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Highly enantioselective vinylogous aldol reaction of dioxinone-derived silyl diene by combined Lewis acid catalyst

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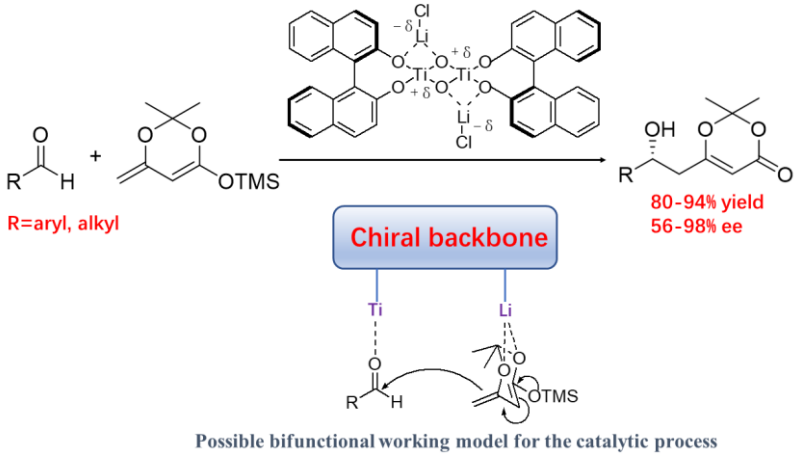
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Abstract

The combined Lewis acid catalytic system, generated from (*R*)-1,1'-bi-2,2'-naphthol [(*R*)-BINOL], Ti(O-*i*Pr)$_4$, H_2O, and lithium chloride, effectively catalyzed the enantioselective vinylogous aldol reaction of aldehyde with diene affording the adducts exclusively in good yields (80-94%) and excellent enantioselectivities (56-98%) under mild conditions. These adducts were characterized by nuclear magnetic resonance, infrared spectroscopy and mass spectrometry. A Lewis acid-Lewis acid bifunctional working model was proposed for the catalytic process based on some control experiments. We obtained the natural product (*S*)-(+)-Dihydrokavain (81% yield, 84% ee) through the method which has been established by the combined Lewis acid catalytic system.



Possible bifunctional working model for the catalytic process

Keywords: Asymmetric aldol reaction, aldehyde, diene, chiral Lewis acid, natural product

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Introduction

The asymmetric vinylogous aldol (AVA) reaction has been one of the versatile C-C bond-forming reactions with extensive application in the synthesis of natural producuts[1]. It was noteworthy that the asymmetric aldol reaction of aldehydes with dioxinone-derived sliyl diene induced chiral alcohol structures with additional four-carbon chains. These adducts containing many functional groups could further react. The β-hydroxy carboxylic acids、β-hydroxy ketones、δ-hydroxy-β-carbonyl esters and six-membered ring lactones were derived from the adducts, which were ubiqutious structural subunits in biologically active natural products such as the polyene macrolide antibiotics、HMG-CoA reductase inhibitors and Vitamin D_3 analogues[2]. Therefore, developing simple and effective methods for the catalytic production of optically active compounds is among the most important tasks in current synthesis of these natural products.

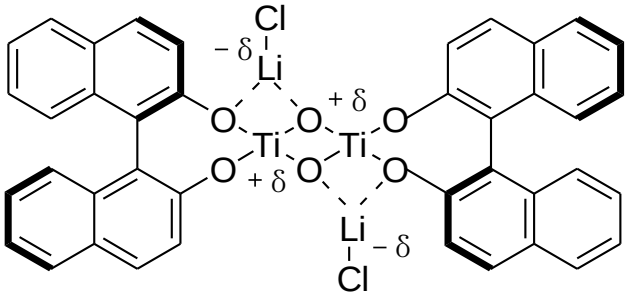


Figure 1. Proposed structure for (*R*)-BTHL.

In the past decades, some successful applications of enantioselective vinylogous aldol reaction catalyzed by chiral metal complexes or small organic molecules have been reported[3-13]. However, those methods still suffered from some drawbacks: unfriendly conditions, expensive reagents, or narrow substrates tolerance. Recently, the strategy of combined Lewis acid has attracted much attention in the design of asymmetric catalyst. Combination of Lewis acids, also referred as Lewis acid assisted Lewis acid, could enhance the inherent acid reactivity by associative interaction, while reorganized structure provides a more efficient chiral induction[14-23]. Especially, Qu and co-workers reported a novel combined Lewis acid catalyst (*R*)-BINOL-Ti-H_2O-LiCl ((*R*)-BTHL) that was generated in situ by equal molar combination of (*R*)-BINOL-Ti species and weak Lewis acid LiCl to effectively promote the AVA reaction between aromatic aldehydes and Brassard's diene (Figure **1**) [24-25]. Consequently, considering the potential utility of dioxinone derivatives, it would be an interesting task to investigate the AVA reaction of dioxinone-derived sliyl diene[26] with aldehydes via the composite metal catalyst under mild conditions.

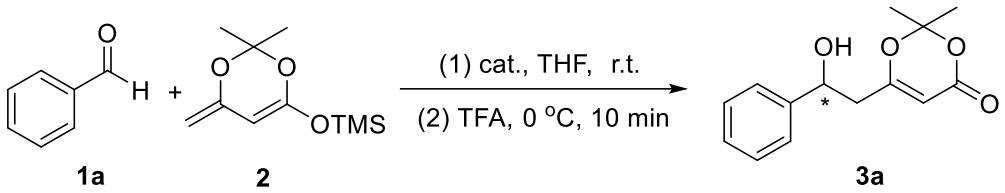
Results and Discussion

Optimization of the (*R*)-BTHL catalyzed enantioselective vinylogous aldol reaction

Initially, the reaction between benzaldehyde and dioxinone-derived sliyl diene (1.2 equiv) was tested in THF at room temperature using 10 mol% (*R*)-BTHL. To our delight, the reaction proceeded through an aldol pathway to give the linear product exclusively after workup with TFA. As shown in Scheme **1** and Table **1**, water and LiCl were indispensible for the high performance of the catalytic reaction system. The simple equal molar combination of (*R*)-BINOL and Ti(O-*i*Pr)$_4$ was tested under identical conditions, and the desired aldol product **3a** was obtained in only 58% yield with disappointing selectivities (54% ee). When the (*R*)-BINOL-Ti complex was hydrolyzed with 1 equiv of water and used as catalyst, the aldol product **3a** was obtained with only 52% yield and 59% ee. When LiCl was added to the (*R*)-BINOL-Ti complex in the absence of H_2O, the yield and

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enantioselectivity of the aldol product **3a** increased significantly (entries 1-4). Then, we investigated what effect the amount of water or LiCl exerted on the performance of the catalytic system. It turned out that increase or decrease of the amount of water or LiCl would cause decreased results (entries 5-8). Additionally, other Lewis acids replacing LiCl have also been shown to be unfavorable for this reaction (entries 9-11).



1a **2** **3a**

Scheme 1. Various (*R*)-BINOL-Ti species catalyzed AVA reaction of benzaldehyde **1a** with dioxinone-derived sliyl diene **2**[a].

Table 1. Various (*R*)-BINOL-Ti species catalyzed AVA reaction of benzaldehyde **1a** with dioxinone-derived sliyl diene **2**[a].

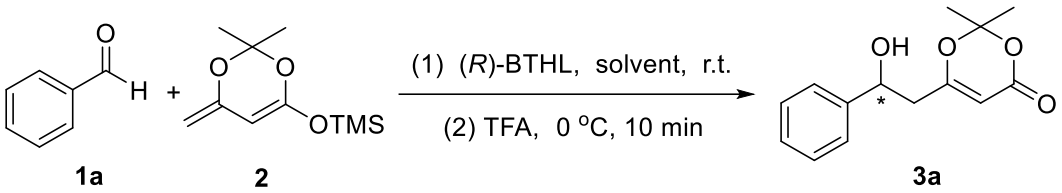
entry	catalyst type	ratio	yield[b](%)	ee[c] (%)
1	BINOL-Ti	1:1	58	54
2	BINOL-Ti-H_2O	1:1:1	52	59
3	BINOL-Ti-LiCl	1:1:1	67	72
4	BINOL-Ti-H_2O-LiCl	1:1:1:1	79	94
5	BINOL-Ti-H_2O-LiCl	1:1:1.5:1	70	92
6	BINOL-Ti-H_2O-LiCl	1:1:0.5:1	67	88
7	BINOL-Ti-H_2O-LiCl	1:1:1:1.5	77	91
8	BINOL-Ti-H_2O-LiCl	1:1:1:0.5	74	93
9	BINOL-Ti-H_2O-LiBr	1:1:1:1	54	59
10	BINOL-Ti-H_2O-$LiOCH_3$	1:1:1:1	61	30
11	BINOL-Ti-H_2O-CsF	1:1:1:1	72	2

[a]Unless specially noted, all reactions were performed with 0.5 mmol of benzaldehyde and diene **2** (0.6 mmol) in 2 mL of THF at 25 °C using 10 mol% catalyst over 6 h, and then cooled to 0 °C and quenched with two drops of TFA.

[b]Isolated yield. [c]The enantiomeric excess was determined by HPLC analysis using chiral OD-H column.

Thus, owing to the promising asymmetric catalytic ability of (*R*)-BTHL (1:1:1:1), we carried out a detailed optimization of the reaction parameters by using this catalyst and the results were summarized in Scheme **2** and Table **2**. At first, increasing the amount of diene to 1.5 equiv, the yield and ee of the aldol product **3a** nearly unchanged. Secondly, when the temperature was lowered to 0 °C, the reaction rate decreased obviously, while the enantioselectivity was still maintained (entries 1-3). We then examined the effect of solvents on this reaction, and found that the enantioselectivity dropped off markedly in solvents such as ether or CH_2Cl_2 because of the bad solubility of (*R*)-BTHL in other solvents except THF (entries 4-5). Increasing the amount of THF, the yield and ee only dropped slightly. Next, reducing the solvent loading from 2 mL to 1 mL, the reaction gave 78% yield and 95% ee. Over extended time to 12 h, the yield increased to 91%, while the ee was still 95% (entries 6-9). Furthermore, it was shown that the reduction in catalyst dosage was detrimental to yield and ee of the aldol product **3a** (entries 10-11). Therefore, we took entry 6 as the optimal conditions for further substrate generality investigation.

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Scheme 2. Reaction condition optimsim of benzaldehyde **1a** with dioxinone-derived sliyl diene **2**[a].

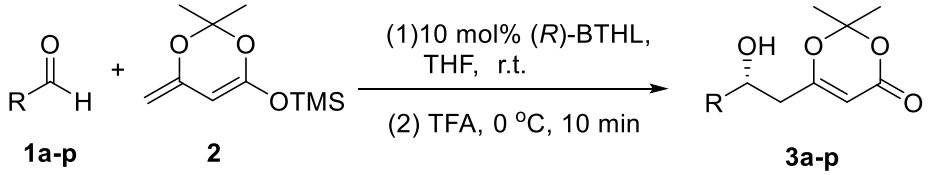
Table 2. Reaction condition optimsim of benzaldehyde **1a** with dioxinone-derived sliyl diene **2**[a].

entry	(*R*)-BTHL (mol %)	solvent	yield[e] (%)	ee[f] (%)
1	10	2 mL THF	77	94
2[b]	10	2 mL THF	78	94
3[c]	10	2 mL THF	45	94
4	10	2 mL ether	51	14
5	10	2 mL CH_2Cl_2	59	2
6	10	1 mL THF	78	95
7	10	3 mL THF	73	93
8	10	4 mL THF	70	92
9[d]	10	1 mL THF	91	95
10	7.5	1 mL THF	71	90
11	5	1 mL THF	67	75

[a]Unless specially noted, all reactions were performed with 0.5 mmol of benzaldehyde and diene **2** (0.6 mmol) at 25 °C over 6 h, and then cooled to 0 °C and quenched with two drops of TFA. [b]The amount of dioxinone-derived sliyl diene was 0.75 mmol. [c]The reaction proceeded at 0 °C. [d]Over 12 h. [e]Isolated yield. [f]The enantiomeric excess was determined by HPLC analysis using chiral OD-H column.

Substrate scope

An array of aromatic aldehydes bearing different substituent groups was reacted with dioxinone-derived sliyl diene. As shown in Scheme **3** and Table **3**, An excellent yield (≥90%) as well as high to excellent enantioselectivity (up to 98% ee) was obtained for aromatic aldehydes modified by a electron donating or electron withdrawing group at meta and para positions of benzene ring. However, being different from the methoxy and fluorine groups, the reaction for the aromatic aldehydes modified by Cl or Br at the ortho position of benzene ring achieved the low enantioselectivity (entries 10 and 16). We speculated that was caused by the combined effect of the lone-pair electrons and steric hindrance of Cl or Br. In addition, various types of aromatic aldehydes such as cinnamaldehyde and furaldehyde were also compatible.



Scheme 3. Substrate generality for the aromatic aldehydes[a].

Table 3. Substrate generality for the aromatic aldehydes[a].

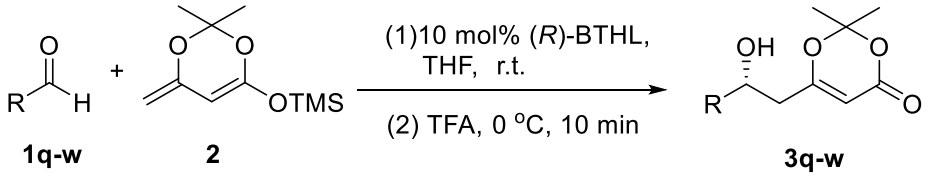
entry	R	yield[b]/%	ee[c]/%	Absolute configuration[d]
1	C_6H_5 **(1a)**	91	95	*R*
2	*p*-$CH_3C_6H_4$ **(1b)**	92	98	*R*
3	*o*-$CH_3OC_6H_4$ **(1c)**	90	90	*R*

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4	*m*-$NO_2C_6H_4$ **(1d)**	90	85	*R*
5	*p*-$NO_2C_6H_4$ **(1e)**	92	85	*R*
6	*p*-$(CH_3)_2NC_6H_4$ **(1f)**	91	94	*R*
7	3, 4, 5-$(CH_3O)_3C_6H_2$ **(1g)**	92	97	*R*
8	*p*-ClC_6H_4 **(1h)**	92	93	*R*
9	*p*-BrC_6H_4 **(1i)**	90	95	*R*
10	*o*-BrC_6H_4 **(1j)**	90	77	*R*
11	*p*-FC_6H_4 **(1k)**	94	96	*R*
12	*o*-FC_6H_4 **(1l)**	91	93	*R*
13	C_6H_5CH=CH **(1m)**	93	93	*R*
14	2-Furyl **(1n)**	90	93	*R*
15	*p*-$CH_3OC_6H_4$ **(1o)**	90	93	*R*
16	*o*-ClC_6H_4 **(1p)**	91	56	*R*

[a]Unless specially noted, all reactions were performed with 0.5 mmol of aromatic aldehydes and diene **2** (0.6 mmol) at 25 °C over 12 h, and then cooled to 0 °C and quenched with two drops of TFA. [b]Isolated yield. [c]The enantiomeric excess was determined by HPLC analysis using chiral OD-H and AD-H column. [d]The absolute configuration was determined by measuring the optical rotation and comparing with the relevant literature.

To further demonstrate the broad generality and reliability of the protocol, we examined the asymmetric reaction by using aliphatic aldehydes as the indole electrophiles. The results are summarized in Scheme **4** and Table **4**. Compared with aromatic aldehydes, the asymmetric catalytic reaction rate of aliphatic aldehydes decreased slightly, but still maintained good enantioselectivity. Extending the reaction time to 22 h, all the combinations of aliphatic aldehydes and the dioxinone-derived sliyl diene could also proceed very cleanly and efficiently under the optimized conditions to afford the desired products **3q**–**3w** in excellent yields (≥80%) as well as high ee values (86–97%). These results unambiguously exemplified that the asymmetric reaction presented herein also displays a broad substrate scope for aldehyde electrophiles.



Scheme 4. Substrate generality for the aliphatic aldehydes[a].

Table 4. Substrate generality for the aliphatic aldehydes[a].

entry	R	yield[b]/%	ee[c]/%	absolute configuration[d]
1	n-C_3H_7 **(1q)**	83	93	*S*
2	$(CH_3)_2CH$ **(1r)**	80	86	*R*
3	n-C_5H_{11} **(1s)**	87	90	*S*
4	n-C_4H_9 **(1t)**	84	92	*S*
5	CH_3CH_2**(1u)**	83	91	*S*
6	CH_3CH=CH **(1v)**	85	97	*R*
7	$C_6H_5CH_2CH_2$ (**1w)**	86	91	*S*

[a]Unless specially noted, all reactions were performed with 0.5 mmol of aliphatic aldehydes and diene **2** (0.6 mmol) at 25 °C over 22 h, and then cooled to 0 °C and quenched with two drops of TFA. [b]Isolated yield. [c]The enantiomeric excess was determined by HPLC analysis using chiral OD-H, AD-H and OJ-H column. [d]The

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absolute configuration was determined by measuring the optical rotation and comparing with the relevant literature.

Study on the catalytic process using combined Lewis acids

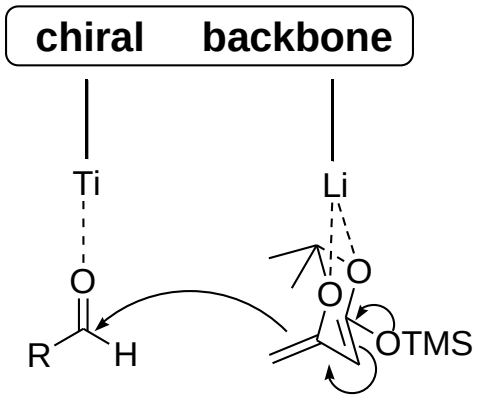


Figure 2. Possible bifunctional working model for the catalytic process.

Based on Qu's outstanding work, we speculated that the strong Lewis acid Ti activated the carbonyl group and the diene would coordinate to the weak Lewis acid Li center in a chelating manner for positioning close to the aldehyde. The two metal centers function differently and both were essential for high selectivity (Figure **2**). For a better understanding of the working model of the asymmetric transformation, we carried out additional nonlinear effect (NLE) experiments for this catalytic system using partially racemic BINOL while keeping the other conditions unchanged. As shown in Figure **3**, Line **1** represented the catalytic results when the R- and S-ligands were mixed together in proportion to prepare BTHL in situ, and Line **2** represented the catalytic results using the catalyst mixing (*R*)-BTHL and (*S*)-BTHL in proportion. The strong positive NLEs implied that an oligomeric titanium structure might work as the active species to promote the reaction. Once the catalyst preparation completed, it was difficult to exchange ligands with each other[27]. Additionally, the improvement of catalytic efficiency also indicated that with the accumulation of aldol addition product, the product also acted as a new type of ligand to complex with metal to form a new catalyst with higher catalytic efficiency[28].

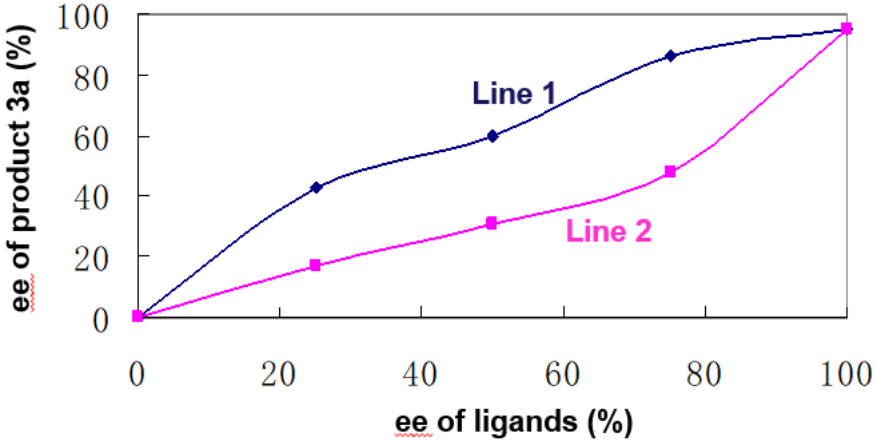


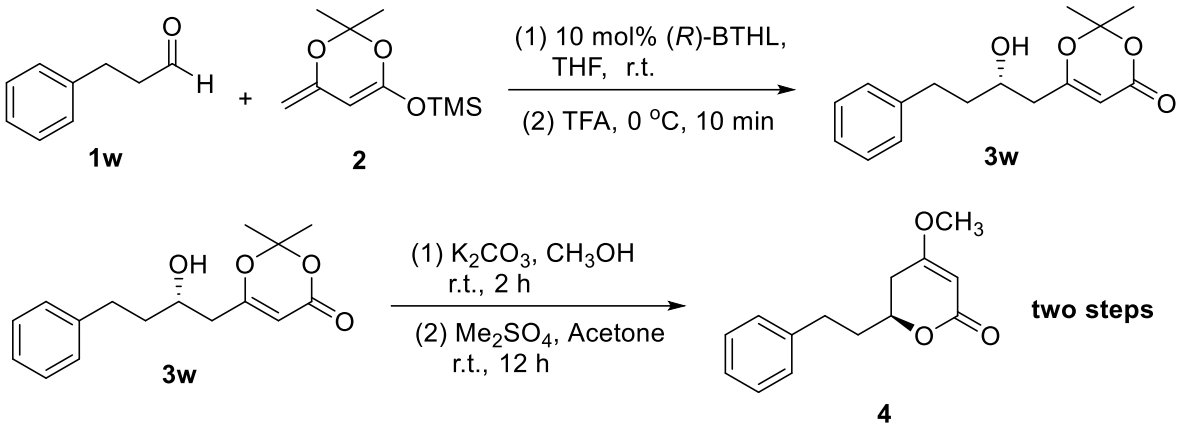
Figure 3. Nonlinear effect (NLE) in the AVA reaction of benzaldehyde with dioxinone-derived sliyl diene **2**.

Application of the AVA reaction in the natural product (S)-(+)-Dihydrokavain

Of note, the natural product (*S*)-(+)-Dihydrokavain has received increasing attention due to its sedative, anticonvulsant, anesthetic and antifungal biological activities[29]. However, the current methods for

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synthesizing (*S*)-(+)-Dihydrokavain suffered from severe drawbacks in both yield and enantioselectivity. As shown in Scheme **5**, using the (*R*)-BTHL, the asymmetric aldol reaction of phenylpropanal **1w** and diene **2** was catalyzed efficiently, and then deprotected to generate lactone[30], and finally obtained the target product **4** (81% yield, 84% ee) after methylation. These transformations broaden the utility of this developed methodology.



Scheme 5. Total synthesis of the natural product (*S*)-(+)-Dihydrokavain.

Conclusions

In summary, we have developed a novel methodology that has realized the asymmetric aldol reaction of aldehydes and dioxinone-derived sliyl diene with high enantioselectivities and good yields through LiCl assisted (*R*)-BINOL-Ti species ((*R*)-BTHL). The protocol exhibited a broad compatibility for these substrates and could proceed in a very simple, clean, mild, and atom-economical manner. In addition, the utility of this protocol was demonstrated in the convenient and formal synthesis of Dihydrokavain.

Experimental Section

General. Anhydrous solvents were obtained by distillation according to standard methods. All starting materials were purchased from Alfa and Aldrich and used directly. Otherwise noted, the ^{1}H NMR spectra were recorded at 400 MHz (Bruker AV) in $CDCl_3$. All shifts are given in ppm. All coupling constants (J values) were reported in Hertz (Hz). HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump, UV detection monitored at 254nm). Chiralpak AD-H, OJ-H and OD-H columns were purchased from Daicel Chemical Industries, LTD. Column chromatography was performed on silica gel 100–200 mesh.

General procedure for the vinylogous aldol reaction of aldehydes and dioxinone-derived sliyl diene 2

Taking benzaldehyde as an example. Under N_2 atmosphere in a dry Schlenk tube, a mixture of Ti(O-*i*Pr)$_4$ (28.4 mg, 0.1 mmol) and (*R*)-BINOL (28.6 mg, 0.1 mmol) was stirred in THF (2 mL) at room temperature for 20 min. Then to this mixture was added H_2O (1.8 mg, 0.1 mmol) with a syringe. After another 20 min, anhydrous LiCl (4.3 mg, 0.1 mmol) kept in a Schlenk tube was quickly added bottle to bottle under N_2 atmosphere. After the mixture was stirred over 30 min, 1 mL of the catalyst solution was transferred to another Schlenk tube and the benzaldehyde **1a** (0.5 mmol) and dioxinone-derived sliyl diene **2** (0.6 mmol) were added successively by a syringe. After being stirred for 12 h at 25 °C, the reaction solution was cooled to 0 °C and quenched with TFA (0.6 mmol). After an additional 15 min, the mixture was neutralized with saturated $NaHCO_3$. After usual

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workup, the residue was purified by chromatography on silica gel (acetone/petroleum ether = 1:3) to afford **(5*R*)-6-(2-Hydroxy-2-phenylethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one**. White, crystalline solid (mp 44°C) in 91% yield: $[\alpha]_D^{20}$ +36.2 (*c* = 0.744, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.4-7.3 (m, 5 H), 5.29 (s, 1 H), 4.98 (m, 1 H), 2.66 (dd, *J* 14.6, 8.2, 1 H), 2.61 (dd, *J* 14.6, 4.8, 1 H), 2.05 (d, *J* 3.2, 1 H), 1.65 (s, 3 H), 1.56 (s, 3 H,); Enantiomeric excess was determined to be 95% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 15.8 min. (major), 27.8 min. (minor).)

(5*R*)-6-(2-Hydroxy-2-(4-methylphenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3b). This product was obtained as a white, crystalline solid (mp 46°C) in 92% yield after column chromatography (acetone/petroleum ether = 1:3). $[\alpha]_D^{19.5}$ +36.4 (*c* = 0.384, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.3-7.1 (m, 4 H), 5.29 (s, 1 H), 4.95 (m, 1 H), 2.69 (dd, *J* 20, 8, 1 H), 2.59 (dd, *J* = 20, 4, 1 H), 2.35 (s, 3H), 2.08 (d, 1 H), 1.67 (s, 3 H), 1.61 (s, 3 H); Enantiomeric excess was determined to be 98% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.6 mL/min, 13.6 min (major), 34.4 min (minor).)

(5*R*)-6-(2-Hydroxy-2-(2-methoxyphenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3c). This product was obtained as a white, crystalline solid (mp 45°C) in 90% yield after column chromatography (acetone/petroleum ether = 1:3). $[\alpha]_D^{19.5}$ +28.4 (*c* = 0.808, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.3-6.8 (m, 4 H), 5.30 (s, 1 H), 5.14 (m, 1 H), 3.88 (s, 3H), 2.75 (dd, 1 H), 2.72 (dd, 1 H), 2.72 (d, 1 H), 1.68 (s, 3 H), 1.67 (s, 3 H); Enantiomeric excess was determined to be 90% (determined by HPLC using chiralcel AD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.4 mL/min, 12.7 min. (major), 13.8 min. (minor).)

(5*R*)-6-(2-Hydroxy-2-(3-nitrophenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3d). This product was obtained as a white, crystalline solid (mp 46°C) in 90% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{15}$ +32.43 (*c* = 1.033, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.3-7.5 (m, 4 H), 5.35 (s, 1 H), 5.14 (m, 1 H), 3.18 (d, 1 H), 2.66 (m, 2 H), 1.69 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 167.8 161.3 148.4 145.2 131.8 129.7 122.9 120.7 106.9 95.6 69.9 43.3 25.3 24.7; ESI-HRMS: $(M+CH_3COO)^-$, calcd. for $C_{16}H_{18}NO_8$: 352.1032, found: 352.0851; Enantiomeric excess was determined to be 85% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 16.6 min. (major), 21.5 min. (minor).)

(5*R*)-6-(2-Hydroxy-2-(4-nitrophenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3e). This product was obtained as a white, crystalline solid (m.p. 49 °C) in 92% yield after column chromatography (acetone/petroleum ether = 1/2). $[\alpha]_D^{20}$ +40.1 (*c* = 0.305, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.3-7.5 (m, 4 H), 5.35 (s, 1 H), 5.14 (m, 1 H), 2.71(d, 1 H) 2.65 (m, 2 H), 1.70 (s, 3 H), 1.63 (s, 3 H); Enantiomeric excess was determined to be 85% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 17.7 min (major), 22 min (minor.)

(5*R*)-6-(2-Hydroxy-2-(4-*N,N*-dimethylaminophenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3f). This product was obtained as a yellow, crystalline solid (mp 49°C) in 91% yield after column chromatography (acetone/petroleum ether = 1:2). $[\alpha]_D^{15}$ +27.7 (*c* = 0.448, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.3-6.7 (m, 4 H), 5.29 (s, 1 H), 4.9 (m, 1 H), 2.98 (s, 6 H), 2.71 (dd, *J* 36, 8, 1 H), 2.60 (dd, *J* = 36, 4, 1 H), 2.17 (d, 1 H), 1.68 (s, 3 H), 1.65 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.7 161.2 150.6 130.2 126.8 112.5 106.6 95.2 71.1 42.9 40.5 25.4 24.8; ESI-HRMS: $(M+CH_3COO)^-$, calcd. for $C_{18}H_{24}NO_6$: 350.1604, found: 350.1609; Enantiomeric excess was determined to be 94% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.6 mL/min, 20.2 min. (major), 33 min. (minor).)

(5*R*)-6-(2-Hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3g). This product was obtained as a white, crystalline solid (mp 47 °C) in 92% yield after column chromatography (acetone/petroleum ether = 1:2). $[\alpha]_D^{15.2}$ +27.04 (*c* = 0.548, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.59 (s, 2 H), 5.35 (s, 1 H), 4.93 (m, 1 H), 3.87 (s, 6H), 3.84 (s, 3H) 2.65 (dd, *J* 12, 8, 1 H), 2.60 (dd, *J* 12, 4, 1 H), 2.18 (d, 1 H), 1.71 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.4 161.1 153.4 138.7 137.6 106.7 102.5 95.4 71.3 60.9 56.2 43.4

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25.5 24.6; ESI-HRMS: $(M+CH_3COO)^-$, calcd. for $C_{19}H_{25}O_9$: 397.1499, found: 397.1342; Enantiomeric excess was determined to be 97% (determined by HPLC using chiralcel AD-H column, 10% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.7 mL/min, 8.4 min (major), 9.7 min (minor)).

(5*R*)-6-(2-Hydroxy-2-(4-chlorophenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3h). This product was obtained as a white, crystalline solid (mp 46°C) in 92% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{15}$ +36.9 (*c* = 1.079, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.3-7.2 (m, 4 H), 5.30 (s, 1 H), 4.98 (m, 1 H), 3.88 (s, 3 H), 2.65 (dd, *J* 24, 8, 1 H), 2.58 (dd, *J* 20, 4, 1 H), 2.39 (d, 1 H), 1.68 (s, 3 H), 1.67 (s, 3 H); Enantiomeric excess was determined to be 93% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 11.9 min. (major), 19 min. (minor).)

(5*R*)-6-(2-Hydroxy-2-(4-bromophenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3i). This product was obtained as a white, crystalline solid (mp 46°C) in 90% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{15.2}$= +33.6 (*c* = 1.072, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.5-7.2 (m, 4 H), 5.30 (s, 1 H), 4.94 (m, 1 H), 3.88 (s, 3 H), 2.64 (dd, 1 H), 2.57 (dd, 1 H), 2.54 (d, 1 H), 1.67 (s, 3 H), 1.66 (s, 3 H); Enantiomeric excess was determined to be 95% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.6 mL/min, 13.1 min (major), 24.8 min.(minor)).

(5*R*)-6-(2-Hydroxy-2-(2-bromophenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3j). This product was obtained as a white, crystalline solid (mp 45 °C) in 90% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{13}$ +53.9 (*c* = 1.114, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.6-7.1 (m, 4 H), 5.35 (s, 1 H), 5.32 (m, 1 H), 3.13 (s, 1 H), 2.74 (dd, *J* 12, 4, 1 H), 2.48 (dd, *J* 12, 4, 1 H), 1.69 (s, 3 H), 1.67 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.9 161.6 141.9 132.8 129.4 127.9 127.3 121.5 106.8 95.1 65.9 65.8 41.5 25.3 24.7 15.2; ESI-HRMS: $(M+Na)^+$, calcd. for $C_{14}H_{15}BrNaO_4$: 349.0051, found: 349.0057; Enantiomeric excess was determined to be 77% (determined by HPLC using chiralcel AD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.6 mL/min, 5.6 min (major), 6.6 min (minor)).

(5*R*)-6-(2-Hydroxy-2-(4-fluorophenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3k). This product was obtained as a white, crystalline solid (mp 46 °C) in 94% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{14}$ +28.5 (*c* = 0.908, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.35-7.02 (m, 4 H), 5.27 (s, 1 H), 4.95 (m, 1 H), 2.99 (s, 1 H), 2.65 (dd, 1 H), 2.55 (dd, 1 H), 1.65 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.5 163.6 161.4 161.1 138.8 138.7 127.5 127.4 115.6 115.4 106.8 95.2 70.3 43.3 25.3 24.6; ESI-HRMS: $(M+Na)^+$, calcd. for $C_{14}H_{15}BFNaO_4$: 289.0852, found: 289.0851; Enantiomeric excess was determined to be 96% (determined by HPLC using chiralcel AD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 10.7 min (major), 12.9 min (minor)).

(5*R*)-6-(2-Hydroxy-2-(2-fluorophenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3l). This product was obtained as a white, crystalline solid (mp 44°C) in 91% yield after column chromatography (acetone/petroleum ether = 1:3). $[\alpha]_D^{14}$ +35.2 (*c* = 0.913, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.51-7.01 (m, 4 H), 5.30 (s, 1 H), 5.26 (m, 1 H), 2.93(d, 1 H), 2.67 (m, 2 H), 1.66 (s, 3 H), 1.63 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.5 161.4 160.8 158.3 129.6 129.5 127.3 127,2 124.5 115.5 115.3 106.8 95.2 65.3 41.9 25.2 24.6; ESI-HRMS: $(M+Na)^+$, calcd. for $C_{14}H_{15}BFNaO_4$: 289.0852, found: 289.0855; Enantiomeric excess was determined to be 93% (determined by HPLC using chiralcel AD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.6 mL/min, 9.4 min. (major), 12.2 min. (minor).)

(5*R*)-6-(2-Hydroxy-4-phenyl-3-butenyl)-2,2-dimethyl-[1,3]-dioxin-4-one(3m). This product was obtained as a white, crystalline solid (mp 45 °C) in 93% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{14}$ +7.4 (*c* = 1.026, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.38-7.25 (m, 5 H), 6.62 (d, 1 H), 6.21 (dd, 1 H) 5.37 (s, 1 H), 4.60 (m, 1 H), 2.56 (m, 2 H), 2.02 (s, 1 H), 1.70 (s, 3 H), 1.69 (s, 3 H); Enantiomeric excess was

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determined to be 93% (determined by HPLC using chiralcel AD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.6 mL/min, 8.3 min (major), 9.2 min. (minor)).

(5*R*)-6-(2-Hydroxy-2-furanylethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3n). This product was obtained as a white, crystalline solid (mp 46°C) in 90% yield after column chromatography (acetone/petroleum ether = 1:3). $[\alpha]_D^{14}$ +24.5 (*c* = 0.827, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.39 (d, 1 H), 6.34 (d, 1 H), 6.29 (d, 1 H) 5.32 (s, 1 H), 5.00 (m, 1 H), 2.79 (m, 2 H), 2.52 (d, 1 H), 1.68 (s, 3 H), 1.64 (s, 3 H); Enantiomeric excess was determined to be 93% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.6 mL/min, 10.8 min (major), 13.2 min (minor)).

(5*R*)-6-(2-Hydroxy-2-(4-methoxyphenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3o). This product was obtained as a white, crystalline solid (m.p. 47 °C) in 90% yield after column chromatography (acetone/petroleum ether = 1:3). $[\alpha]_D^{24.7}$ +20.5 (*c* = 0.457, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.3-6.8 (m, 4 H), 5.28 (s, 1 H), 4.93 (m, 1 H), 3.81 (s, 3 H), 2.70 (dd, *J* 12, 4, 1 H), 2.58 (dd, *J* 8, 4, 1 H), 2.17 (d, 1 H), 1.67 (s, 3 H), 1.65 (s, 3 H); Enantiomeric excess was determined to be 93% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 15.1 min (major), 27.1 min (minor)).

(5*R*)-6-(2-Hydroxy-2-(2-chlorophenyl)ethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3p). This product was obtained as a white, crystalline solid (mp 46°C) in 91% yield after column chromatography (acetone/petroleum ether = 1:3). $[\alpha]_D^{13}$ +53.9 (*c* = 1.114, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.6-7.2 (m, 4 H), 5.39 (m, 1 H), 5.35 (s, 1 H), 2.92 (d, 1 H), 2.73 (dd, *J* 12, 4, 1 H), 2.52 (dd, *J* 12, 4, 1 H), 1.69 (s, 3 H), 1.66 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.7 161.5 140.3 131.5 129.5 129.1 127.4 127.0 106.8 95.2 67.8 41.4 25.3 24.7; ESI-HRMS: $(M+Na)^+$, calcd. for $C_{14}H_{15}ClNaO_4$: 305.0557, found: 305.0559; Enantiomeric excess was determined to be 56% (determined by HPLC using chiralcel AD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 5.5 min (major), 6.3 min (minor)).

(5*S*)-6-(2-Hydroxypentyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3q). This product was obtained as a colorless oil in 83% yield after column chromatography (acetone/petroleum ether = 1:3). $[\alpha]_D^{14}$ +15.1 (*c* = 0.686, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.32 (s, 1 H), 3.92 (m, 1 H), 2.36 (m, 2 H), 1.98 (s, 1 H), 1.70 (s, 6 H), 1.50 (m, 2 H), 1.40 (m, 2 H), 0.95 (t, 3 H); Enantiomeric excess was determined to be 93% (determined by HPLC using chiralcel AD-H column, 10% *i*PrOH/Hexanes, λ = 254 nm, 30 ,°C, 0.6 mL/min, 7.7 min (major), 8.7 min (minor)).

(5*R*)-6-(2-Hydroxy-2-methylbutyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3r). This product was obtained as a colorless oil in 80% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{13}$ +53.9 (*c* = 1.114, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.34 (s, 1 H), 3.69 (m, 1 H), 2.35 (m, 2 H), 2.09 (s, 1 H), 1.71 (m, 1 H), 1.70 (d, 6 H), 0.96 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.1 161.4 106.6 94.9 73.4 38.7 33.9 25.4 24.7 18.6 17.2; ESI-HRMS: $(M+Na)^+$, calcd. for $C_{11}H_{18}NaO_4$: 237.1103, found: 237.1107; Enantiomeric excess was determined to be 86% (determined by HPLC using chiralcel AD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.6 mL/min, 7.4 min (major), 8.9 min (minor)).

(5*S*)-6-(2-Hydroxyheptyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3s). This product was obtained as a colorless oil in 87% yield after column chromatography (acetone/petroleum ether = 1:3). $[\alpha]_D^{24}$ +14.3 (*c* = 0.635, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.32 (s, 1 H), 3.91 (m, 1 H), 2.36 (m, 2 H), 1.68 (m, 5 H), 1.61 (s, 1 H), 1.50 (m, 4 H), 1.30 (m, 2 H), 0.91 (t, 3 H); Enantiomeric excess was determined to be 90% (determined by HPLC using chiralcel OD-H column, 20% *i*PrOH/Hexanes, λ = 254 nm, 30°C, 0.6 mL/min, 6.9 min. (major), 7.4 min. (minor)).

(5*S*)-6-(2-Hydroxyhexyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3t). This product was obtained as a colorless oil in 84% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{24}$ +14.6 (*c* = 0.820, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.33 (s, 1 H), 3.90 (m, 1 H), 2.38 (m, 2 H), 2.25 (d, 1 H), 1.70 (s, 6 H), 1.50 (m, 2 H), 1.40 (m, 2 H), 1.30 (m, 2 H), 0.91 (t, 3 H); Enantiomeric excess was determined to be 92% (determined by HPLC

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using chiralcel OD-H column, 10% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 11.1 min (major), 11.9 min (minor)).

(5*S*)-6-(2-Hydroxybutyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3u). This product was obtained as a colorless oil in 83% yield after column chromatography (acetone/petroleum ether = 1:3). $[\alpha]_D^{22}$ +24.4 (*c* = 0.330, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.33 (s, 1 H), 3.85 (m, 1 H), 2.37 (m, 2 H), 2.02 (d, 1 H), 1.71 (s, 6 H), 1.55 (d, 2 H), 0.99 (s, 3 H), ; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.5 161.2 106.6 95.0 70.1 41.2 30.3 25.3 24.8 9.8; ESI-HRMS: $(M+Na)^+$, calcd. for $C_{10}H_{16}NaO_4$: 223.0946, found: 223.0944; Enantiomeric excess was determined to be 91% (determined by HPLC using chiralcel AD-H column, 10% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 8.5 min (major), 9.1 min (minor)).

(5*R*)-6-(2-Hydroxy-3-butenyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3v).This product was obtained as a colorless oil in 85% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{25}$ +6.5 (*c* = 0.306, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.73 (m, 1 H), 5.50 (m, 1 H), 5.32 (m, 1 H), 4.35 (m, 1 H), 2.44 (m, 2H), 1.72 (d, 1 H), 1.69 (s, 6 H); Enantiomeric excess was determined to be 97% (determined by HPLC using chiralcel OD-H column, 10% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 13.4 min (major), 14.6 min (minor)).

(5*S*)-6-(2-Hydroxy-4-phenylbutyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3w). This product was obtained as a white,crystalline solid in 86% yield after column chromatography (acetone/petroleum ether = 1/3). $[\alpha]_D^{25}$ +2.7 (*c* = 0.627, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.31- 7.18 (m, 5 H), 5.31 (s, 1 H), 3.92 (m, 1 H), 2.81 (m, 1 H), 2.69 (m, 1 H), 2.40 (m, 2 H), 2.37 (s, 1 H), 1.83 (q, 2 H), 1.67 (s, 3 H), 1.66 (s, 3 H); Enantiomeric excess was determined to be 91% (determined by HPLC using chiralcel AD-H column, 10% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.6 mL/min, 9.8 min (major), 11.6 min (minor)).

Synthesis of the natural product (S)-(+)-Dihydrokavain 4

Using the above Vinylogous Aldol Reaction of Phenylpropyl aldehyde **1x** and dioxinone-derived sliyl diene **2** to prepare the intermediate **3w**. To a solution of **3w** (607 mg, 2.2 mmol) in 9.5 mL methanol at room temperature, anhydrous K_2CO_3 (4.4 mmol) was added and the reaction was stirred for 2 h. Then, the solvent was removed under vacuum, 9.5 mL of acetone and Me_2SO_4 (4.4 mmol) were added at room temperature. After being stirred for 12 h, the reaction solution was cooled to 0 °C and quenched with five drops of 0.5 M HCl. After usual workup, the residue was purified by chromatography on silica gel (ethyl acetate/petroleum ether = 1:5) to afford **4** as a white, crystalline solid (m.p. = 59 °C) in 81% total yield: ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.31-7.2 (m, 5 H), 5.14 (s, 1 H), 4.35 (m, 1 H), 3.73 (s, 3 H), 2.85 (m, 2 H), 2.50 (m, 1 H), 2.30 (m, 1 H), 2.17 (m, 1 H), 1.93 (m, 1 H), 1.66 (s, 3 H); Enantiomeric excess was determined to be 84% (determined by HPLC using chiralcel OJ-H column, 10% *i*PrOH/Hexanes, λ = 254 nm, 30 °C, 0.7 mL/min, 65.9 min (minor), 78.2 min. (major)).

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Supplementary Material

The analytic data and NMR spectra for the corresponding compounds

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