JOC Article

# Synthesis of Catechins via Thiourea/$AuCl_3$-Catalyzed Cycloalkylation of Aryl Epoxides

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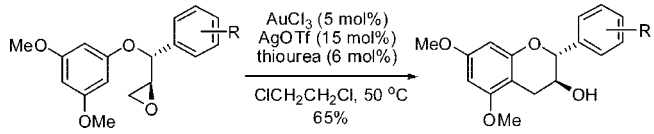


A diversity-oriented approach for the synthesis of structurally diverse catechins was achieved in good yields via thiourea/$AuCl_3$/AgOTf-catalyzed annulations of aryl epoxides under mild conditions. This new protocol provides a highly efficient entry to a library of catechins-derived natural products, notably anti-HIV agent 8-*C*-ascorbyl-(−)-epigallocatechin.

## Introduction

Catechin is a ubiquitous structural motif found in numerous naturally occurring molecules, particularly those abundant in green teas and red wines (Figure 1).[1] The biological activities of these compounds are very wide-ranging, including antioxidative,[2] anticarcinogenic,[3] antiarteriosclerotic,[4] and antibacterial effects.[5] These compounds have long served as key components in many herb medical formulations[6] and thus in recent years have attracted intensive research activity directed toward their efficient syntheses.[7]

Several approaches have been developed for the syntheses of catechin and eipgallocatechin-3-gallate, as well as their other derivatives.[7] However, the development of flexible strategy that

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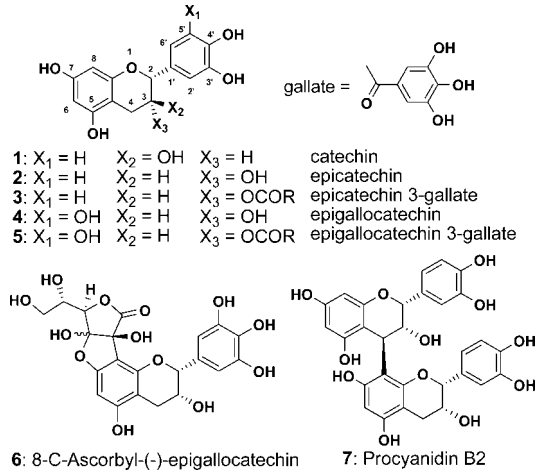


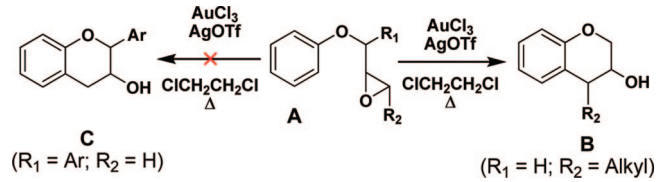

**FIGURE 1.** Catechin and its related natural products.

allows regio- and stereoselective construction of multisubstituted catechins with the defined configuration at the C-2 and C-3 positions (Figure 1) employing versatile building blocks is highly desirable.

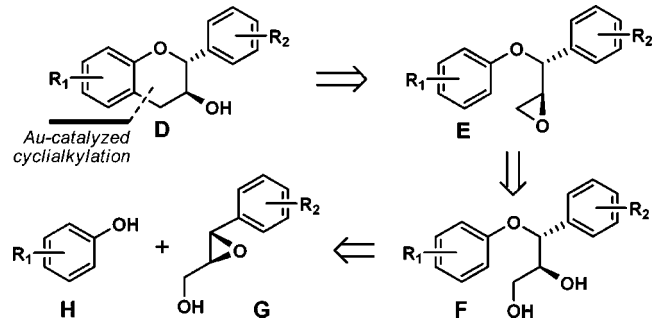
Recently, the development of C−H activation/C−C bond-forming reactions catalyzed by transition metals has received much attention.[8] As a result, a wide range of metal-catalyzed C−H cycloarylations has been applied to the syntheses of structurally diverse scaffolds.[9] In this context, the electronically soft $AuCl_3$ had been shown to be capable of forming arylgold(III) complexes with aromatic groups under anhydrous conditions,[10] and this remarkable activity is presumably responsible for the facile conversion of epoxide **A** into 3-chromanol **B** that was discovered by Shi and He in 2004.[11] Its mechanistic course was conceived to involve an Au-mediated aryl C−H functionalization.[12]

Inspired by the versatility of this Au-catalyzed cycloarylation, we wished to use this annulation reaction to synthesize catechin scaffold **D** from its precursor **E** (Scheme 1). Retrosynthetically,

**SCHEME 1. Au-Catalyzed Annulations**




**SCHEME 2**




the intermediate **E** could be prepared via a tosylate-mediated cyclization reaction from diol **F**, which in turn could be readily accessed through nucleophilic addition of phenol **H** to epoxide **G**.[13]

The original catalytic reaction protocol, however, could not be directly applied to the synthesis of catechins with regard to the existence of the liable benzylic ether moiety (Scheme 2) which might undergo decomposition when exposed to Lewis acid $AuCl_3$.[14] Herein, we describe that thiourea is a unique ligand that can moderate the Lewis acidity of $AuCl_3$/AgOTf, thereby realizing a concise route to generate catechins from benzylic ether-based aryl epoxides. That method constitutes a novel and complementary route to biologically important catechins.

## Results and Discussion

We studied the Au-catalyzed annulation with **11** as a substrate in which the two aromatic rings are electronically biased in such a way that the more electronic-rich ring A should preferentially interact with an incoming Au complex to initiate the desired annulation process in a regioselective manner. The preparation of **11** is illustrated in Scheme 3. Starting from benzaldehyde, the epoxide **8** was synthesized in 68% yield via an olefination−reduction−epoxidation sequence and was next combined with phenol **9** to give diol **10** in 75% yield under sonication conditions.[15] Intramolecular displacement of the monotosylate of **10** thus yielded cleanly **11** in 82% yield.

With substrate **11** in hand, we then set out to investigate its Au-catalyzed annulation, and profiled its reaction under various conditions. We found that in most of the cases the starting material **11** underwent decomposition, and only complex mixtures were obtained, presumably because of the liability of benzylic ether moiety in the substrate toward the Au catalyst.

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However, when the reaction was carried out in $ClCH_2CH_2Cl$ at 50 °C for 4 h in the presence of $AuCl_3$/AgOTf (5 mol %), the expected product **12** with an *endo*-selectivity[11] was indeed obtained, but in merely 20% yield.

To improve the reactivity, we resort to electronic tuning of the Au catalyst through its ligation with several ligands, such as lutidine,[12d] $Ph_3P$,[16] $PCy_3$, BINAP, bisoxazoline,[17] and thioureas **A**−**C**.[18] The performance of these complexes was next screened in a variety of solvents including THF, benzene, toluene, DMF, DMSO, $CH_3CN$, $CH_2Cl_2$, and $ClCH_2CH_2Cl$. Gratifyingly, the best result was obtained when $AuCl_3$/AgOTf/thiourea **A** was utilized, and the desired product **12** was formed in 65% yield (Scheme 3). It is worthwhile to note that the complexes generated from $AuCl_3$/AgOTf with thioureas **B** and **C** gave the lower yields of product **12** (in 52% and 45% yields, respectively), indicating that the oxazoline part of thiourea **A** is essential to get the higher yield (Scheme 3).

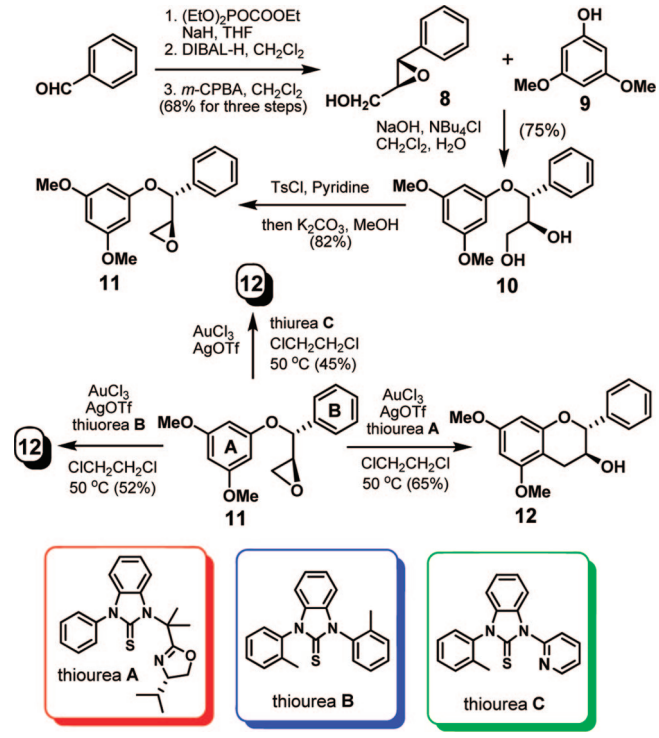
We reasoned that the beneficial effect of ligand **A** on the reaction could be derived from its steric effect and bidentate coordination feature, which might stabilize the metal complexes in $ClCH_2CH_2Cl$. Although $CH_2Cl_2$ shares the similar polarity feature with $ClCH_2CH_2Cl$, its low boiling point prevents it from being used at higher temperature. For other polar solvents (such as THF, DMF, DMSO, $CH_3CN$), the low yields in those reactions might be due to their destabilizing effect on the formation of metal complexes, which might cause the catalyst precipitation.

With this promising initial result, we embarked on a systematic evaluation of the catalytic system in a variety of substituted aryl epoxides. To our delight, all the selected substrates gave good yields and the reaction went to completion at 50 °C in less than 24 h. The formation of catechins bearing electron-withdrawing groups on the aryl B-ring proceeded in high yields (entries 3−12). It is worthwhile to mention that the products with halogens could be potentially used to generate molecular complexity and diversity via metal-catalyzed coupling reactions.

We next examined the dependence of the reaction yield and regioselectivity on substrates bearing an asymmetrically substituted A-ring. The reaction mechanistic scenario suggests that a decreased electron density on the A-ring would weaken the splitting of C−H on the Au center and thus retard the reaction progress. In fact, when eight additional substrates **11m**−**11t** with no or only one alkoxy group on the A-ring were selected and annulated in this process, the reaction speed decreased substantially and little product was formed under conditions employed previously in Table 1, although more product could be obtained at higher temperature and/or with longer time (Table 2). In all cases, the cycloalkylation occurred preferentially at less-hindered aryl ring site.

In summary, we have reported here for the first time the Au-catalyzed cycloalkylation of aryl epoxides to generate a variety of catechins in the presence of thiourea A and demonstrated

**SCHEME 3. Synthesis of Compound 11 and Its Au-Catalyzed Cycloalkylations**




significant ligand effect on tuning the reactivity of the catalysts. Noticing scarce studies on the ligand effect in the Au(III)-catalyzed reactions, we hope our results can benefit other types of Au(III)-catalyzed reactions applied in complex natural product syntheses. Moreover, the constructed catechins are endowed with suitable functionalities that are amenable for further structural elaboration toward more complex molecules with useful biological activities. Integration of this robust method in the asymmetric synthesis of a library of 8-*C*-ascorbyl-(−)-epigallocatechin[19] from chiral epoxides generated by Sharpless epoxidation[20] is currently underway in our laboratory and will be reported in due course.

## Experimental Section

Additional information regarding the synthesis is provided in Supporting Information.

**General Procedure for the Syntheses of Epoxides 11a-3 to 11i-3.** To a suspension of sodium hydride (0.96 g, 60% in mineral oil, 24 mmol) in anhydrous THF (15 mL) was added triethyl phosphonoacetate (4.0 mL, 20 mmol) dropwise at 0 °C under $N_2$, and the mixture was stirred at the same temperature for 30 min. To above solution was added a solution of aldehyde (20 mmol) in THF (10 mL) via a cannula, and the reaction mixture was warmed to room temperature and stirred for 4.0 h. The reaction was worked up by addition of a saturated aqueous $NaHCO_3$ solution (50 mL), the formed organic layer was separated, and the aqueous layer was then extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (3 × 30 mL) and dried over anhydrous

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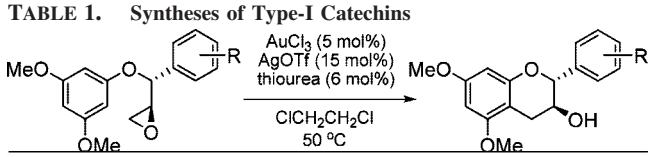
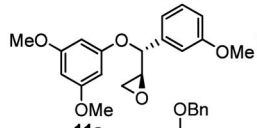
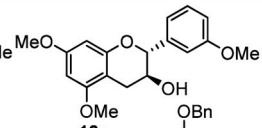
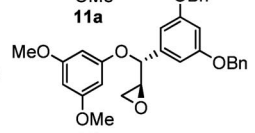
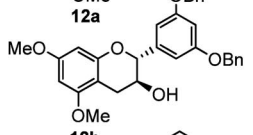
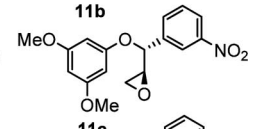
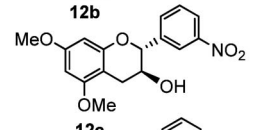
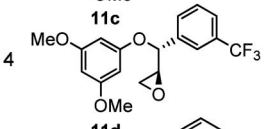
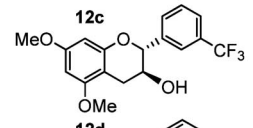
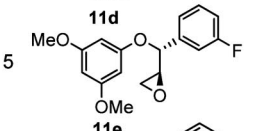
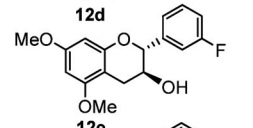
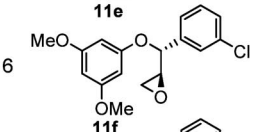
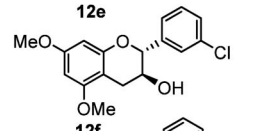
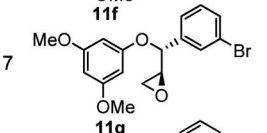
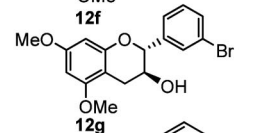
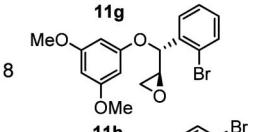
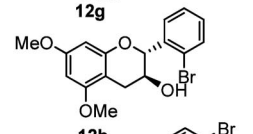
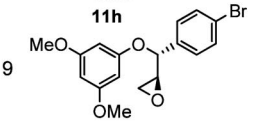
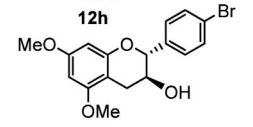
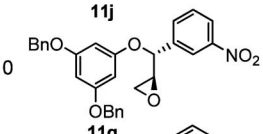
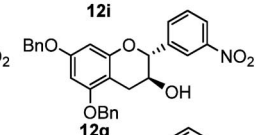
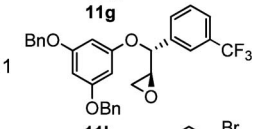
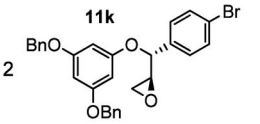
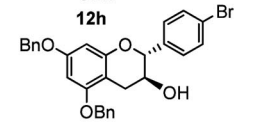
**TABLE 1. Syntheses of Type-I Catechins**

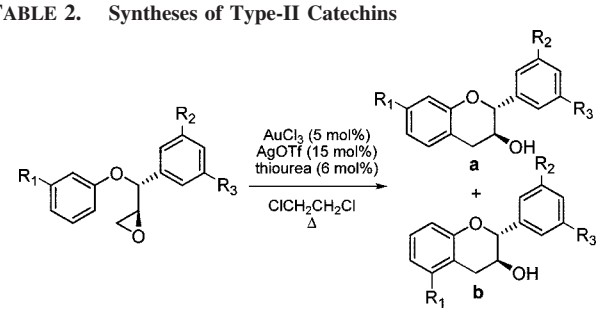


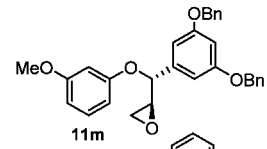
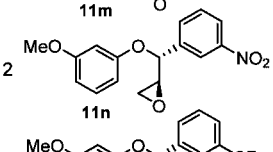
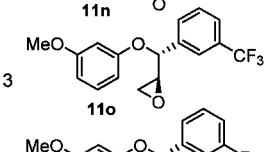
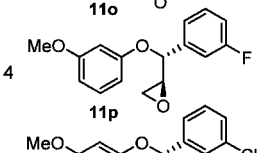
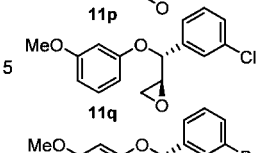
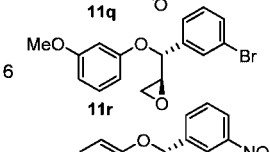
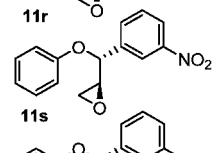
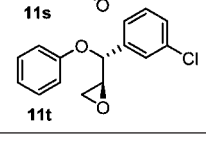

| entry | substrate | product | yield (%) |
|---|---|---|---|
| 1 |  **11a** |  **12a** | 50 |
| 2 |  **11b** |  **12b** | 56 |
| 3 |  **11c** |  **12c** | 90 |
| 4 |  **11d** |  **12d** | 89 |
| 5 |  **11e** |  **12e** | 87 |
| 6 |  **11f** |  **12f** | 74 |
| 7 |  **11g** |  **12g** | 72 |
| 8 |  **11h** |  **12h** | 69 |
| 9 |  **11j** |  **12i** | 79 |
| 10 |  **11g** |  **12g** | 88 |
| 11 |  **11k** |  **12h** | 90 |
| 12 |  **11l** |  **12i** | 74 |

$Na_2SO_4$. The solvent was removed under vacuum, and the residue was used in the next step without further purification.

To a solution of the ester (20 mmol) generated above in dry $CH_2Cl_2$ (25 mL) was added DIBAL-H (50 mL, 1.0 M in hexane, 50 mmol) in a dropwise manner at −78 °C under $N_2$, and the mixture was then stirred at the same temperature until the reaction was completed. The reaction was worked up by careful addition of a saturated aqueous solution of Rochelle salt (100 mL), and the formed mixture was stirred until two phases became clear. The aqueous layer was first extracted with EtOAc (3 × 50 mL), then washed with brine (3 × 30 mL), and finally dried over anhydrous $Na_2SO_4$. The solvent was removed under vacuum, and the residue was then dissolved in $CH_2Cl_2$. To this solution was added *m*-CPBA (6.9 g, 30 mmol) in a portion-wise manner at 0 °C, and the mixture was stirred at the same temperature for 3 h. The reaction was worked up by addition of a solution of $NaHCO_3$ (30% aqueous solution, 100 mL), and the formed aqueous phase was first extracted with EtOAc (3 × 50 mL). The combined organic phase was first washed with brine (3 × 30 mL) and then dried over anhydrous $Na_2SO_4$. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel to give the desired product.

**TABLE 2. Syntheses of Type-II Catechins**




| entry | substrate | product a | product b | yield (%) ratio (a/b) |
|---|---|---|---|---|
| 1 |  **11m** | **12ma** | **12mb** | 50 (4.6/1) |
| 2 |  **11n** | **12na** | **12nb** | 81 (4.5/1) |
| 3 |  **11o** | **12oa** | **12ob** | 74 (4.4/1) |
| 4 |  **11p** | **12pa** | **12pb** | 54 (4.4/1) |
| 5 |  **11q** | **12qa** | **12qb** | 67 (5.1/1) |
| 6 |  **11r** | **12ra** | **12rb** | 66 (5.6/1) |
| 7 |  **11s** | **12sa** | | 56 |
| 8 |  **11t** | **12ta** | | 55 |

**Synthesis of *rac*-(2*S*,3*S*)-3-(3-Methoxyphenyl)-oxiran-2-yl Methanol (11a-3).** The residue was purified by a flash chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to give product **11a-3** (2.95 g) in 82% yield; $^1H$ NMR (300 MHz, $CDCl_3$)

$\delta$ 7.27 (t, $J$ = 7.8 Hz, 1H), 6.78−6.91 (m, 3H), 4.06 (dd, $J_1$ = 2.1 Hz, $J_2$ = 1.6 Hz, 1H), 3.92 (d, $J$ = 2.1 Hz, 1H), 3.83 (s, 3H), 3.22 (dd, $J_1$ = 3.9 Hz, $J_2$ = 2.4 Hz, 1H), 2.10 (br, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.5, 138.1, 129.3, 117.9, 113.7, 110.5, 62.4, 61.1, 55.4, 54.9; MS (EI) calcd for $C_{10}H_{12}O_3$ ($M^+$) 180, found 180.

**General Procedure for the Syntheses of Diols 11a-4 to 11t-4.** To a solution of phenol (12 mmol) in $CH_2Cl_2$ (20 mL) and $H_2O$ (5 mL) was added sodium hydroxide (0.48 g, 12 mmol) and tetrabutyl ammonium chloride (0.56 g, 2.0 mmol) at room temperature, and the mixture was stirred at the same temperature for 0.5 h. To the mixture was added a solution of epoxides **11a-3** to **11i-3** (10 mmol) in $CH_2Cl_2$ (10 mL), and the mixture was then stirred at 65 °C for 6 h. After cooling to room temperature, the reaction was quenched by addition of brine (25 mL), and the formed mixture was extracted with EtOAc (3 × 40 mL). The combined organic phase was washed with water (2 × 30 mL) and dried over anhydrous $Na_2SO_4$. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel to give the desired product.

**Synthesis of *rac*-(2*S*,3*R*)-3-(3,5-Dimethoxyphenoxy)-3-(3-methoxyphenyl)-propane-1,2-diol (11a-4).** The residue was purified by a flash chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to give product **11a-4** (2.00 g) in 60% yield; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.30 (d, $J$ = 7.8 Hz, 1H), 6.97 (d, $J$ = 7.8 Hz, 1H), 6.92 (t, $J$ = 2.4 Hz, 1H), 6.84 (ddd, $J_1$ = 8.4 Hz, $J_2$ = 2.7 Hz, $J_3$ = 0.9 Hz, 1H), 6.03 (s, 3H), 2.22 (d, $J$ = 5.7 Hz, 1H), 2.05 (t, $J$ = 5.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.3, 159.9, 159.3, 139.3, 129.9, 119.0, 113.5, 112.3, 94.7, 93.4, 80.6, 74.7, 62.8, 55.2, 55.1; MS (EI) calcd for $C_{18}H_{22}O_6$ ($M^+$) 334, found 334.

**General Procedures for the Syntheses of Epoxides 11a−11t.** To a solution of the diol (5 mmol) in dry pyridine (10 mL) was added *p*-toluenesulfonyl chloride (0.95 g, 5 mmol) in a portionwise manner at 0 °C, and the resulted mixture was stirred at room temperature overnight. The reaction was worked up by addition of aqueous HCl solution (1 M, 50 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was sequentially washed with brine (2 × 20 mL), 30% aqueous solution of $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL) and finally dried over anhydrous $Na_2SO_4$. The solvent was removed under vacuum, and the residue was dissolved in dry methanol (15 mL). To this solution was added $K_2CO_3$ (0.83 g, 6.0 mmol), and the formed mixture was stirred at room temperature for 4 h. The reaction was worked up by addition of water, and the formed aqueous phase was extracted with ether (3 × 20 mL). The combined organic phase was washed with brine (3 × 15 mL) and dried over anhydrous $Na_2SO_4$. The solvent was removed under vacuum, and the residue was purified by a flash chromatography to give the product.

**Synthesis of *rac*-(*S*)-(2-(*R*)-(3,5-dimethoxyphenoxy)-(3-methoxyphenyl)-methyl)-oxirane (11a).** The residue was purified by a flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give product **11a** (0.885 g) in 56% yield; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.28 (t, $J$ = 8.1 Hz, 1H), 6.95−7.00 (m, 1H), 6.85 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.7 Hz, 1H), 6.03−6.06 (m, 1H), 5.06 (d, $J$ = 4.2 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.32 (dd, $J_1$ = 7.2 Hz, $J_2$ = 3.3 Hz, 1H), 2.83 (d, $J$ = 3.0 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.2, 159.7, 159.3, 138.9, 129.6, 118.9, 113.6, 112.2, 94.8, 93.4, 78.8, 55.1, 55.0, 54.2, 44.9; MS (EI) calcd for $C_{18}H_{20}O_5$ ($M^+$) 316, found 316.

**General Procedure for the Syntheses of Catechins 12, 12a−12i, 12ma−12ta, 12mb−12rb.** A mixture of thiourea A (0.06 mmol), AgOTf (0.15 mmol), and $AuCl_3$ (0.05 mmol) in $ClCH_2CH_2Cl$ (3 mL) was stirred at room temperature under $N_2$ for 1 h. A solution of aryl epoxide (1.0 mmol) in $ClCH_2CH_2Cl$ (2 mL) was added, and the reaction was warmed to 50 °C and stirred until completion. The mixture was then concentrated, and the residue was filtered through a pad of silica gel and washed with EtOAc. The filtrate was concentrated, and the residue was purified by silica gel flash chromatography.

**Synthesis of *rac*-(2*R*,3*S*)-5,7-Dimethoxy-2-(3-methoxy-phenyl)-chroman-3-ol (12a).** The residue was purified by a flash chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give product **12a** (0.158 g) in 50% yield; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 7.8 Hz, 1H), 7.02 (d, $J$ = 7.8 Hz, 1H), 6.99 (m, 1H), 6.90 (ddd, $J_1$ = 8.1 Hz, $J_2$ = 2.7 Hz, $J_3$ = 0.9 Hz, 1H), 6.15 (d, $J$ = 2.4 Hz, 1H), 6.11 (d, $J$ = 2.4 Hz, 1H), 4.75 (d, $J$ = 8.1 Hz, 1H), 4.07−4.11 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 3.01 (dd, $J_1$ = 16.5 Hz, $J_2$ = 5.7 Hz, 1H), 2.62 (dd, $J_1$ = 16.5 Hz, $J_2$ = 8.4 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.7, 159.5, 158.6, 154.9, 139.7, 129.6, 119.2, 113.9, 112.4, 101.3, 92.8, 91.7, 81.4, 67.9, 55.3, 55.2, 55.1, 27.1; HRMS (EI) calcd for $C_{18}H_{20}O_5$ ($M^+$) 316.1311, found 316.1314.

**Syntheses of *rac*-(2*R*,3*S*)-2-(3,5-Bis(benzyloxy)-phenyl)-7-methoxychroman-3-ol (12ma) and *rac*-(2*R*,3*S*)-2-(3,5-Bis(benzyloxy)-phenyl)-5-methoxy chroman-3-ol (12mb).** The reaction was carried out at 80 °C for 24 h, and the residue was purified by a flash chromatography on silica gel (petroleum ether/ethyl acetate = 7/1) to give product **12ma** (0.192 g) in 41% yield and compound **12mb** (0.042 g, 9% yield). For compound **12ma**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.31−7.43 (m, 10H), 7.00 (d, $J$ = 8.4 Hz, 1H), 6.69 (d, $J$ = 2.1 Hz, 2H), 6.62 (t, $J$ = 2.1 Hz, 1H), 6.49−6.54 (m, 2H), 5.03 (s, 4 H), 4.73 (d, $J$ = 7.8 Hz, 1H), 4.07 (dt, $J_1$ = 5.1 Hz, $J_2$ = 8.4 Hz, 1H), 3.77 (s, 3H), 3.01 (dd, $J_1$ = 15.6 Hz, $J_2$ = 5.1 Hz, 1H), 2.82 (dd, $J_1$ = 15.6 Hz, $J_2$ = 8.7 Hz, 1H), 1.82 (br, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 160.1, 159.2, 154.4, 140.4, 136.5, 130.4, 128.5, 128.0, 127.5, 111.8, 108.0, 106.0, 102.0, 101.1, 81.1, 70.0, 68.0, 55.2, 31.9; HRMS (EI) calcd for $C_{30}H_{28}O_5$ ($M^+$) 468.1937, found 468.1941. For compound **12mb**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.29−7.43 (m, 10H), 7.12 (t, $J$ = 8.1 Hz, 1H), 6.70 (d, $J$ = 2.1 Hz, 2H), 6.58−6.62 (m, 2H), 6.48 (d, $J$ = 8.1 Hz, 1H), 5.03 (s, 4H), 4.68 (d, $J$ = 8.4 Hz, 1H), 4.05−4.07 (m, 1H), 3.84 (s, 3H), 3.08 (dd, $J_1$ = 16.8 Hz, $J_2$ = 5.7 Hz, 1H), 2.66 (dd, $J_1$ = 16.8 Hz, $J_2$ = 9.0 Hz, 1H), 1.73 (d, $J$ = 3.6 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 160.2, 159.3, 154.5, 140.3, 136.5, 130.4, 128.6, 128.1, 127.6, 111.8, 108.2, 106.0, 102.2, 101.2, 81.8, 70.1, 68.2, 32.0; HRMS (EI) calcd for $C_{30}H_{28}O_5$ ($M^+$) 468.1937, found 468.1943.

**Acknowledgment.** We gratefully acknowledge financial support by the National Science Foundation of China (Grants 20672004, 20521202). We also thank Professor David Zhigang Wang of the Laboratory of Chemical Genomics of Peking University for useful discussion.

**Supporting Information Available:** Experimental procedure and $^1$H NMR and $^{13}$C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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