ESI-TOF): Calcd for $C_{21}H_{18}{}^{36.9659}ClNO_5S$ $[M + Na]^+$ 456.0456, Found: 456.0464.

N-((4-Chlorophenyl)(6-hydroxybenzo[d][1,3]dioxol-5-yl)methyl)-4-methylbenzenesulfonamide ***3i***. Yield: 32.4 mg, 75%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 75/25, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 9.97 min, t_r(minor) = 13.95 min, *ee* = 94%. $[\alpha]_D^{19.3}$ = 20.9 (c = 0.59, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, J = 8.2 Hz, 2H), 7.17−7.15 (m, 2H), 7.11−7.09 (m, 4H), 6.28 (s, 1H), 6.23 (s, 1H), 6.03 (s, 1H), 5.92 (d, J = 8.8 Hz, 1H), 5.82 (s, 2H), 5.49 (d, J = 8.8 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.0, 147.7, 143.6, 141.3, 138.4, 136.6, 133.2, 129.4, 128.4, 128.3, 127.1, 117.7, 108.6, 101.3, 99.1, 57.9, 21.5. HRMS (ESI-TOF): Calcd for $C_{21}H_{18}{}^{34.9689}ClNO_5S$ $[M + Na]^+$ 454.0486, Found: 454.0493. HRMS (ESI-TOF): Calcd for $C_{21}H_{18}{}^{36.9659}ClNO_5S$ $[M + Na]^+$ 456.0456, Found: 456.0476.

N-((3-Bromophenyl)(6-hydroxybenzo[d][1,3]dioxol-5-yl)methyl)-4-methylbenzenesulfonamide ***3j***. Yield: 30.5 mg, 64%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 8.92 min, t_r(minor) = 11.86 min, *ee* = 92%. $[\alpha]_D^{26.0}$ = 10.4 (c = 0.79, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.1 Hz, 1H), 7.25 (s, 1H), 7.08 (tt, J = 15.7, 7.8 Hz, 4H), 6.38 (s, 1H), 6.28 (s, 1H), 6.24 (s, 1H), 6.11 (d, J = 8.9 Hz, 1H), 5.80 (d, J = 0.8 Hz, 2H), 5.49 (d, J = 8.8 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.0, 147.7, 143.6, 141.2, 139.0, 136.6, 131.4, 129.4, 128.7, 127.1, 121.3, 117.5, 108.6, 101.3, 99.0, 58.0, 21.5. HRMS (ESI-TOF): Calcd for $C_{21}H_{18}{}^{78.9183}BrNO_5S$ $[M + Na]^+$ 497.9981, Found: 497.9990.

N-((6-Hydroxybenzo[d][1,3]dioxol-5-yl)(3-(trifluoromethyl)phenyl)methyl)-4-methylbenzenesulfonamide ***3k***. Yield: 41.9 mg, 90%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 75/25, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 6.69 min, t_r(minor) = 7.55 min, *ee* = 96%. $[\alpha]_D^{16.3}$ = 19.2 (c = 0.88, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (d, J = 8.3 Hz, 2H), 7.46−7.35 (m, 3H), 7.31 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.30 (d, J = 2.8 Hz, 1H), 6.25 (s, 1H), 6.16 (dd, J = 34.9, 15.7 Hz, 1H), 6.06 (d, J = 8.9 Hz, 1H), 5.82 (dd, J = 3.3, 1.3 Hz, 2H), 5.58 (dd, J = 8.6, 3.8 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.0, 147.9, 143.6, 141.4, 141.0, 136.6, 133.6 (d, J = 594.9 Hz), 130.4, 129.4, 128.8, 127.0, 124.2 (d, J = 4.0 Hz), 123.9 (d, J = 272.7 Hz), 123.5 (d, J = 3.0 Hz), 117.4, 108.5, 101.3, 99.0, 58.1, 21.4. HRMS (ESI-TOF): Calcd for $C_{22}H_{18}F_3NO_5S$ $[M + Na]^+$ 488.0750, Found: 488.0757.

N-((6-Hydroxybenzo[d][1,3]dioxol-5-yl)(4-(trifluoromethyl)phenyl)methyl)-4-methylbenzenesulfonamide ***3l***. Yield: 33.0 mg, 71%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 75/25, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 7.12 min, t_r(minor) = 8.80 min, *ee* = 89%. $[\alpha]_D^{26.0}$ = 27.1 (c = 0.92, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 7.9 Hz, 2H), 6.46−6.34 (m, 1H), 6.28 (dd, J = 14.3, 9.2 Hz, 3H), 5.80 (s, 2H), 5.56 (d, J = 8.9 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.1, 147.8, 144.0, 143.7, 141.3, 136.6, 129.3 (d, J = 32.3 Hz), 129.4, 127.2, 127.1, 125.2 (d, J = 4.0 Hz), 124.0 (d, J = 273.7 Hz), 117.3, 108.5, 101.3, 99.0, 58.2, 21.3. HRMS (ESI-TOF): Calcd for $C_{22}H_{18}F_3NO_5S$ $[M + Na]^+$ 488.0750, Found: 488.0751.

tert-Butyl 6-(Furan-2-yl(4-methylphenylsulfonamido)methyl)-benzo[d][1,3]dioxol-5-yl Carbonate ***3m***. Yield: 39.0 mg, 80%, yellow oil. HPLC (chiralcel IE, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 27.08 min, t_r(minor) = 30.15 min, *ee* = 86%. $[\alpha]_D^{10.8}$ = 44.3 (c = 0.57, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 0.9 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 6.55 (d, J = 7.2 Hz, 2H), 6.17 (dd, J = 3.2, 1.8 Hz, 1H), 6.01 (d, J = 3.2 Hz, 1H), 5.90 (dd, J = 4.9, 1.2 Hz, 2H), 5.69 (d, J = 8.0 Hz, 1H), 5.51 (d, J = 8.0 Hz, 1H), 2.36 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.5, 151.2, 147.6, 145.2, 143.1, 142.7, 142.6, 137.3, 129.2, 127.2, 122.7, 110.3, 107.7, 104.4, 101.9, 84.1, 51.5, 27.6, 21.5. HRMS (ESI-TOF): Calcd for $C_{24}H_{25}NO_8S$ $[M + Na]^+$ 510.1193, Found: 510.1200.

N-((6-Hydroxybenzo[d][1,3]dioxol-5-yl)(thiophen-2-yl)methyl)-4-methylbenzenesulfonamide ***3n***. Yield: 12.9 mg, 32%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 75/25, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 14.69 min, t_r(minor) = 20.16 min, *ee* = 83%. $[\alpha]_D^{27.9}$ = 14.7 (c = 0.21, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.61 (d, J = 8.3 Hz, 2H), 7.16 (dd, J = 3.4, 1.3 Hz, 2H), 7.14 (s, 1H), 6.84 (dd, J = 5.1, 3.6 Hz, 1H), 6.71 (dd, J = 2.4, 1.1 Hz, 1H), 6.41 (s, 1H), 6.28 (s, 1H), 5.86 (s, 2H), 5.77 (dd, J = 23.1, 8.7 Hz, 2H), 5.59 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.04, 147.95, 144.36, 143.47, 141.51, 136.81, 129.34, 127.21, 126.85, 125.43, 125.34, 118.39, 108.26, 101.33, 99.39, 55.04, 21.49. HRMS (ESI-TOF): Calcd for $C_{19}H_{17}NO_5S_2$ $[M + Na]^+$ 426.0440, Found: 426.0444.

N-((6-Hydroxybenzo[d][1,3]dioxol-5-yl)(naphthalen-2-yl)methyl)-4-methylbenzenesulfonamide ***3o***. Yield: 23.7 mg, 53%, yellow oil.

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HPLC (chiralcel ID, hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 16.314 min, t_r(minor) = 21.921 min, *ee* = 86%. $[\alpha]_D^{27.9}$ = 34.0 (*c* = 0.53, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80−7.71 (m, 1H), 7.64 (dd, *J* = 13.6, 6.4 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 3H), 7.47−7.37 (m, 2H), 7.27 (d, *J* = 1.6 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.32 (s, 1H), 6.29 (s, 1H), 6.08 (s, 1H), 5.92 (dd, *J* = 8.7, 3.7 Hz, 1H), 5.85−5.76 (m, 2H), 5.72 (d, *J* = 8.7 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.35, 147.71, 143.43, 141.34, 136.81, 136.71, 132.99, 132.59, 129.27, 128.27, 128.03, 127.53, 127.16, 126.20, 126.10, 125.54, 125.09, 118.09, 108.68, 101.24, 99.26, 58.36, 21.36. HRMS (ESI-TOF): Calcd for $C_{25}H_{21}NO_5S$ $[M+K]^+$ 486.0772, Found: 486.0766.

N-((6-Hydroxybenzo[d][1,3]dioxol-5-yl)phenyl)methyl)benzenesulfonamide ***3p***. Yield: 32.6 mg, 85%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 10.19 min, t_r(minor) = 11.99 min, *ee* = 92%. $[\alpha]_D^{19.3}$ = 24.3 (*c* = 0.79, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 6.4 Hz, 1H), 7.29 (d, *J* = 1.7 Hz, 1H), 7.25 (d, *J* = 0.6 Hz, 1H), 7.17 (d, *J* = 1.3 Hz, 5H), 6.27 (d, *J* = 11.5 Hz, 2H), 6.24−6.10 (m, 1H), 6.10−5.98 (m, 1H), 5.79 (d, *J* = 4.7 Hz, 2H), 5.59 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.2, 147.6, 141.2, 139.8, 139.7, 132.5, 128.7, 128.4, 127.4, 127.1, 126.9, 118.0, 108.6, 101.2, 99.1, 58.4. HRMS (ESI-TOF): Calcd for $C_{20}H_{17}NO_5S$ $[M + Na]^+$ 406.0720, Found: 406.0726.

4-Chloro-N-((6-hydroxybenzo[d][1,3]dioxol-5-yl)(phenyl)methyl)-benzenesulfonamide ***3q***. Yield: 33.4 mg, 80%, yellow oil. HPLC (chiralcel ID, hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 7.30 min, t_r(minor) = 9.36 min, *ee* = 95%. $[\alpha]_D^{19.3}$ = 23.3 (*c* = 0.73, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 8.6 Hz, 2H), 7.26−7.12 (m, 7H), 6.25 (d, *J* = 9.5 Hz, 2H), 6.04 (d, *J* = 8.9 Hz, 1H), 5.91 (s, 1H), 5.84 (d, *J* = 2.6 Hz, 2H), 5.58 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.9, 147.7, 141.4, 139.4, 138.9, 138.4, 128.9, 128.6, 128.5, 127.6, 126.8, 117.7, 108.7, 101.4, 99.0, 58.4. HRMS (ESI-TOF): Calcd for $C_{20}H_{16}{}^{34.9689}ClNO_5S$ $[M + Na]^+$ 440.0330, Found: 440.0339. HRMS (ESI-TOF): Calcd for $C_{20}H_{16}{}^{36.9659}ClNO_5S$ $[M + Na]^+$ 442.0300, Found: 442.0294.

(R)-tert-Butyl (6-(tert-Butoxycarbonyloxy)benzo[d][1,3]dioxol-5-yl)(3-fluorophenyl)methyl(tosyl)carbamate ***4***. Yield: 59.1 mg, 99%, white foam. HPLC (chiralcel ID, hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 9.43 min, t_r(minor) = 10.82 min, *ee* = 95%. $[\alpha]_D^{27.3}$ = −31.3 (*c* = 3.51, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ =δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.24−7.10 (m, 3H), 6.96−6.73 (m, 5H), 6.63 (s, 1H), 5.89 (d, *J* = 2.5 Hz, 2H), 2.32 (s, 3H), 1.32 (s, 9H), 1.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.6 (d, *J* = 246.4 Hz), 150.4, 149.7, 146.6, 144.3, 143.3, 142.6, 140.7 (d, *J* = 8.1 Hz), 135.7, 128.6 (d, *J* = 8.1 Hz), 128.1, 127.6, 122.3, 122.2 (d, *J* = 3.0 Hz), 113.8 (d, *J* = 23.2 Hz), 112.9 (d, *J* = 21.2 Hz), 108.7, 102.8, 100.9, 83.8, 82.8, 57.1, 26.7, 26.4, 20.6. HRMS (ESI-TOF): Calcd for $C_{31}H_{34}FNO_9S$ $[M + Na]^+$ 638.1831, Found: 638.1841.

■ ASSOCIATED CONTENT

Supporting Information

Full optimization details, ^{1}H and ^{13}C NMR spectra, HPLC analyses for all the products, and X-ray crystal data of compound **4** (CIF) are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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