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Asymmetric synthesis of 3-substituted 3,4-dihydroisocoumarins via stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines to aldehydes followed by diastereomer-selective lactonization

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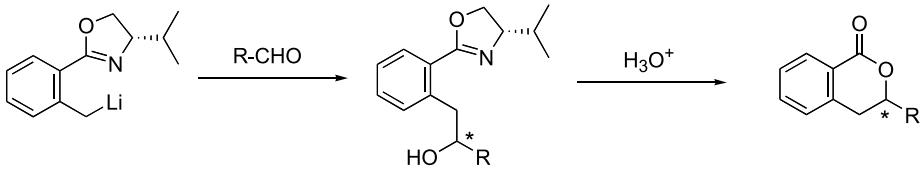
Abstract—Lateral lithiation of (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline in diethyl ether followed by the reaction with aldehydes in the presence of TMEDA produced the addition products with stereoselectivities up to 84% de. Utilization of TMEDA as a ligand is essential for the good selectivity. Rationale for the stereoselectivity is proposed based on ab initio calculation of the lateral lithio species. The major (*S*,*S*)-products lactonized faster than the minor (*S*,*R*)-products to the corresponding 3,4-dihydroisocoumarins under acidic conditions. Thus, (3*S*)-3,4-dihydroisocoumarins were obtained in good optical purities up to 97% ee by sequential application of these matched stereoselective reactions.

1. Introduction

A number of functional groups promote *ortho*-lithiation to produce relatively stable functionalized aryl- and heteroaryllithiums.[1] Such functional groups also assist lateral lithiation at the benzylic position of the *ortho*-alkyl substituent.[2] These directed lithiations have been extensively studied to produce a variety of regiospecifically substituted aromatic and heteroaromatic compounds. Utilization of the oxazoline ring as a directing group in aromatic lithiation was demonstrated by both Gschwend and Meyers in 1975.[3] Recently, we reinvestigated the lithiation of 4,4-dimethyl-2-(*o*-tolyl)oxazolines and discovered that the regioselectivity (*ortho* or lateral) can be simply controlled by the presence or absence of TMEDA.[4] The selectivity has been rationalized by steric interaction between TMEDA and C-4 substituents on the oxazoline ring in the transition states of deprotonation. This interesting and unique reactivity has been successfully applied to an efficient synthesis of 3-substituted 8-hydroxy-3,4-dihydroisocoumarins including the natural products (±)-hydrangenol and (±)-phyllodulcin.[5] As an extension of these studies, we planned to investigate an asymmetric synthesis of optically enriched 3-substituted 3,4-dihydroisocoumarins via stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines to aldehydes followed by acid-catalyzed lactonization (Scheme 1). Asymmetric syntheses of 3-substituted 3,4-dihydroisocoumarins[6] have been achieved by using several



Scheme 1.

Keywords: 2-(*o*-Tolyl)oxazoline; Lateral lithiation; Asymmetric synthesis; 3,4-Dihydroisocoumarin; Ab initio calculation.
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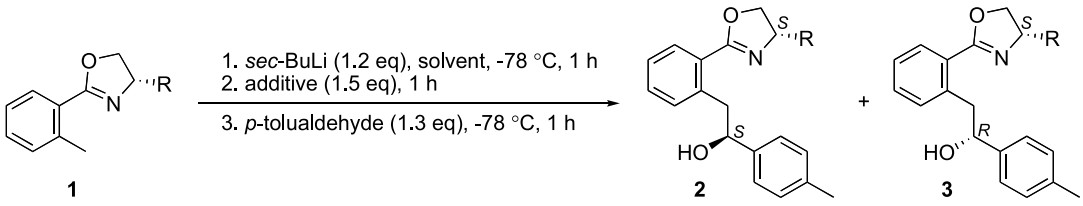
Table 1. Stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines **1** to *p*-tolualdehyde



Entry	1	R	Solvent	Additive	Adduct	Yield (%)[a]	dr (**2**:**3**)[b]
1	**1a**	*i*-Pr	Et_2O	None	**2a**, **3a**	93	1.5:1
2	**1a**	*i*-Pr	THF	None	**2a**, **3a**	93	2.7:1
3	**1a**	*i*-Pr	Et_2O	TMEDA	**2a**, **3a**	99	7.6:1
4	**1a**	*i*-Pr	Et_2O	PMDTA	**2a**, **3a**	66	1.8:1
5	**1a**	*i*-Pr	Et_2O	$MgBr_2$	**2a**, **3a**	93	1:1.5
6	**1a**	*i*-Pr	Et_2O	$MgBr_2$+TMEDA	**2a**, **3a**	90	1.2:1
7	**1b**	Me	Et_2O	TMEDA	**2b**, **3b**	91	6.1:1
8	**1c**	Bn	Et_2O	TMEDA	**2c**, **3c**	82	4.0:1
9	**1d**	*t*-Bu	Et_2O	TMEDA	**2d**, **3d**	97	5.4:1

[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AD).

different types of key reactions, such as (1) ring-opening of chiral epoxides with metallated aromatics,[6a–c] (2) asymmetric dihydroxylation of olefinic side-chain of aromatic substrates,[6d–f] (3) CBS reduction of aryl *o*-carbamoylbenzyl ketones,[6g] (4) stereoselective addition of laterally metallated *o*-toluates to chiral aldehydes[6h–j] or to prochiral aldehydes in the presence of chiral ligands.[6k,l] Our approach using chiral 2-(*o*-tolyl)oxazolines as the chiral *o*-toluate equivalents has not been reported so far.[7]

2. Results and discussion

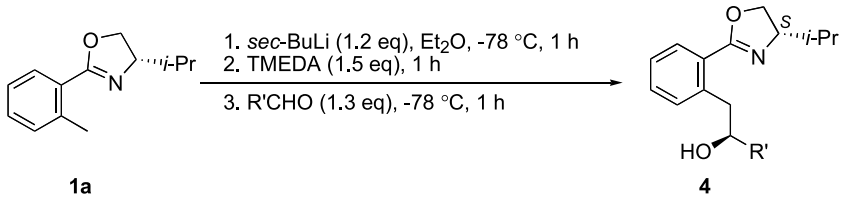
2.1. Stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazolines to aldehydes

Initially, we examined the addition of the lithiated (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline (**1a**) to *p*-tolualdehyde under a variety of conditions. Thus, (*S*)-4-isopropyl-2-(*o*-tolyl)-oxazoline (**1a**) was lithiated regioselectively at the lateral methyl group in diethyl ether or THF by treatment with 1.2 equiv of *sec*-BuLi at −78 °C for 1 h.[4] After injection of an appropriate additive, the lithiated species[8] was reacted with *p*-tolualdehyde at −78 °C for 1 h. A diastereomeric mixture of the addition products, **2a** and **3a**, was readily isolated by column chromatography in good yields. The diastereomer ratio was estimated by HPLC analysis. The results are summarized in Table 1. When diethyl ether was used as a solvent without additive, the diastereomer ratio was found to be only 1.5:1 (entry 1). The ratio was somewhat improved by using THF as a solvent (entry 2). To our surprise, when the addition was carried out in diethyl ether in the presence of TMEDA, the selectivity was dramatically improved to 7.6:1 (entry 3). These results suggested that utilization of solvents or ligands possessing high coordinating ability are advantageous for the stereoselective addition. Therefore, we tested tridentate PMDTA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) as an additive. In this case, however, both the diastereomer ratio and the chemical yield decreased considerably (entry 4). The characteristic deep purple color of the anion did not fade under these conditions indicating the poor reactivity of the PMDTA complex towards the aldehyde. Next, we examined the metal exchange of lithium to the more Lewis acidic magnesium. However, the results were disappointing even in the presence of TMEDA (entries 5 and 6). Finally, effects of an alkyl substituent on the oxazoline 4-position were inspected under the diethyl ether–TMEDA conditions. Although we tested easily synthesized methyl-, benzyl-, and *tert*-butyloxazolines **1b–d**, all of these substrates were less selectively reacted with *p*-tolualdehyde than **1a** (entries 7–9). Thus, we conclude the stereoselective addition of the laterally lithiated **1** can be most satisfactorily achieved by using the isopropyl oxazoline as an auxiliary group, diethyl ether as a solvent, and TMEDA as an additive.

Following these preliminary experiments, we surveyed the scope and limitations of this stereoselective addition using a variety of aldehydes (Table 2). Common aromatic aldehydes including cinnamaldehyde reacted with the lithiated **1a** in the presence of TMEDA in excellent yields to give adducts **4** in over 70% de (entries 1–3, 5–6). The stereoselectivity, however, decreased in the reactions with electron-deficient *p*-chlorobenzaldehyde (entry 4). An aliphatic and bulky pivalaldehyde was reacted in high stereoselectivity (entry 8). On the other hand, linear octylaldehyde gave a disappointing result (entry 9).

It is quite interesting that the transfer of chirality from the oxazoline to the prochiral aldehydes can be effected via the lateral lithio species only in the presence of TMEDA. Thus, we tried to reveal the structures of the lithio species by means of ab initio calculations. All calculations were performed by the DFT method implemented in the Gaussian 98 program package.[9] Geometry optimizations were carried out at the B3LYP/6-31G(d) level. The optimized structures of the parent oxazoline **5**, the laterally lithiated oxazoline **6**, and the laterally lithiated oxazoline coordinated with two ammonia molecules **7** as a model of the TMEDA complex are shown in Figure 1. It has been presumed that the lateral litho species generated from *o*-toluic acid derivatives

Table 2. Stereoselective addition of laterally lithiated chiral 2-(*o*-tolyl)oxazoline **1a** to aldehydes



1a **4**

Entry	Aldehyde	Adduct[a]	R′	Yield (%)[b]	dr[c,d]	% de
1	Benzaldehyde	**4a**	Phenyl	94	8.2:1	78
2	*p*-Tolualdehyde	**4b**	*p*-Tolyl	99	7.6:1	77
3	*p*-Anisaldehyde	**4c**	*p*-Methoxyphenyl	95	6.2:1	72
4	*p*-Chlorobenzaldehyde	**4d**	*p*-Chlorophenyl	97	3.2:1	53
5	Veratraldehyde	**4e**	3,4-Dimethoxyphenyl	97	5.7:1	70
6	1-Naphthaldehyde	**4f**	1-Naphthyl	95	5.7:1	70
7	Cinnamaldehyde	**4g**	(*E*)-Styryl	87	7.1:1	75
8	Pivalaldehyde	**4h**	*t*-Butyl	91	11.8:1	84
9	Octylaldehyde	**4i**	Heptyl	75	2.1:1[e]	35

[a] Diastereomeric mixture.
[b] Isolated yield.
[c] Diastereomer ratio of (*S*,*S*)- to (*S*,*R*)-isomer unless otherwise mentioned.
[d] Determined by HPLC analysis (Daicel Chiralpak AD).
[e] Diastereomer ratio of (*S*,*R*)- to (*S*,*S*)-isomer.

possess *o*-quinodimethane (extended enolate) structures.[10] Comparison of the relative bond lengths (C_1–C_2, C_2–C_3, C_3–C_4, C_4–N) of our calculated models **5**, **6**, and **7** clearly indicated that the lithiated oxazolines, especially when lithium is coordinated with ammonia, are nicely represented as the *N*-lithio-*o*-quinodimethane structures. The other characteristic features of the lithiated species are as follows. The aromatic and oxazoline rings are twisted with each other by about 20° in both **6** and **7**. The lithium in **6** exists essentially in the same plane of the oxazoline ring, whereas the lithium in **7** bends upward about 25° from the oxazoline plane.

Next, we examined the structures of the TMEDA complex. For simplification, the calculations were performed on a complex derived from the (*S*)-4-methyl-2-(*o*-tolyl)oxazoline. The complex can exists as an *anti*- or a *syn*-isomer with respect to 4-methyl and *N*-Li-TMEDA. The optimized structures of the *anti*-isomer **8a** and the *syn*-isomer **8b** are shown in Figure 2. The calculation indicated the *anti*-isomer

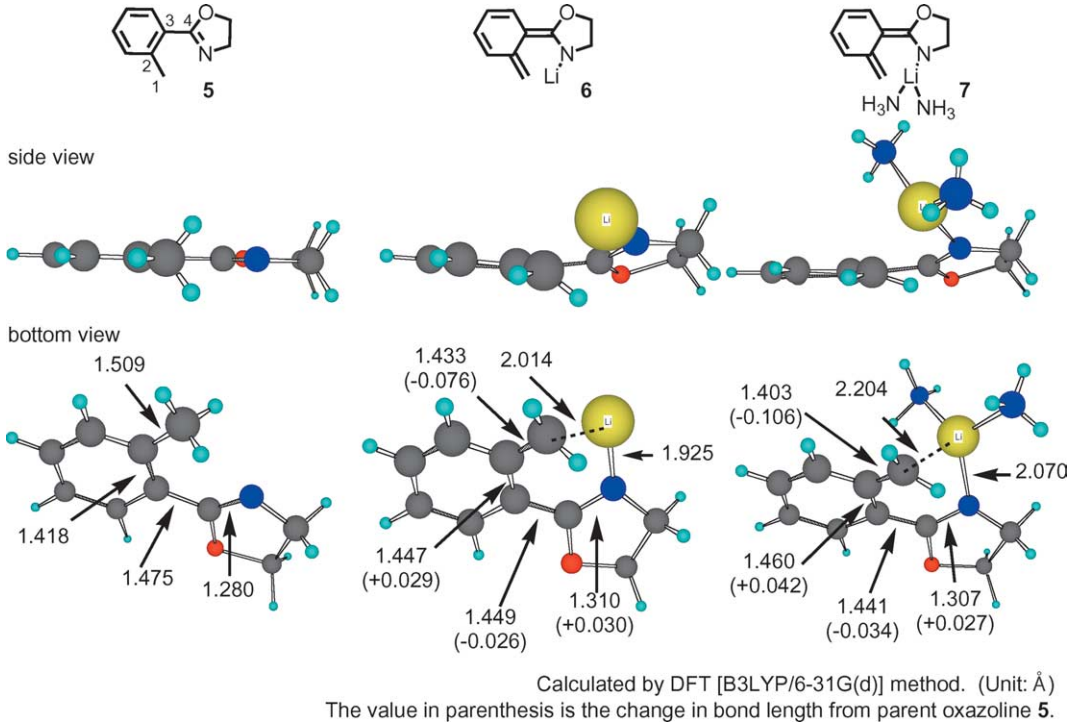


Figure 1. The optimized structures of **5**, **6** and **7**.

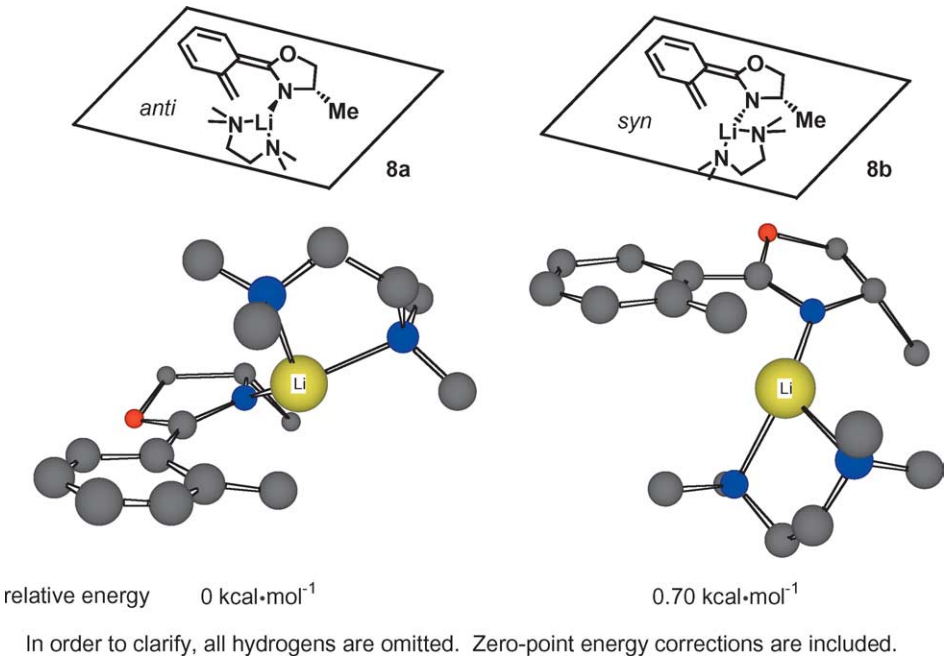
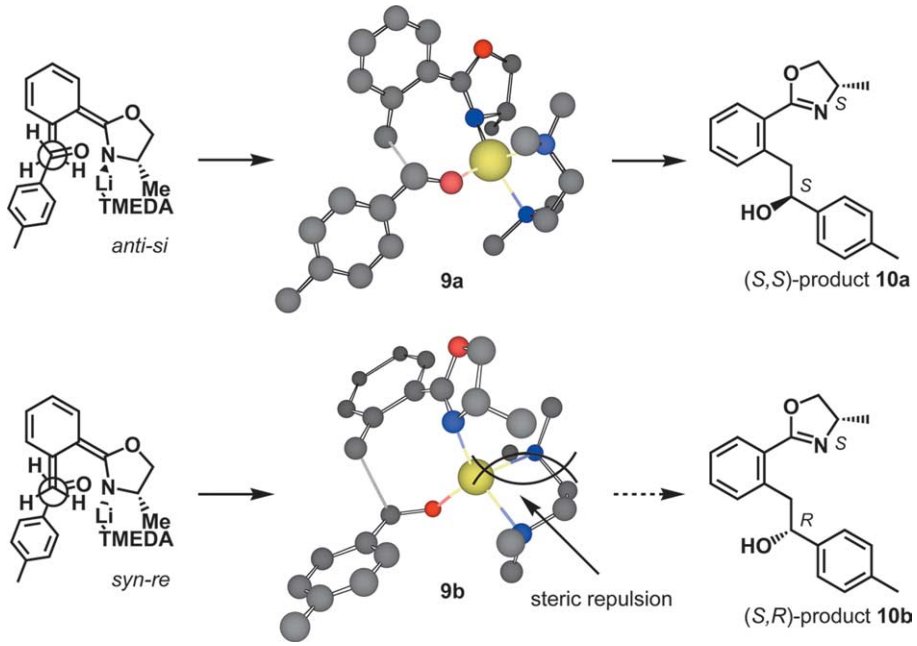


Figure 2. The TMEDA complexes of lithiated chiral oxazoline **1b**.

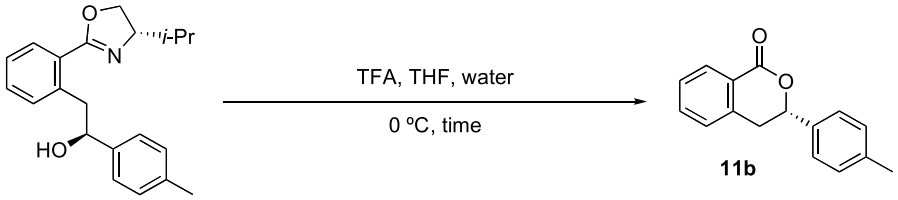
8a is more stable than the *syn*-isomer **8b** by 0.70 kcal mol^{-1} apparently due to unfavorable steric interactions between the 4-methyl group and TMEDA.[11]

By considering the computer-generated models **8a** and **8b**, a plausible mechanism for the stereoselective addition to *p*-tolualdehyde is proposed (Scheme 2). The stereoselectivity can be rationalized by assuming eight-membered ring transition states, **9a** and **9b**, in which the lithium is chelated to the carbonyl oxygen. The more stable *anti*-quinodimethane **8a** may attack the *si*-face of the aldehyde preferentially to give the (*S*,*S*)-product **10a** via the transition state **9a** in which unfavorable steric interactions between the quinodimethane ring and the aromatic ring of the aldehyde are minimized. The less stable *syn*-quinodimethane **8b** may attack the *re*-face preferentially to give (*S*,*R*)-product **10b** via a similar chelation-controlled mechanism. In this case, however, severe steric repulsion between TMEDA and the substituent of the oxazoline ring must be generated in the transition state **9b**. Thus, the (*S*,*S*)-isomer **10a** is formed as a major product through the energetically favorable transition state **9a**. The loss of the stereoselectivity in the presence of



Scheme 2. Plausible addition mechanism.

Table 3. Acid-catalyzed lactonization of the addition product **4b**



4b (77% de)

Entry	Time (h)	3,4-Dihydroisocoumarin **11b**		Unreacted **4b**	
		Yield (%)[a]	% ee[b]	Yield (%)[a]	% de[b]
1	1	11	95	86	74
2	2	15	95	84	73
3	4	28	94	66	70
4	6	37	94	62	66
5	12	63	93	36	52
6	24	77	91	19	25
7	48	89	88	9	−34
8[c]	48	99	77	0	—

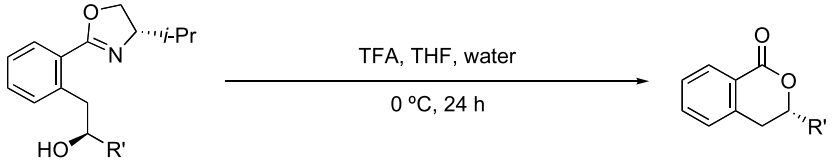
[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AD).
[c] Reaction at room temperature.

tridentate PMDTA strongly supports this chelation-controlled mechanism. The effects of alkyl substituent on the C-4 position of the oxazoline ring cannot be clearly understood at the present stage. We suppose, however, the transition states described above are rather tight and sensitive to the steric effects. Thus, a very large substituent such as *t*-butyl group may exert some unfavorable steric effects even in the transition state of type **9a** and consequently induce the decrease of stereoselectivity.

2.2. Diastereomer-selective lactonization of the addition products

Lactonization of the addition product **4b** (77% de sample) to the corresponding 3,4-dihydroisocoumarin **11b** was carried out carefully at 0 °C in aqueous THF in the presence of trifluoroacetic acid (TFA). The reaction was stopped after appropriate time and the 3,4-dihydroisocoumarin **11b** and the unreacted **4b** were isolated by flash chromatography. The yields of **11b** and **4b** and their ee or de in each reaction are summarized in Table 3. The reaction is rather slow under these conditions, and, to our surprise, the optical purity of the 3,4-dihydroisocoumarin **11b** isolated was found to be much higher than that expected from the de of the starting material. For example, a 95% ee sample of **11b** was isolated in 11% yield after 1 h (entry 1). With the elapse of the reaction time, yield of **11b** increased and its optical purity decreased gradually. These results clearly indicated that the lactonization rate of the major (*S*,*S*)-diastereomer is faster than that of the minor (*S*,*R*)-diastereomer. The cyclization

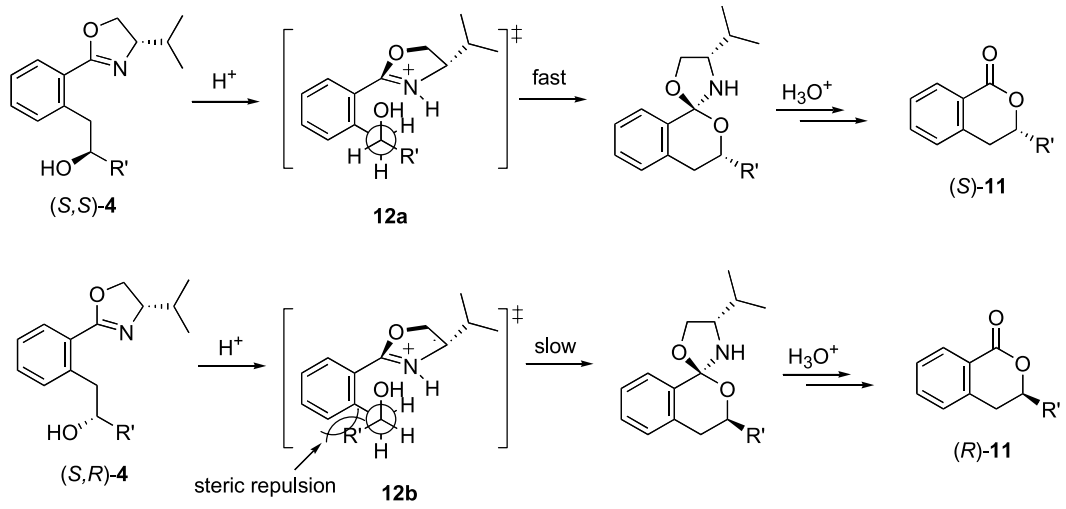
Table 4. Synthesis of optically enriched 3,4-dihydroisocoumarins **11** via diastereomer-selective lactonization



4 **11**

Entry	Addition product			3,4-Dihydroisocoumarin		
	4	R′	% de	**11**	Yield (%)[a]	% ee
1	**4a**	Phenyl	78	**11a**	84	89[b]
2	**4b**	*p*-Tolyl	77	**11b**	77	91[b]
3	**4c**	*p*-Methoxyphenyl	72	**11c**	72	86[b]
4	**4d**	*p*-Chlorophenyl	53	**11d**	83	73[b]
5	**4e**	3,4-Dimethoxyphenyl	70	**11e**	57	82[c]
6	**4f**	1-naphthyl	70	**11f**	72	92[b]
7	**4g**	(*E*)-styryl	75	**11g**	67	88[c]
8	**4h**	*t*-Butyl	84	**11h**	56	97[c]
9	**4i**	Heptyl	35	**11i**	43	79[b]

[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AD).
[c] Determined by HPLC analysis (Daicel Chiralpak AS).



Scheme 3. Rationale for diastereomer-selective lactonization.

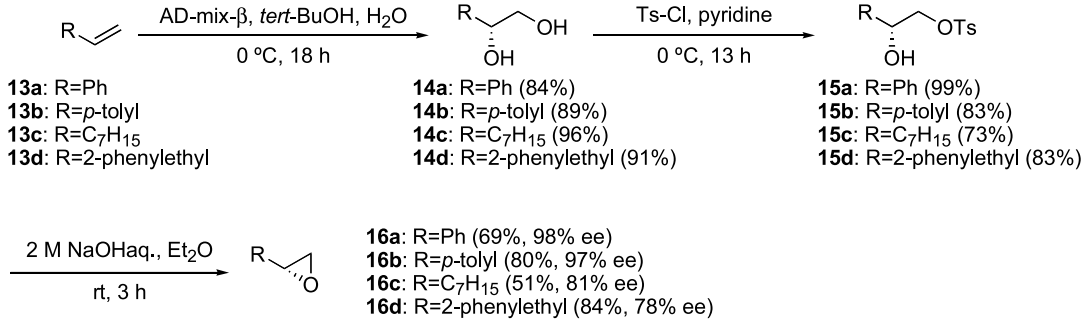
rates of both diastereomers fit to the first-order kinetics and the relative rate [$k(S,S)/k(S,R)$] is estimated to be approximately 5 from the data shown in Table 3.

The generality of this diastereomer-selective lactonization was tested using a variety of adducts **4a–i**. The reactions were carried out at 0 °C for 24 h. As shown in Table 4, the selective cyclization was observed in all cases under these restricted conditions and the optically enriched (3*S*)-3,4-dihydroisocoumarins **11a–i** were isolated in 69–97% ee.

The preferential lactonization of (*S*,*S*)-**4** can be explained as follows. The cyclization may proceed via initial and rate-determining addition of the hydroxy group to the C=N bond of the protonated oxazoline. It is reasonable to assume that the addition proceeds most readily when the oxazoline ring takes near-perpendicular conformations against the benzene ring due to deconjugation between oxazoline C=N and aromatic π-systems. In such conformations, the hydroxy group attacks the less hindered *re*-face of the oxazoline preferentially in order to avoid unfavorable steric interactions between isopropyl and lateral substituents. In such mode of cyclization, the transition state **12a** is expected to be more stable in energy than the transition state **12b** in which the *gauche* interaction between the aromatic ring and the substituent R′ is unfavorable. Thus, (*S*,*S*)-**4** cyclizes faster than (*S*,*R*)-**4** (Scheme 3).

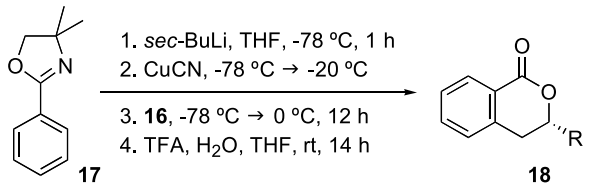
2.3. Determination of the absolute configurations

The absolute configurations of the 3-substituted 3,4-dihydroisocoumarins were determined by unequivocal syntheses. The chiral epoxides **16a–d** were synthesized using the established procedures (Scheme 4).[6j,12,13] Thus, the olefins **13a–d** were converted to the chiral diols **14a–d** using AD-mix-β.[12] The diols were transformed to the (*R*)-epoxides **16a–d** via the tosylate intermediates **15a–d**.[13] The optical purities of the epoxides varied from 78 to 98% ee depending on the substituent R. The oxazoline **17** was *ortho*-lithiated with *sec*-BuLi and, after conversion to the cyanocuprate, reacted with the epoxides **16a–d**. The crude products were treated with TFA in aq THF to give *S* (R=Ph, *p*-Tol) or *R* (R=2-phenylethyl, *n*-heptyl) dihydroisocoumarins **18a–d** in modest yields (Table 5). The absolute configurations of the 3,4-dihydroisocoumarins **11a**,**b**,**i** are shown to be identical with the authentic samples **18a–c**, respectively, by comparison of their specific rotations and HPLC profiles. The configuration of **11g** is correlated to **18d** after hydrogenation of its styryl side chain (Scheme 5). The absolute configurations of other dihydroisocoumarins **11c–f**,**h** were determined



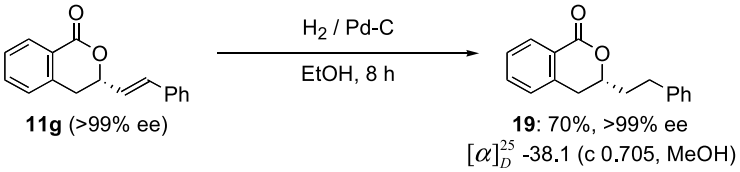
Scheme 4. Synthesis of chiral epoxides **16a–d**.

Table 5. Synthesis of chiral 3,4-dihydroisocoumarins **18a–d**



Entry	Epoxide	18	R	Yield (%)[a]	% ee	$[\alpha]_D^{25}$
1	**16a**	**18a**	Phenyl	27	98 (*S*)[b]	−151 (*c* 1.53, MeOH)
2	**16b**	**18b**	*p*-Tolyl	26	98 (*S*)[b]	−124 (*c* 1.46, MeOH)
3	**16c**	**18c**	C_7H_{15}	38	84 (*R*)[b]	−51.9 (*c* 1.00, MeOH)
4	**16d**	**18d**	2-Phenylethyl	62	79 (*R*)[c]	−30.4 (*c* 1.00, MeOH)

[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralpak AD).
[c] Determined by HPLC analysis (Daicel Chiralpak AS).



Scheme 5.

by comparison of their CD spectra with those of **11a**,**b**,**i** (Figs. 3 and 4).

3. Conclusion

We have discovered that the stereoselective addition of the laterally lithiated chiral 2-(*o*-tolyl)oxazolines to aldehydes proceeds in diethyl ether in the presence of TMEDA. The stereoselectivity has been rationalized by chelation-controlled addition of the TMEDA complexes, which are nicely represented as *N*-lithio-*o*-quinodimethane structures by ab initio calculations. We have also discovered that the major addition products lactonize much faster than the minor adducts under acidic conditions to give optically enriched 3,4-dihydroisocoumarins. The procedure presented herein is simple and practically useful to produce a variety of optically active 3-substituted 3,4-dihydroisocoumarins.

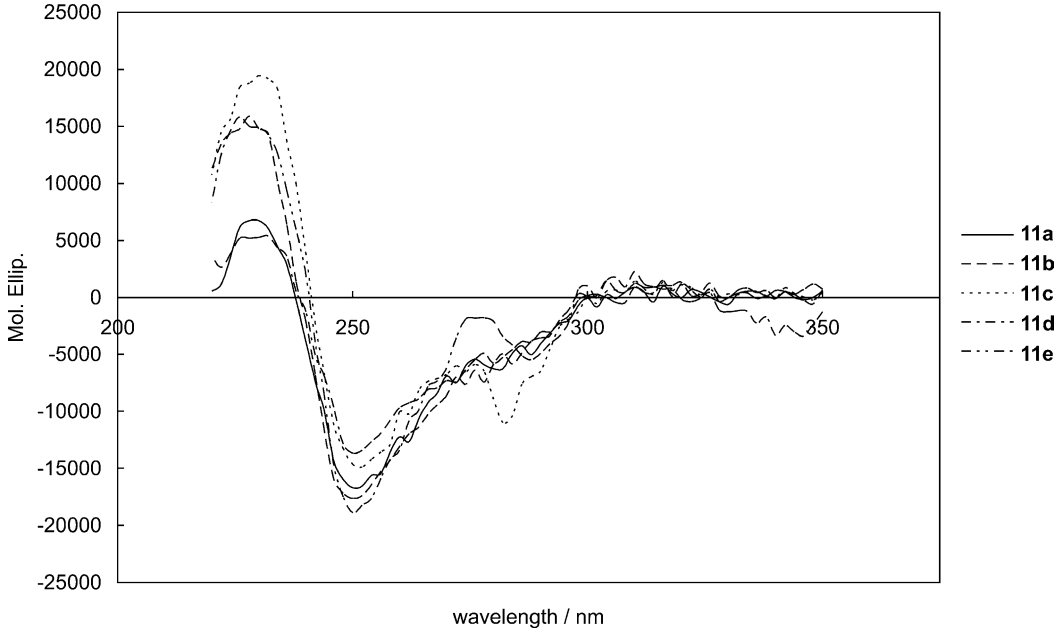


Figure 3. CD spectra of 3,4-dihydroisocoumarins **11a–e**.

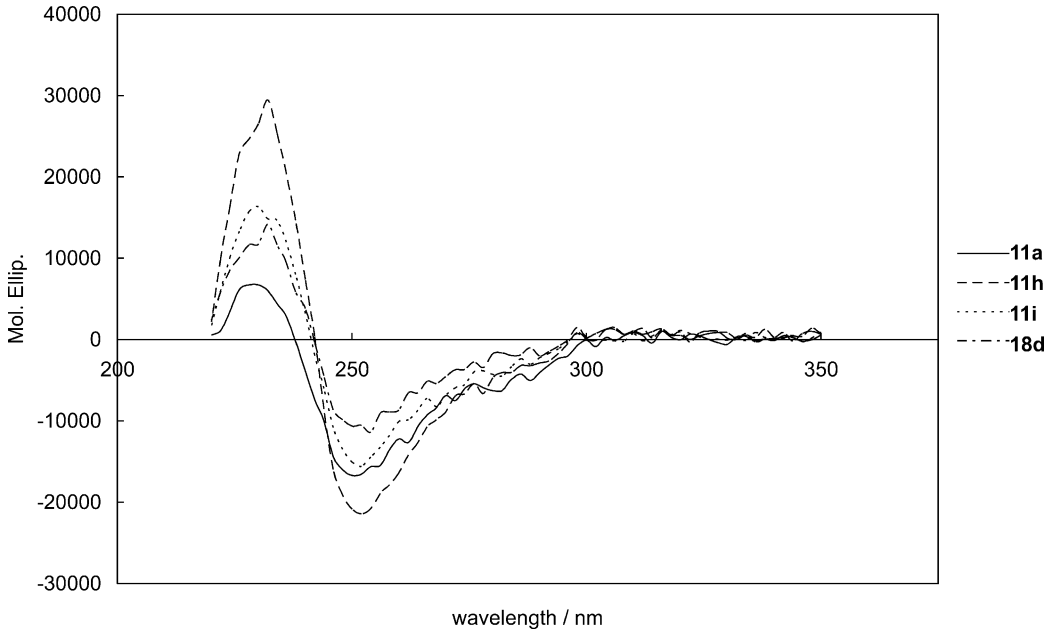


Figure 4. CD spectra of 3,4-dihydroisocoumarins **11a**, **11h**, **11i** and **18d**.

4. Experimental

4.1. General

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer System 2000 instrument. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini-300 instrument using TMS as an internal standard. ^{13}C NMR spectra were obtained at 100 MHz on a JEOL JNM-AL400 instrument using TMS as an internal standard. High resolution mass spectra were recorded on a JEOL JMS-DX303 spectrometer. HPLC analyses were performed on a Shimadzu LC-6A apparatus. Optical rotations were measured on a JASCO DPI-1000 digital polarimeter at ambient temperature. Flash chromatography was conducted on Silica Gel 60N, 40–50 μm (Kanto Chemical Co., Inc.). Column chromatography was conducted on Silica Gel 60N, 63–210 μm (Kanto Chemical Co., Inc.) or Chromatorex NH-DM1020 silica gel (Fuji Silysia Chemical Ltd). *sec*-BuLi was purchased from Kanto Chemical Co., Inc. and used after titration with 2,5-dimethoxybenzyl alcohol. AD-mix-β was purchased from Aldrich Chemical Co., Inc. Diethyl ether and THF were dried over Na-benzophenone ketyl under Ar and distilled immediately before use. Dichloromethane was distilled from CaH_2.

4.2. Synthesis of (*S*)-4-alkyl-2-(*o*-tolyl)oxazoline 1. General procedure

A solution of *o*-toluoyl chloride (4.90 mL, 38 mmol) in THF (46 mL) was added dropwise to a mixed solution of (*S*)-2-amino-2-alkylethanol (34 mmol) and triethylamine (5.6 mL, 40 mmol) in THF (46 mL) at 0 °C. After being stirred for 1 h, saturated aqueous $NaHCO_3$ was added and the mixture was evaporated. The residue was extracted with dichloromethane and the extract was washed with brine, dried over Na_2SO_4, and evaporated. The residual solid was dried in vacuo to give the intermediate *o*-toluamide. Thionyl chloride (21.5 mL, 295 mmol) was added dropwise to the amide at 0 °C and mixture was stirred for 1 h. Methanol (21.5 mL) was added 0 °C to decompose excess of thionyl chloride. When gas evolution ceased, the solution was made basic with 10% aqueous KOH. After stirring for 30 min at room temperature, the mixture was extracted with dichloromethane. The extract was washed with brine, dried over Na_2SO_4, and evaporated. The residual oil was purified by bulb-to-bulb distillation to give the oxazoline **1**.

4.2.1. (*S*)-4-Isopropyl-2-(*o*-tolyl)-4,5-dihydrooxazole (1a). According to the general procedure, (*S*)-2-amino-3-methyl-1-butanol (3.50 g, 34 mmol) was reacted to give **1a** as colorless oil (6.02 g, 87%). Bp 90 °C (1.6 mmHg, bulb-to-bulb); IR (neat): 2960, 1646, 1576, 1493, 1456, 1385, 1348, 1307, 1274, 1246, 1053, 972, 904, 775, 728, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, J=6.8 Hz, 3H), 1.04 (d, J=6.8 Hz, 3H), 1.80–1.93 (m, 1H), 2.58 (s, 3H), 4.05–4.18 (m, 2H), 4.30–4.42 (m, 1H), 7.17–7.35 (m, 3H), 7.76 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.20, 18.81, 21.58, 32.86, 69.34, 72.91, 125.33, 127.37, 129.57, 130.15, 130.91, 138.42, 163.63; $[\alpha]_D^{26}=-76.2$ (*c* 1.03, MeOH). HREIMS *m*/*z*. Calcd for $C_{13}H_{17}NO$ (M^+): 203.1310. Found: 203.1349.

4.2.2. (*S*)-4-Methyl-2-(*o*-tolyl)-4,5-dihydrooxazole (1b). According to the general procedure, (*S*)-2-amino-1-propanol (1.31 g, 17 mmol) was reacted to give **1b** as colorless oil (2.22 g, 72%). Bp 105 °C (2.0 mmHg, bulb-to-bulb); IR (neat): 3064, 3027, 2967, 2926, 2894, 1644, 1603, 1574, 1492, 1475, 1454, 1374, 1353, 1337, 1304, 1287, 1248, 1205, 1163, 1140, 1124, 1106, 1065, 1038, 974, 931, 888, 851, 776, 729, 683, 664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (d, J=6.7 Hz, 3H), 2.57 (s, 3H), 3.92 (t,

J=6.7 Hz, 1H), 4.32–4.50 (m, 2H), 7.17–7.36 (m, 3H), 7.77 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.54, 21.63, 62.20, 73.31, 125.36, 127.22, 129.63, 130.26, 130.93, 138.40, 163.82; $[\alpha]_D^{27}=-64.9$ (c 1.00, MeOH). HREIMS m/z. Calcd for $C_{11}H_{13}NO$ (M^+): 175.0997. Found: 175.0984.

4.2.3. (*S*)-4-Benzyl-2-(*o*-tolyl)-4,5-dihydrooxazole (1c). According to the general procedure, (*S*)-2-amino-3-phenyl-1-propanol (709 mg, 4.7 mmol) was reacted to give **1c** as colorless oil (753 mg, 64%). Bp 160 °C (1.0 mmHg, bulb-to-bulb); IR (neat): 3062, 3027, 2963, 2924, 1770, 1651, 1644, 1604, 1574, 1552, 1494, 1473, 1454, 1383, 1352, 1310, 1270, 1250, 1203, 1178, 1163, 1133, 1123, 1075, 1050, 1031, 970, 916, 776, 753, 728, 700, 682, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H), 2.76 (dd, J=8.4, 13.7 Hz, 1H), 3.22 (dd, J=5.2, 13.7 Hz, 1H), 4.11 (dd, J=7.3, 8.4 Hz, 1H), 4.30 (dd, J=8.4, 9.2 Hz, 1H), 4.55–4.69 (m, 1H), 7.17–7.36 (m, 8H), 7.76 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.66, 41.82, 68.11, 70.91, 125.36, 126.30, 127.06, 128.32, 129.17, 129.63, 130.33, 130.97, 137.85, 138.53, 164.27; $[\alpha]_D^{27}=-15.2$ (c 1.00, MeOH). HREIMS m/z. Calcd for $C_{17}H_{17}NO$ (M^+): 251.1310. Found: 251.1297.

4.2.4. (*S*)-4-(*t*-Butyl)-2-(*o*-tolyl)-4,5-dihydrooxazole (1d). According to the general procedure, (*S*)-2-amino-3,3-dimethyl-1-butanol (1.00 g, 8.5 mmol) was reacted to give **1d** as colorless oil (1.72 g, 93%). Bp 120 °C (1.0 mmHg, bulb-to-bulb); IR (neat): 3063, 3028, 2957, 2903, 2869, 1651, 1604, 1575, 1493, 1478, 1456, 1393, 1383, 1364, 1352, 1334, 1306, 1288, 1248, 1209, 1194, 1162, 1123, 1070, 1049, 1025, 992, 971, 931, 901, 775, 731, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 9H), 2.59 (s, 3H), 4.08 (dd, J=8.0, 10.2 Hz, 1H), 4.18 (t, J=8.0 Hz, 1H), 4.30 (dd, J=8.0, 10.2 Hz, 1H), 7.17–7.35 (m, 3H), 7.75 (d, J=7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.60, 25.88, 33.90, 67.88, 76.60, 125.33, 127.40, 129.54, 130.11, 130.90, 138.46, 163.53; $[\alpha]_D^{27}=-76.1$ (c 1.00, MeOH). HREIMS m/z. Calcd for $C_{14}H_{19}NO$ (M^+): 217.1467. Found: 217.1482.

4.3. Stereoselective addition of laterally lithiated (*S*)-4-alkyl-2-(*o*-tolyl)oxazolines 1 to *p*-tolualdehyde (Table 1). General procedure

Under an argon atmosphere, a hexane-cyclohexane solution of *sec*-BuLi (12 mmol) was added dropwise to a solution of the oxazoline **1** (10 mmol) in diethyl ether or THF (50 mL) at −78 °C. After being stirred for 1 h, an appropriate additive (15 mmol) was added as a neat liquid or diethyl ether solution and the mixture was stirred for 1 h at −78 °C. A solution of *p*-tolualdehyde (1.53 mL, 13 mmol) in diethyl ether or THF (10 mL) was added and the solution was stirred for an additional 1 h at −78 °C. The reaction mixture was quenched with H_2O at the same temperature and allowed to warm to room temperature. The products were extracted with diethyl ether and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over Silica Gel 60N using the following eluents: hexane–ethyl acetate=10:1 containing 1% triethylamine for **2a**, **3a** and **2d**, **3d**; hexane–ethyl acetate=3:1 containing 1% triethylamine for **2b**, **3b** and **2c**, **3c**. The diastereoselectivity was determined by HPLC analysis (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1).

4.3.1. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(*p*-tolyl)ethanol (2a, 3a). According to the general procedure, **1a** (2.03 g, 10 mmol) was reacted under the conditions shown in Table 1, entry 3, to give a 7.6:1 mixture of **2a** and **3a** as colorless semisolid (3.21 g, 99%). IR (KBr): 2965, 1645, 1513, 1492, 1358, 1252, 1064, 958, 853, 806, 747, 557 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J=6.7 Hz, 3H, both isomers), 1.08 (d, J=6.7 Hz, 3H, both isomers), 1.84–1.98 (m, 1H, both isomers), 2.34 (s, 0.35H, minor isomer), 2.36 (s, 2.65H, major isomer), 3.06–3.20 (m, 1H, both isomers), 3.47 (dd, J=9.4, 13.3 Hz, 0.12H, minor isomer), 3.58 (t, J=9.8, 13.3 Hz, 0.88H, major isomer), 4.10–4.30 (m, 2H, both isomers), 4.36–4.51 (m, 1H, both isomers), 4.95 (br d, J=9.1 Hz, 1H, both isomers), 7.10–7.44 (m, 7H, both isomers), 7.73–7.80 (m, 1H, both isomers). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.68; H, 8.04; N, 4.09.

4.3.2. (*S*)- and (*R*)-2-{2-[(*S*)-4-Methyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(*p*-tolyl)ethanol (2b, 3b). According to the general procedure, **1b** (175 mg, 1.0 mmol) was reacted under the conditions shown in Table 1, entry 7, to give a 6.1:1 mixture of **2b** and **3b** as colorless oil (268 mg, 91%). IR (neat): 3224, 3057, 3022, 2968, 2924, 2867, 1726, 1644, 1600, 1575, 1513, 1493, 1446, 1376, 1358, 1342, 1307, 1252, 1199, 1177, 1127, 1104, 1055, 966, 893, 851, 807, 776, 738, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (d, J=6.6 Hz, 0.42H, minor isomer), 1.44 (d, J=6.3 Hz, 2.58H, major isomer), 2.35 (s, 2.58H, major isomer), 2.38 (s, 0.42H, minor isomer), 3.02 (dd, J=2.9, 16.3 Hz, 0.14H, minor isomer), 3.09 (dd, J=3.4, 13.3 Hz, 0.86H, major isomer), 3.43–3.62 (m, 1H, both isomers), 3.97–4.20 (m, 1H, both isomers), 4.42–4.60 (m, 2H, both isomers), 4.88–4.99 (m, 1H, both isomers), 7.12–7.44 (m, 7H, both isomers), 7.71–7.80 (m, 1H, both isomers). HREIMS m/z. Calcd for $C_{19}H_{21}NO_2$ (M^+): 295.1572. Found: 295.1554.

4.3.3. (*S*)- and (*R*)-2-{2-[(*S*)-4-Benzyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(*p*-tolyl)ethanol (2c, 3c). According to the general procedure, **1c** (251 mg, 1.0 mmol) was reacted under the conditions shown in Table 1, entry 8, to give a 4.0:1 mixture of **2c** and **3c** as colorless oil (306 mg, 82%). IR (neat): 3238, 3061, 3027, 2922, 1726, 1644, 1603, 1575, 1514, 1494, 1454, 1358, 1309, 1274, 1225, 1178, 1118, 1063, 1031, 1001, 967, 914, 878, 852, 808, 776, 737, 700, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 2.40H, major isomer), 2.37 (s, 0.60H, minor isomer), 2.76–2.98 (m, 1H, both isomers), 3.00–3.20 (m, 1H, both isomers), 3.31 (dd, J=5.3, 13.7 Hz, 0.80H, major isomer), 3.41 (dd, J=9.5, 13.3 Hz, 0.20H, minor isomer), 3.50–3.68 (m, 1H, both isomers), 4.14–4.22 (m, 1H, both isomers), 4.41 (t, J=9.1 Hz, 0.80H, major isomer), 4.46 (t, J=8.9 Hz, 0.20H, minor isomer), 4.61–4.80 (m, 1H, both isomers), 4.85–4.98 (m, 1H, both isomers), 7.00–7.50 (m, 12H, both isomers), 7.68–7.80 (m, 1H, both isomers). HREIMS m/z. Calcd for $C_{25}H_{25}NO_2$ (M^+): 371.1885. Found: 371.1884.

4.3.4. (*S*)- and (*R*)-2-{2-[(*S*)-4-(*t*-Butyl)-4,5-dihydrooxazol-2-yl]phenyl}-1-(*p*-tolyl)ethanol (2d, 3d). According to the general procedure, **1d** (217 mg, 1.0 mmol) was reacted under the conditions shown in Table 1, entry 9, to give a 5.4:1 mixture of **2d** and **3d** as colorless solid (326 mg, 97%). Mp 79–85 °C; IR (KBr): 3224, 3060, 3021, 2959, 2868, 1645, 1600, 1576, 1513, 1494, 1478, 1445,1396, 1358, 1340, 1309, 1252, 1210, 1196, 1176, 1128, 1074, 1056, 997, 966, 911, 854, 806, 773, 740, 666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 9H, both isomers), 2.36 (s, 3H, both isomers), 3.10 (dd, J=2.7, 13.5 Hz, 0.84H, major isomer), 3.20 (dd, J=3.7, 13.3 Hz, 0.16H, minor isomer), 3.44 (dd, J=9.2, 13.3 Hz, 0.16H, minor isomer), 3.63 (dd, J=9.9, 13.5 Hz, 0.84H, major isomer), 4.15–4.30 (m, 2H, both isomers), 4.35–4.48 (m, 1H, both isomers), 4.90–5.01 (m, 1H, both isomers), 7.12–7.48 (m, 7H, both isomers), 7.72–7.81 (m, 1H, both isomers). HREIMS *m/z*. Calcd for $C_{22}H_{27}NO_2$ (M^+): 337.2042. Found: 337.2027.

4.4. Stereoselective addition of laterally lithiated (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline (1a) to aldehydes (Table 2). General procedure

Under an argon atmosphere, a hexane-cyclohexane solution of *sec*-BuLi (2.4 mmol) was added dropwise to a solution of **1a** (2.0 mmol) in diethyl ether (10 mL) at −78 °C. After being stirred for 1 h, TMEDA (452 μL, 3.0 mmol) was added as a neat liquid and the mixture was stirred for 1 h at −78 °C. A solution of an appropriate aldehyde (2.6 mmol) in diethyl ether (2.0 mL) was added and the reaction mixture was stirred for an additional 1 h at −78 °C. The reaction mixture was quenched with water at the same temperature and allowed to warm to room temperature. The products were extracted with diethyl ether and the extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography to give **4** as a diastereomeric mixture.

4.4.1. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-phenylethanol (4a). According to the general procedure, **1a** (407 mg, 2.0 mmol) and benzaldehyde (264 μL, 2.6 mmol) were reacted. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate =20:1), **4a** was obtained as colorless powder (584 mg, 94%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 78% de. Mp 105–110 °C; IR (KBr): 3199, 2959, 1647, 1491, 1452, 1358, 1248, 1201, 1164, 1087, 1062, 998, 960, 758, 703, 556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J=6.6 Hz, 3H, both isomers), 1.09 (d, J=6.6 Hz, 2.67H, major isomer), 1.12 (d, J=6.7 Hz, 0.33H, minor isomer), 1.82–2.00 (m, 1H, both isomers), 3.11–3.23 (m, 1H, both isomers), 3.47 (dd, J=9.3, 13.5 Hz, 0.11H, minor isomer), 3.57 (dd, J=9.6, 13.5 Hz, 0.89H, major isomer), 4.13–4.28 (m, 2H, both isomers), 4.45–4.51 (m, 1H, both isomers), 4.96–5.02 (m, 1H, both isomers), 7.15–7.52 (m, 8H, both isomers), 7.76–7.80 (m, 1H, both isomers). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.57; H, 7.58; N, 4.48.

4.4.2. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(4-methoxyphenyl)ethanol (4c). According to the general procedure, **1a** (609 mg, 3.0 mmol) and *p*-anisaldehyde (531 mg, 3.9 mmol) were reacted. After chromatographic purification over Silica Gel 60N (hexane–ethyl acetate=5:1 containing 1% triethylamine), **4c** was obtained as colorless oil (966 mg, 95%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 72% de. IR (neat): 3213, 2961, 1733, 1652, 1646, 1616, 1586, 1516, 1464, 1362, 1247, 1172, 1065, 965, 825, 777, 741, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (d, J=6.9 Hz, 3H, both isomers), 1.09 (d, J=6.9 Hz, 2.58H, major isomer), 1.11 (d, J=7.1 Hz, 0.42H, minor isomer), 1.84–1.98 (m, 1H, both isomers), 3.11–3.23 (m, 1H, both isomers), 3.44 (dd, J=9.0, 13.3 Hz, 0.14H, minor isomer), 3.54 (dd, J=9.3, 13.5 Hz, 0.86H, major isomer), 3.82 (s, 3H, both isomers), 4.05–4.30 (m, 2H, both isomers), 4.45–4.51 (m, 1H, both isomers), 4.90–5.00 (m, 1H, both isomers), 6.85–6.95 (m, 2H, both isomers), 7.23–7.45 (m, 5H, both isomers), 7.75–7.79 (m, 1H, both isomers). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.24; H, 7.51; N, 4.04.

4.4.3. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(4-chlorophenyl)ethanol (4d). According to the general procedure, **1a** (203 mg, 1.0 mmol) and *p*-chlorobenzaldehyde (182 mg, 1.3 mmol) were reacted. After chromatographic purification over Silica Gel 60N (hexane–ethyl acetate=20:1 containing 1% triethylamine), **4d** was obtained as colorless semisolid (334 mg, 97%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 53% de. IR (KBr): 1641, 1490, 1065, 972, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J=6.7 Hz, 2.30H, major isomer), 1.02 (d, J=6.9 Hz, 0.70H, minor isomer), 1.07 (d, J=6.7 Hz, 2.30H, major isomer), 1.11 (d, J=6.9 Hz, 0.70H, minor isomer), 1.82–1.98 (m, 1H, both isomers), 3.16–3.27 (m, 1H, both isomers), 3.37 (dd, J=8.5, 13.5 Hz, 0.23H, minor isomer), 3.47 (dd, J=9.1, 13.5 Hz, 0.77H, major isomer), 4.14–4.27 (m, 2H, both isomers), 4.46–4.52 (m, 1H, both isomers), 4.99 (br d, J=7.4 Hz, 1H, both isomers), 7.08 (dd, J=1.1, 6.6 Hz, 0.23H, minor isomer), 7.15 (dd, J=1.1, 7.7 Hz, 0.77H, major isomer), 7.25–7.42 (m, 6H, both isomers), 7.55–7.66 (m, 1H, both isomers), 7.75–7.79 (m, 1H, both isomers). Anal. Calcd for $C_{20}H_{22}ClNO_2$: C, 69.86; H, 6.45; N, 4.07. Found: C, 69.75; H, 6.64; N, 4.08.

4.4.4. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(3,4-dimethoxyphenyl)ethanol (4e). According to the general procedure, **1a** (203 mg, 1.0 mmol) and veratraldehyde (216 mg, 1.3 mmol) were reacted. After chromatographic purification over Silica Gel 60N (hexane–ethyl acetate=2:1 containing 1% triethylamine), **4e** was obtained as colorless oil (358 mg, 97%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 70% de. IR (neat): 3208, 2960, 1726, 1652, 1593, 1516, 1464, 1418, 1362, 1265, 1139, 1029, 963, 911, 862, 808, 761, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (d, J=6.7 Hz, 3H, both isomers), 1.11 (d, J=6.7 Hz, 2.55H, major isomer), 1.13 (d, J=5.6 Hz, 0.45H, minor isomer), 1.81–1.97 (m, 1H, both isomers), 3.17 (dd, J=3.0, 13.4 Hz, 0.85H, major isomer), 3.27 (dd, J=3.8, 13.5 Hz, 0.15H, minor isomer), 3.41 (dd, J=8.7, 13.5 Hz, 0.15H, minor isomer), 3.54 (dd, J=9.3, 13.4 Hz, 0.85H, major isomer), 3.86 (s, 0.45H, minor isomer), 3.88 (s, 2.55H, major isomer), 3.89 (s, 3H, both isomers), 4.10–4.28 (m, 2H, both isomers), 4.42–4.55 (m, 1H, both isomers), 4.91–5.01

(m, 1H, both isomers), 6.83–7.12 (m, 3H, both isomers), 7.17–7.49 (m, 4H, both isomers), 7.75–7.80 (m, 1H, both isomers). HREIMS *m/z*. Calcd for $C_{22}H_{27}NO_4$ (M^+): 369.1940. Found: 369.1940.

4.4.5. (*S*)- and (*R*)-2-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-1-(1-naphthyl)ethanol (4f). According to the general procedure, **1a** (203 mg, 1.0 mmol) and 1-naphthaldehyde (203 mg, 1.3 mmol) were reacted. After chromatographic purification over Silica Gel 60N (hexane–ethyl acetate = 10:1 containing 1% triethylamine), **4f** was obtained as colorless oil (341 mg, 95%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 1:1): 70% de. IR (neat): 3202, 2961, 1728, 1645, 1598, 1578, 1494, 1467, 1360, 1254, 1064, 965, 799, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, J = 6.7 Hz, 2.55H, major isomer), 1.09 (d, J = 6.6 Hz, 0.45H, minor isomer), 1.11 (d, J = 6.7 Hz, 2.55H, major isomer), 1.18 (d, J = 6.6 Hz, 0.45H, minor isomer), 1.85–2.00 (m, 1H, both isomers), 3.37–3.47 (m, 1H, both isomers), 3.55 (dd, J = 8.6, 13.6 Hz, 0.15H, minor isomer), 3.65 (dd, J = 9.2, 13.6 Hz, 0.85H, major isomer), 4.15–4.33 (m, 2H, both isomers), 4.47–4.54 (m, 1H, both isomers), 5.77–5.87 (m, 1H, both isomers), 7.08–7.62 (m, 6H, both isomers), 7.67–7.93 (m, 4H, both isomers), 8.21–8.28 (m, 1H, both isomers). HREIMS *m/z*. Calcd for $C_{24}H_{25}NO_2$ (M^+): 359.1885. Found: 359.1883.

4.4.6. (2*S*,3*E*)- and (2*R*,3*E*)-1-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-4-phenyl-3-buten-2-ol (4g). According to the general procedure, **1a** (609 mg, 3.0 mmol) and cinnamaldehyde (515 mg, 3.9 mmol) were reacted. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate = 5:1), **4g** was obtained as colorless solid (877 mg, 87%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 1:1): 75% de. Mp 69–72 °C; IR (KBr): 3211, 2961, 1647, 1600, 1577, 1494, 1446, 1356, 1250, 1104, 1065, 965, 747, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (d, J = 6.6 Hz, 0.37H, minor isomer), 1.00 (d, J = 6.9 Hz, 2.63H, major isomer), 1.08 (d, J = 6.9 Hz, 3H, both isomers), 1.75–1.90 (m, 1H, both isomers), 3.15 (dd, J = 3.6, 13.3 Hz, 1H, both isomers), 3.38 (dd, J = 9.1, 13.3 Hz, 1H, both isomers), 4.10–4.21 (m, 2H, both isomers), 4.44–4.53 (m, 1H, both isomers), 4.53–4.65 (m, 1H, both isomers), 6.38 (dd, J = 5.6, 15.8 Hz, 0.12H, minor isomer), 6.39 (dd, J = 5.5, 15.8 Hz, 0.88H, major isomer), 6.68 (d, J = 15.8 Hz, 0.12H, minor isomer), 6.72 (dd, J = 0.8, 15.8 Hz, 0.88H, major isomer), 7.19–7.47 (m, 8H, both isomers), 7.76 (dd, J = 1.2, 7.8 Hz, 1H, both isomers). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.59; H, 7.59; N, 4.03.

4.4.7. (*S*)- and (*R*)-1-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}-3,3-dimethylbutan-2-ol (4h). According to the general procedure, **1a** (203 mg, 1.0 mmol) and pivalaldehyde (149 μL, 1.3 mmol) were reacted. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate = 20:1), **4h** was obtained as colorless semisolid (262 mg, 91%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 9:1): 84% de. IR (KBr): 3267, 2959, 1648, 1480, 1359, 1247, 1065, 965, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, J = 6.8 Hz, 3H, both isomers), 1.00 (s, 0.70H, minor isomer), 1.02 (s, 8.30H, major isomer), 1.03 (d, J = 6.8 Hz, 3H, both isomers), 1.84–1.98 (m, 1H, both isomers), 2.71–2.83 (m, 1H, both isomers), 3.33–3.45 (m, 2H, both isomers), 4.08–4.27 (m, 2H, both isomers), 4.38–4.45 (m, 1H, both isomers), 6.42 (br s, 1H, both isomers), 7.21–7.32 (m, 2H, both isomers), 7.37–7.45 (m, 1H, both isomers), 7.68–7.76 (m, 1H, both isomers). HREIMS *m/z*. Calcd for $C_{18}H_{27}NO_2$ (M^+): 289.2042. Found 289.2018.

4.4.8. (*R*)- and (*S*)-1-{2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]phenyl}nonane-2-ol (4i). According to the general procedure, **1a** (203 mg, 1.0 mmol) and octylaldehyde (203 μL, 1.3 mmol) were reacted. After chromatographic purification over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate = 20:1), **4i** was obtained as colorless oil (247 mg, 75%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH = 9:1): 35% de; IR (neat): 3273, 2927, 1733, 1646, 1601, 1576, 1493, 1467, 1355, 1308, 1249, 1115, 1065, 967, 909, 776, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.77–1.02 (m, 9H, both isomers), 1.16–1.58 (m, 12H, both isomers), 1.68–1.83 (m, 1H, both isomers), 2.87 (dd, J = 3.2, 13.2 Hz, 0.68H, major isomer), 2.98 (dd, J = 3.8, 13.3 Hz, 0.32H, minor isomer), 3.08 (dd, J = 7.8, 13.3 Hz, 0.32H, minor isomer), 3.19 (dd, J = 9.1, 13.2 Hz, 0.68H, major isomer), 3.75 (br s, 1H, both isomers), 4.00–4.13 (m, 2H, both isomers), 4.30–4.42 (m, 1H, both isomers), 6.30 (br s, 1H, both isomers), 7.14–7.25 (m, 2H, both isomers), 7.33 (dt, J = 1.3, 7.4 Hz, 1H, both isomers), 7.66 (dd, J = 1.1, 7.7 Hz, 1H, both isomers). Anal. Calcd for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23. Found: C, 75.94; H, 10.22; N, 4.19.

4.5. Acid-catalyzed lactonization of the addition product 4b (Table 3)

The 77% de sample of **4b** (100 mg, 0.309 mmol) was dissolved in 4.0 mL of a mixed solvent (THF–H_2O–TFA = 10:1.5:0.5) at 0 °C. After being stirred for an appropriate reaction time, the mixture was quenched with saturated aqueous $NaHCO_3$ and the product was extracted with diethyl ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The product **11b** and the unreacted **4b** were separated by column chromatography over Silica Gel 60N using hexane–ethyl acetate = 20:1 containing 1% triethylamine as an eluent. Both ee of **11b** and de of **4b** were determined by HPLC analyses (Daicel Chiralpak AD: hexane–*i*-PrOH = 7:3 for **11b**, hexane–*i*-PrOH = 1:1 for **4b**). The results are in Table 3.

4.6. Synthesis of optically enriched 3,4-dihydroisocoumarins 11 via diastereomer-selective lactonization (Table 4). General procedure

The addition product **4** (1.6 mmol) was dissolved in 20 mL of a mixed solvent (THF–H_2O–TFA = 10:1.5:0.5) at 0 °C. After being stirred for 24 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and the product was extracted with diethyl ether. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N using the following eluents: toluene–ethyl acetate = 20:1 for **11a**, **11d**, **11f**, **11g**, **11h** and **11i**; hexane–ethyl acetate = 10:1 for **11c**; toluene–ethyl acetate = 5:1 for

11e. Recrystallizations of **11a**, **11b**, **11f**, **11g** and **11h** afforded the optically pure samples (>99% ee).

4.6.1. (*S*)-3-Phenyl-3,4-dihydroisocoumarin (11a). According to the general procedure, **4a** (500 mg, 1.6 mmol) was reacted to give **11a** as colorless solid (304 mg, 84%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 89% ee. Recrystallization from diethyl ether–hexane gave an optically pure sample as colorless needles. Mp 76.5–77.0 °C; IR (KBr): 1717, 1604, 1488, 1458, 1349, 1278, 1226, 1117, 1090, 1072, 1031, 999, 923, 802, 762, 748, 701, 640, 575, 511, 433 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.14 (dd, J=3.3, 16.5 Hz, 1H), 3.35 (dd, J=12.0, 16.5 Hz, 1H), 5.56 (dd, J=3.3, 12.0 Hz, 1H), 7.29 (d, J=7.4 Hz, 1H), 7.33–7.52 (m, 6H), 7.57 (dt, J=1.4, 7.6 Hz, 1H), 8.16 (dd, J=1.1, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.51, 79.84, 124.93, 125.94, 127.20, 127.69, 128.46, 128.50, 130.21, 133.74, 138.36, 138.75, 165.10; $[\alpha]_D^{26}=-158$ (*c* 0.990, MeOH, >99% ee) {lit.[6g] $[\alpha]_D=+89$ [*c* 1, $CHCl_3$, ca. 45% ee, (*R*)-isomer]}. Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.10; H, 5.33.

4.6.2. (*S*)-3-(*o*-Tolyl)-3,4-dihydroisocoumarin (11b). According to the general procedure, **4b** (102 mg, 0.32 mmol) was reacted to give **11b** as colorless solid (57.9 mg, 77%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 91% ee. Recrystallization from diethyl ether–hexane gave an optically pure sample as colorless needles. Mp 98.0–98.5 °C; IR (KBr): 1719, 1604, 1516, 1464, 1344, 1276, 1226, 1121, 1083, 1066, 1029, 1006, 913, 820, 747, 692, 530, 508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.11 (dd, J=3.2, 16.5 Hz, 1H), 3.34 (dd, J=12.0, 16.5 Hz, 1H), 5.53 (dd, J=3.2, 12.0 Hz, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.28 (d, J=7.6 Hz, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.43 (t, J=7.6 Hz, 1H), 7.57 (dt, J=1.4, 7.6 Hz, 1H), 8.15 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.15, 35.48, 79.80, 125.01, 125.93, 127.19, 127.63, 129.14, 130.20, 133.67, 135.43, 138.28, 138.86, 165.18; $[\alpha]_D^{26}=-132$ (*c* 1.02, MeOH, >99% ee). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.41; H, 5.95.

4.6.3. (*S*)-3-(4-Methoxyphenyl)-3,4-dihydroisocoumarin (11c). According to the general procedure, **4c** (729 mg, 2.1 mmol) was reacted to give **11c** as colorless solid (393 mg, 72%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=1:1): 86% ee. Mp 84.0–86.0 °C; IR (KBr): 1717,1612, 1516, 1460, 1279, 1249, 1181, 1119, 1072, 1027, 999, 828, 742, 687, 615, 523 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.09 (dd, J=3.0, 16.4 Hz, 1H), 3.35 (dd, J=12.0, 16.4 Hz, 1H), 3.82 (s, 3H), 5.50 (dd, J=3.0, 12.0 Hz, 1H), 6.93 (d, J=8.7 Hz, 2H), 7.28 (d, J=7.5 Hz, 1H), 7.40 (d, J=8.7 Hz, 2H), 7.42 (t, J=7.5 Hz, 1H), 7.56 (t, J=7.5 Hz, 1H), 8.14 (d, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.37, 55.24, 79.71, 113.85, 124.98, 127.20, 127.48, 127.63, 130.18, 130.46, 133.68, 138.90, 159.62, 165.25; $[\alpha]_D^{26}=-93.8$ (*c* 1.02, MeOH, 86% ee). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.53; H, 5.57.

4.6.4. (*S*)-3-(4-Chlorophenyl)-3,4-dihydroisocoumarin (11d). According to the general procedure, **4d** (138 mg, 0.40 mmol) was reacted to give **11d** as colorless solid (85.5 mg, 83%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 73% ee. Mp 74.5–75.0 °C; IR (KBr): 3071, 2907, 1725, 1606, 1495, 1461, 1418, 1346, 1271, 1225, 1116, 1084, 1031, 1016, 914, 894, 817, 744, 704, 686, 646, 624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.12 (dd, J=3.3, 16.4 Hz, 1H), 3.30 (dd, J=11.8, 16.4 Hz, 1H), 5.54 (dd, J=3.3, 11.8 Hz, 1H), 7.29 (d, J=7.5 Hz, 1H), 7.36–7.43 (m, 4H), 7.44 (t, J=7.5 Hz, 1H), 7.58 (dt, J=1.3, 7.5 Hz, 1H), 8.15 (d, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.47, 79.04, 124.80, 127.20, 127.32, 127.83, 128.72, 130.28, 133.86, 134.28, 136.93, 138.42, 164.81; $[\alpha]_D^{26}=-91.3$ (*c* 1.01, MeOH, 73% ee). Anal. Calcd for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29. Found: C, 69.72; H, 4.72.

4.6.5. (*S*)-3-(3,4-Dimethoxyphenyl)-3,4-dihydroisocoumarin (11e). According to the general procedure, **4e** (148 mg, 0.40 mmol) was reacted to give **11e** as colorless solid (64.8 mg, 57%). HPLC (Daicel Chiralpak AS, hexane–EtOH=3:7): 82% ee. Mp 73.5–74.5 °C; IR (KBr): 2941, 1716, 1607, 1518, 1461, 1427, 1388, 1348, 1278, 1240, 1157, 1142, 1123, 1075, 1024, 996, 909, 866, 822, 734, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.11 (dd, J=3.0, 16.4 Hz, 1H), 3.37 (dd, J=12.1, 16.4 Hz, 1H), 3.91 (s, 3H), 3.92 (s, 3H), 5.51 (dd, J=3.0, 12.1 Hz, 1H), 6.88 (d, J=8.2 Hz, 1H), 6.99 (dd, J=1.9, 8.2 Hz, 1H), 7.04 (d, J=1.9 Hz, 1H), 7.29 (d, J=7.5 Hz, 1H), 7.44 (t, J=7.5 Hz, 1H), 7.58 (dt, J=1.4, 7.5 Hz, 1H), 8.16 (d, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.53, 55.88, 55.91, 79.85, 109.26, 110.83, 118.55, 124.96, 127.19, 127.67, 130.23, 130.94, 133.72, 138.86, 148.96, 149.11, 165.22; $[\alpha]_D^{26}=-85.1$ (*c* 0.995, MeOH, 82% ee). HREIMS *m*/*z*. Calcd for $C_{17}H_{16}O_4$ (M^+): 284.1048. Found: 284.1066.

4.6.6. (*S*)-3-(1-Naphthyl)-3,4-dihydroisocoumarin (11f). According to the general procedure, **4f** (100 mg, 0.28 mmol) was reacted to give **11f** as colorless solid (54.6 mg, 72%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 92% ee. Recrystallization from CH_2Cl_2–hexane gave an optically pure sample as colorless needles. Mp 189.0–189.5 °C; IR (KBr): 3041, 1711, 1602, 1514, 1459, 1431, 1343, 1287, 1238, 1123, 1098, 1087, 1032, 1008, 995, 967, 921, 909, 777, 738, 729, 693, 640, 534, 498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.33 (dd, J=3.2, 16.6 Hz, 1H), 3.48 (dd, J=11.9, 16.6 Hz, 1H), 6.33 (dd, J=3.2, 11.9 Hz, 1H), 7.32 (d, J=7.6 Hz, 1H), 7.48 (t, J=7.6 Hz, 1H), 7.51–7.58 (m, 3H), 7.61 (dt, J=1.4, 7.6 Hz, 1H), 7.82 (d, J=7.1 Hz, 1H), 7.88 (d, J=8.2 Hz, 1H), 7.90–7.94 (m, 1H), 7.97–8.10 (m, 1H), 8.22 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.06, 77.09, 122.30, 123.79, 125.01, 125.25, 125.65, 126.46, 127.20, 127.80, 128.97, 129.82, 130.37, 133.57, 133.80, 139.01, 165.30; $[\alpha]_D^{26}=-178$ (*c* 0.100, MeOH, >99% ee); $[\alpha]_D^{26}=-252$ (*c* 1.00, $CHCl_3$, >99% ee). HREIMS *m*/*z*. Calcd for $C_{19}H_{14}O_2$ (M^+): 274.0994. Found 274.0994.

4.6.7. (*S*)-3-[(*E*)-Styryl]-3,4-dihydroisocoumarin (11g). According to the general procedure, **4g** (700 mg, 2.1 mmol) was reacted to give **11g** as colorless solid (351 mg, 67%). HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=1:1): 88% ee. Recrystallization from diethyl ether gave an optically pure sample as colorless needles. Mp 92.0–92.5 °C; IR (KBr): 1707, 1605, 1460, 1378, 1278, 1256, 1223, 1138, 1105, 1084, 995, 971, 914, 804, 762, 747, 696, 589, 512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.11

(dd, J=4.1, 16.2 Hz, 1H), 3.19 (dd, J=9.9, 16.2 Hz, 1H), 5.16–5.26 (m, 1H), 6.34 (dd, J=6.4, 16.1 Hz, 1H), 6.79 (d, J=16.1 Hz, 1H), 7.27–7.44 (m, 7H), 7.56 (dt, J=1.2, 7.6 Hz, 1H), 8.13 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.71, 78.54, 124.99, 125.68, 126.55, 127.29, 127.66, 128.17, 128.51, 130.17, 133.12, 133.68, 135.64, 138.43, 164.89; $[\alpha]_D^{25}=-53.3$ (c 1.03, MeOH, >99% ee). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.38; H, 5.64.

4.6.8. (*S*)-3-(*t*-Butyl)-3,4-dihydroisocoumarin (11h). According to the general procedure, **4h** (200 mg, 0.69 mmol) was reacted to give **11h** as colorless solid (79.7 mg, 56%). HPLC (Daicel Chiralpak AS, hexane–EtOH=9:1): 97% ee. Recrystallization from diethyl ether–hexane gave an optically pure sample as colorless needles. Mp 82.5–83.5 °C (diethyl ether); IR (KBr): 2967, 1716, 1608, 1459, 1346, 1281, 1237, 1121, 1085, 998, 909, 746, 694, 639 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (s, 9H), 2.84 (dd, J=2.7 and 16.1 Hz, 1H), 3.02 (dd, J=12.6, 16.1 Hz, 1H), 4.17 (dd, J=2.7, 12.6 Hz, 1H), 7.26 (d, J=7.4 Hz, 1H), 7.38 (t, J=7.4 Hz, 1H), 7.53 (t, J=7.4 Hz, 1H), 8.09 (d, J=7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.60, 28.41, 33.99, 86.05, 125.09, 127.33, 127.35, 130.01, 133.38, 139.53, 165.81; $[\alpha]_D^{26}=-107$ (c 1.04, MeOH, >99% ee). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.10; H, 8.28.

4.6.9. (*R*)-3-Heptyl-3,4-dihydroisocoumarin (11i). According to the general procedure, **4i** (161 mg, 0.49 mmol) was reacted to give **11i** as colorless oil (51.8 mg, 43%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=9:1): 79% ee. IR (neat): 2927, 2857, 1733, 1609, 1461, 1359, 1277, 1116, 1086, 1031, 914, 802, 745, 716, 694, 604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J=6.7 Hz, 3H), 1.24–1.62 (m, 10H), 1.66–1.78 (m, 1H), 1.82–1.96 (m, 1H), 2.90 (dd, J=4.1, 16.2 Hz, 1H), 2.99 (dd, J=10.6, 16.2 Hz, 1H), 4.47–4.58 (m, 1H), 7.24 (d, J=7.6 Hz, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.53 (dt, J=1.3, 7.6 Hz, 1H), 8.09 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.07, 22.60, 24.89, 29.11, 29.32, 31.72, 33.18, 34.94, 78.68, 125.09, 127.19, 127.40, 130.06, 133.45, 139.06, 165.49; $[\alpha]_D^{25}=-50.4$ (c 1.01, MeOH, 79% ee). HREIMS m/z. Calcd for $C_{16}H_{22}O_2$ (M^+): 246.1620. Found 246.1624.

4.7. Synthesis of chiral epoxides 16. General procedure

AD-mix-β (14 g) was dissolved in a mixture of *tert*-butyl alcohol (50 mL) and water (50 mL). The olefin **13** (10 mmol) was added dropwise to this mixture at 0 °C. After being stirred for 18 h at 0 °C, Na_2SO_3 (15 g, 119 mmol) was added to the mixture. The mixture was extracted with diethyl ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N using hexane–ethyl acetate=1:1 as an eluent. Yields of the diol intermediates **14** after chromatography are shown in Scheme 4.

p-Toluenesulfonyl chloride (1.29 g, 6.76 mmol) was added portionwise to a solution of diol **14** (6.14 mmol) in pyridine (5 mL) at 0 °C. After being stirred for 13 h at 0 °C, the mixture was quenched with water and the product was extracted with diethyl ether. The extract was washed successively with 2 M aqueous HCl, water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N using the following eluents: hexane–ethyl acetate=3:1 for **15a**, **15b** and **15d**; hexane–ethyl acetate=5:1 for **15c**. Yields of the tosylate intermediates **15** after chromatography are shown in Scheme 4.

To a solution of the tosylate **15** (3.9 mmol) in diethyl ether (20 mL) was added 2 M aqueous NaOH (10 mL) at room temperature. After being stirred for 3 h, the mixture was extracted with diethyl ether. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by distillation. Yields of the epoxides **16** after distillation are shown in Scheme 4.

4.7.1. (*R*)-Phenyloxirane (16a). Bp 85–120 °C (24 mmHg, bulb-to-bulb); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (dd, J=2.5, 5.5 Hz, 1H), 3.15 (dd, J=4.0, 5.5 Hz, 1H), 3.86 (dd, J=2.5, 4.0 Hz, 1H), 7.23–7.40 (m, 5H); HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=30:1): 98% ee; $[\alpha]_D^{26}=+45.9$ (c 0.652, benzene), {lit.[13] $[\alpha]_D^{22}=-44.5$ (c 1.15, benzene): (*S*)-isomer (99% ee)}.

4.7.2. (*R*)-(*p*-Tolyl)oxirane (16b). Bp 105–120 °C (10 mmHg, bulb-to-bulb); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.80 (dd, J=2.0, 6.0 Hz, 1H), 3.12 (dd, J=4.0, 6.0 Hz, 1H), 3.83 (dd, J=2.0, 4.0 Hz, 1H), 7.17 (s, 4H); HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=30:1): 97% ee; $[\alpha]_D^{26}=+26.7$ (c 1.12, benzene), {lit.[13] $[\alpha]_D^{22}=-25.9$ (c 1.02, benzene): (*S*)-isomer (97% ee)}.

4.7.3. (*R*)-Heptyloxirane (16c). Bp 40–50 °C (1.0 mmHg, bulb-to-bulb); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J=6.0 Hz, 3H), 1.20–1.60 (m, 12H), 2.46 (dd, J=3.5, 6.0 Hz, 1H), 2.75 (t, J=6.0 Hz, 1H), 2.85–2.95 (m, 1H); $[\alpha]_D^{24}=+7.21$ (c 1.01, $CHCl_3$), {lit.[14] $[\alpha]_D^{24}=-8.9$ (c 1.14, $CHCl_3$): (*S*)-isomer (>97% ee)}. Optical purity of **16c** was estimated to be 81% ee from the lit. $[\alpha]_D$.

4.7.4. (*R*)-(2-Phenylethyl)oxirane (16d). Bp 90–110 °C (7.0 mmHg, bulb-to-bulb); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76–1.93 (m, 2H), 2.47 (dd, J=3.5, 5.0 Hz, 1H), 2.65–2.90 (m, 3H), 2.90–3.00 (m, 1H), 7.12–7.36 (m, 5H); HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH=9:1): 78% ee; $[\alpha]_D^{26}=+15.8$ (c 1.24, acetone), {lit.[15] $[\alpha]_D^{23}=+16.4$ (c 1.4, acetone): (*R*)-isomer (96% ee)}.

4.8. Synthesis of chiral 3,4-dihydroisocoumarins 18. General procedure

Under an argon atmosphere, a hexane-cyclohexane solution of *sec*-BuLi (3.1 mmol) was added dropwise to a solution of oxazoline **17** (491 mg, 2.8 mmol) in THF (5.0 mL) at −78 °C. After being stirred for 1 h, the reaction mixture was added dropwise to a suspension of copper cyanide (125 mg, 1.4 mmol) at −78 °C. The mixture was gradually warmed to −20 °C over 3 h, and then cooled to −78 °C. The epoxide **16** in THF (2.0 mL) was added to the mixture at −78 °C. The mixture was gradually warmed to 0 °C over

4 h and then stirred for additional 12 h at 0 °C. The reaction mixture was quenched with a mixture of 28% aqueous NH_3 (10 mL) and saturated aqueous NH_4Cl (15 mL) and the product was extracted with diethyl ether. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in 36 mL of a mixed solvent (THF–H_2O–TFA=10:1.5:0.5) at room temperature. After being stirred for 14 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and the product was extracted with diethyl ether. The extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N using the following eluents: hexane–ethyl acetate=10:1 for **18a** and **18b**; hexane–ethyl acetate=5:1 for **18c** and **18d**.

4.8.1. (*S*)-3-Phenyl-3,4-dihydroisocoumarin (18a). According to the general procedure, **16a** (120 mg, 1.0 mmol) was reacted to give **18a** as colorless solid (58.4 mg, 27%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 98% ee. Mp 73.0–75.0 °C; $[\alpha]_D^{25}=-151$ (*c* 1.53, MeOH). Other spectroscopic data are identical with those of **11a**.

4.8.2. (*S*)-3-(*p*-Tolyl)-3,4-dihydroisocoumarin (18b). According to the general procedure, **16b** (134 mg, 1.0 mmol) was reacted to give **18b** as colorless solid (62.4 mg, 26%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=7:3): 98% ee. Mp 88.0–90.0 °C; $[\alpha]_D^{25}=-124$ (*c* 1.46, MeOH). Other spectroscopic data are identical with those of **11b**.

4.8.3. (*R*)-3-Heptyl-3,4-dihydroisocoumarin (18c). According to the general procedure, **16c** (142 mg, 1.0 mmol) was reacted to give **18c** as colorless oil (94.8 mg, 38%). HPLC (Daicel Chiralpak AD, hexane–*i*-PrOH=9:1): 84% ee. $[\alpha]_D^{25}=-51.9$ (*c* 1.00, MeOH). Other spectroscopic data are identical with those of **11i**.

4.8.4. (*R*)-3-(2-Phenylethyl)-3,4-dihydroisocoumarin (18d). According to the general procedure, **16d** (148 mg, 1.0 mmol) was reacted to give **18d** as colorless oil (157 mg, 62%). HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=7:3): 79% ee. IR (neat): 3063, 3028, 2948, 1722, 1606, 1496, 1456, 1362, 1280, 1159, 1123, 1030, 942, 913, 803, 745, 701, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.96–2.08 (m, 1H), 2.16–2.29 (m, 1H), 2.79–3.07 (m, 4H), 4.47–4.56 (m, 1H), 7.16–7.33 (m, 6H), 7.38 (t, J=7.6 Hz, 1H), 7.52 (dt, J=1.4, 7.6 Hz, 1H), 8.10 (dd, J=1.1, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.98, 33.21, 36.57, 77.49, 124.95, 125.95, 127.17, 127.45, 128.31, 128.35, 130.07, 133.51, 138.85, 140.71, 165.32; $[\alpha]_D^{25}=-30.4$ (*c* 1.00, MeOH). HREIMS *m*/*z*. Calcd for $C_{17}H_{16}O_2$ (M^+): 252.1150. Found 252.1056.

4.9. Catalytic hydrogenation of 11g

Under a hydrogen atmosphere, a mixture of 3,4-dihydroisocoumarin **11g** (>99% ee) (20.0 mg, 0.0799 mmol), 5% palladium carbon (2.0 mg), and ethanol (2.0 mL) was vigorously stirred at room temperature for 8 h. The mixture was passed through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane–ethyl acetate=10:1) to give **19** (14.1 mg, 70%). HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH=7:3): >99% ee. $[\alpha]_D^{25}=-38.1$ (*c* 0.705, MeOH). Other spectroscopic data are identical with those of **18d**.

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