DOI: 10.1002/ejoc.200800089

Guanidine-Catalyzed Asymmetric Synthesis of 2,2-Disubstituted Chromane Skeletons by Intramolecular Oxa-Michael Addition

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Keywords: Asymmetric synthesis / Organocatalysis / Chromane / Guanidine / Michael addition

The guanidine-catalyzed 6-*exo*-*trig*-type intramolecular asymmetric oxa-Michael addition of α,β-unsaturated esters with a 2-hydroxyaryl moiety at the C-5 carbon has been examined for the construction of chromane skeletons with a quaternary carbon chiral center. The bulkiness of the alkyl group and the *E*/*Z* geometry of the α,β-unsaturated ester function played important roles in the asymmetric induction and (4*S*,5*S*)-2-[(*R*)-1-hydroxymethyl-2-phenylethylimino]-1,3-dimethylimidazolidine (or its enantiomer) carrying aryl pendants at the 4- and 5-positions was found to be the most effective catalyst among 18 chiral guanidines examined. In this way, the *Z* isomer of the less bulky methyl ester was subjected to the cyclization reaction, affording chiral chromane in up to 83% yield with 76% *ee*.
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Introduction

Important biological activities have been reported for 2,2-disubstituted chiral chromanes: Vitamin E (**1**)[1] with lipophilic antioxidant activity, *trans*-δ-tocotrienoloic acid (**2**)[2] with antibacterial activity, rhododaurichromanic acid A (**3**)[3] with anti-HIV effects, and siccanin (**4**)[4] with strong antifungal activity (Figure 1). The enantioselective synthesis of 2,2-disubstituted chromane skeletons, for the purpose of further therapeutic modification, is an important issue in the synthesis of these important natural products. Hayashi,[5] Achiwa,[6] Trost,[7] and Tietze[8] and their co-workers have reported the palladium-catalyzed asymmetric synthesis of 2,2-disubstituted chiral chromanes. However, although much attention has been focused on the use of organocatalysts instead of metal catalysts in asymmetric synthesis,[9] there has been no report of the construction of the 2,2-disubstituted chiral chromane skeletons by the oxa-Michael reaction using organocatalysts.[10] We have previously developed a 6-*endo*-*trig*-type intramolecular asymmetric oxa-Michael addition catalyzed by quinine for the preparation of the 2,3-disubstituted chroman-4-one system and applied the method to the enantioselective synthesis of anti-HIV-1-active coumarins such as (+)-calanolide A.[11] In addition, we have discovered the potential usefulness of guanidine compounds as chiral auxiliaries.[12] Herein we report the asymmetric construction of the 2,2-disubstituted chromane skeleton from phenols with trisubstituted α,β-unsaturated esters by a 6-*exo*-*trig*-type intramolecular oxa-Michael addition reaction catalyzed by chiral guanidine.

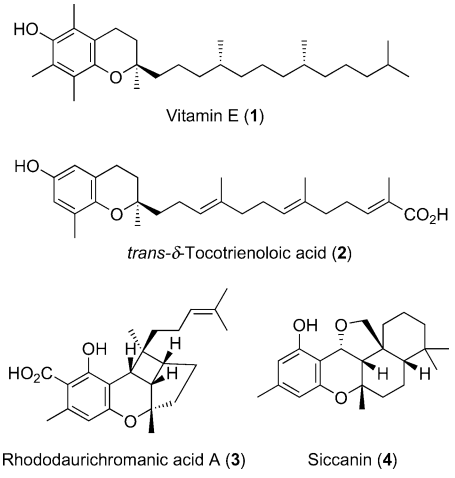

Figure 1. Examples of natural products with a 2,2-disubstituted chromane skeleton.

Results and Discussion

We have designed a synthesis for the construction of chiral chromane skeleton **5** with a quaternary carbon chiral center at the 2-position by a 6-*exo*-*trig*-type intramolecular asymmetric oxa-Michael addition assisted by an organocatalyst from phenol bearing α,β-unsaturated esters at the *ortho* position, derived from 2-hydroxybenzaldehyde (**6**) by elongation of the carbon unit and a Horner–Wadsworth–Emmons (HWE) reaction (Scheme 1).

Benzylideneacetone **7** was obtained from aldehyde **6** by aldol condensation[13] and then the phenol group of **7** was protected with a methoxyethoxymethyl (MEM) group. Catalytic hydrogenation of the protected ketone **8** gave satu-

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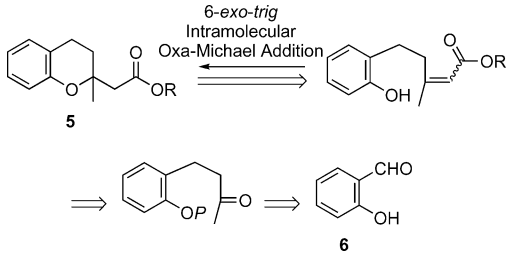
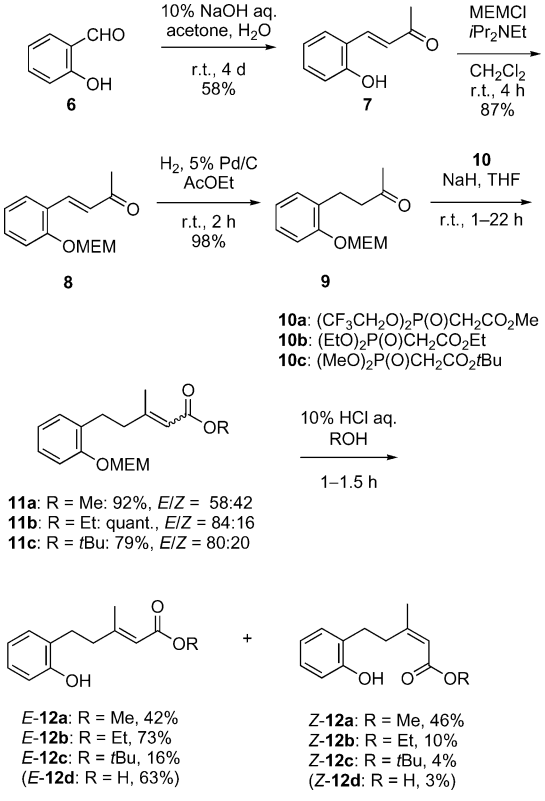


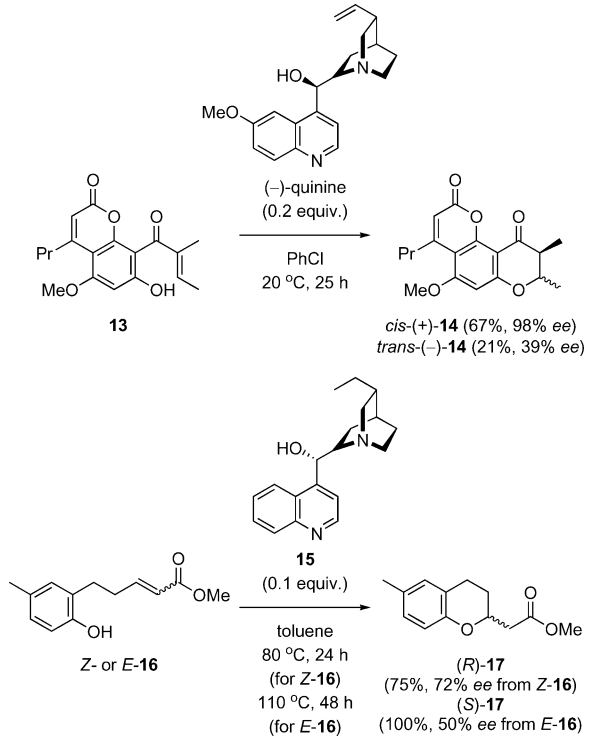
Scheme 1. Retrosynthesis of chromane skeletons **5**.

rated ketone **9**, and HWE reaction in which three kinds of phosphonates **10** were used afforded the corresponding α,β-unsaturated esters **11** as an inseparable mixture of *E*/*Z* isomers. As both *E*/*Z* isomers were necessary to examine the effect of stereochemistry, these conditions were adopted even though the stereoselectivity was low in the case of **11a**. The MEM group of α,β-unsaturated esters **11** was removed under conventional acidic conditions to give *E* and *Z* diastereoisomers **12**, respectively, after purification by silica gel column chromatography. Overdeprotection of the ester alkyl group was observed in the case of *tert*-butyl ester **11c** (Scheme 2). The stereochemistry of the *E*/*Z* isomers was determined by NOE experiments.

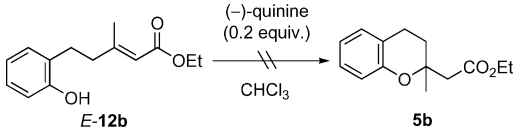


Scheme 2. Synthesis of substrates **12** for intramolecular oxa-Michael addition.

As the *E* isomer of ethyl ester *E*-**12b** was obtained in good yield, it was used as a standard substrate for the screening of conditions for the intramolecular oxa-Michael addition. Previously we reported the asymmetric synthesis of the 2,3-dimethylchroman-4-one skeleton **14** by intramolecular oxa-Michael addition of *o*-tigloylphenol **13** using (–)-quinine as the catalyst in which 6-*endo*-*trig* cyclization occurred.[11] Furthermore, in the course of our study on this chromane cyclization, Merschaert et al.[10a] reported the asymmetric construction of 2-monosubstituted chromane **17** by a 6-*exo*-*trig*-type intramolecular oxa-Michael addition catalyzed by dihydrocinchonine (**15**) that is quite similar to our strategy (Scheme 3). Thus, first we applied (–)-quinine to the intramolecular oxa-Michael addition of *E* unsaturated ethyl ester *E*-**12b** for the synthesis of 2,2-disubstituted chromane. However, no reaction was observed (Scheme 4). Therefore, various base catalysts for the synthesis of the 2,2-disubstituted chromane system **5b** were screened (Table 1).



Scheme 3. Reported intramolecular oxa-Michael additions catalyzed with quinine and dihydrocinchonine (**15**) for asymmetric chromane ring constructions.



Scheme 4. Quinine-catalyzed 6-*exo*-*trig*-type asymmetric oxa-Michael addition of phenol *E*-**12b** for the synthesis of 2,2-disubstituted chromane system **5b**.

As expected, the reaction did not proceed with triethylamine (TEA) (entry 1) and the utilization of a stronger inorganic base, NaH, led to the formation of a complex mixture (entry 2). We previously had reported chiral guanidine-assisted asymmetric syntheses, including an intermolecular oxa-Michael addition reaction.[12c,12h] Therefore we explored the potential of guanidine in the reaction system

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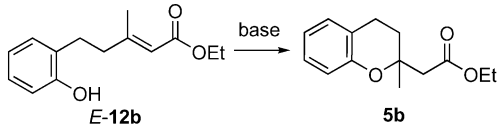
Table 1. Screening of base catalysts for the intramolecular oxa-Michael addition of *E*-**12b**.



E-**12b** **5b**

entry	base (equiv.)	solvent	temp.	time (h)	results
1	TEA (3.2)	$CHCl_3$	r.t.–reflux	7.5	no reaction
2	NaH (3.2)	PhH	reflux	3	a complex mixture
3	TMG (3.0)	$CHCl_3$	r.t.	48	76%[a]
4	TMG (0.2)	$CHCl_3$	r.t.	48	75%[b]

[a] Isolated yield. [b] Estimated by ^{1}H NMR analysis.

studied in this work. Thus, treatment with excess tetramethylguanidine (TMG) in chloroform at room temp. for 48 h gave the desired cyclized compound (entry 3). Similarly, the reaction proceeded even when a catalytic amount of TMG (0.2 equiv.) was used (entry 4). The synthesized racemic chromane **5b** could be detected as two separate peaks by chiral HPLC.

For the asymmetric intramolecular oxa-Michael addition, the reactions of a series of chiral guanidines[12a,12f,14] (Figure 2) were examined. The reactions were carried out under the same conditions as those used in entry 4 of Table 1 and the results are summarized in Table 2. Yields are given as isolated yields unless mentioned otherwise. The enantioselectivity (% *ee*) was estimated by chiral HPLC. Promising cyclization reactions with asymmetric induction were observed when NMe-type guanidines substituted with a 1-hydroxymethyl-2-phenylethyl moiety on the external nitrogen atom (**25**, **26**, and **28**) were used as catalysts, with chromane **5b** being obtained in moderate yields and enantioselectivities (entries 8, 9, and 11). For the NMe-type guanidines, the stereochemistry induced in the products was controlled by the substituent on the external nitrogen and not by those in the ring. The absolute configurations of the products were chemically determined by derivatization to a known compound, as noted later.

Next, we examined the effect of solvent on the cyclization by using **28** as the standard guanidine (Table 3). Less polar solvents showed better yields and enantioselectivities (entries 1–5). When highly polar solvents such as ethanol, DMF, or acetonitrile were used, the enantioselectivity was lowered (entries 6–8). Rate acceleration and in some cases improvements in the *ee* were observed in guanidine-catalyzed reactions performed without solvent.[12c] However, the expected rate acceleration and/or improvements in the *ee* were not obtained in this chromane construction (entry 9).

For further optimization of the reaction conditions, the effects of ester functionality and the geometry of the substrate were investigated. Thus, the *E*/*Z* isomers of methyl, ethyl, and *tert*-butyl esters, and the (*E*)-carboxylic acid *E*-**12d** were examined as substrates (Table 4). The enantioselectivities of the methyl (**5a**) and *tert*-butyl esters (**5c**) were estimated by chiral HPLC under conditions similar to those used with ethyl ester **5b**. When the carboxylic acid *E*-**12d** was used, the reaction did not proceed (entry 1). The use of methyl ester *E*-**12a** led to a slightly higher yield and enantioselectivity (entry 2) compared with ethyl ester *E*-**12b** (entry 3), whereas the opposite results were obtained in the case of the bulky *tert*-butyl ester *E*-**12c** (entry 4), which suggests that the *tert*-butyl ester might sterically disturb the interaction between the substrate and the guanidine catalyst

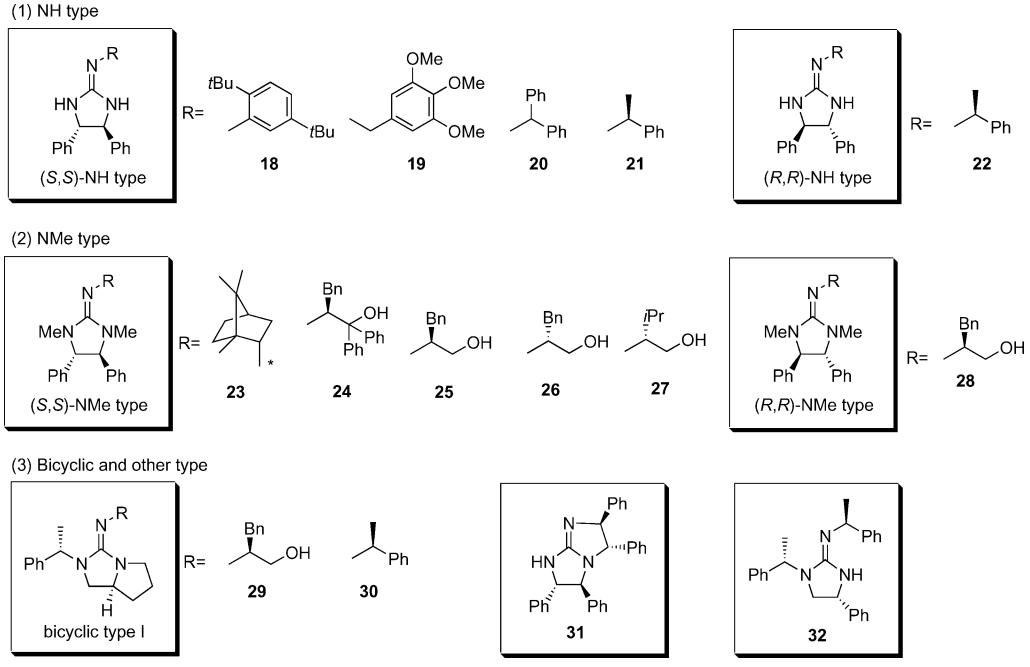


Figure 2. Chiral guanidines used in the intramolecular oxa-Michael addition reaction.

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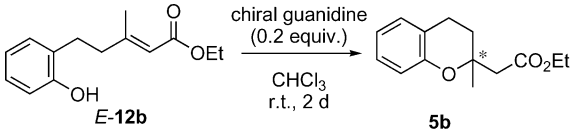
Table 2. Screening of chiral guanidines for the cyclization of *E*-**12b** to chromanes.



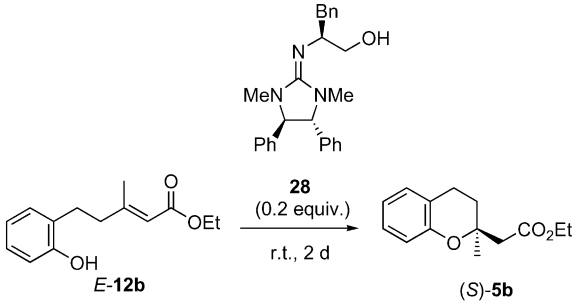
entry	chiral guanidine	yield (%)[a]	*ee* (%)[b] (config.)
1	**18**	0	–
2	**19**	63	0
3	**20**	36	21 (*S*)
4	**21**	65	21 (*S*)
5	**22**	60	15 (*R*)
6	**23**	25	1 (*S*)
7	**24**	18	5 (*S*)
8	**25**	41	24 (*S*)
9	**26**	50	31 (*R*)
10	**27**	49	21 (*R*)
11	**28**	51	28 (*S*)
12	**29**	10	2 (*R*)
13	**30**	39	1 (*S*)
14	**31**	0	–
15	**32**	19	0

[a] Isolated non-optimized yield. [b] Estimated by chiral HPLC analysis.

in the transition state. Use of the *Z* isomers instead of the *E* isomers resulted in large improvements in both the yields and the enantioselectivities (entries 5 and 6): Chromane **5a** was obtained in 75% yield with 71% *ee* of the opposite enantiomer when methyl ester *Z*-**12a** was used as the substrate (entry 5) (see entry 2). Similar results were observed in the dihydrocinchonine-catalyzed oxa-Michael addition by Merschaert et al.[10a] (Scheme 3).

Recently we prepared modified guanidines based on **28**:[15] Displacement of the phenyl pendants with *o*-tolyl moieties in **33** and substitution of the methyl groups on the ring nitrogen atoms in **35**. These chiral guanidines were used in this chromane cyclization reaction (Table 5). The reaction was greatly accelerated by using the former **33**, but no effect on enantioselectivity was observed (entry 1). The enantioselectivity was improved to 80 from 76% when the reaction was carried out at 0 °C (entry 2). On the other hand, the diastereoisomer **34** and the *N*-benzylated guanidine **35** were found to be ineffective catalysts (entries 3 and

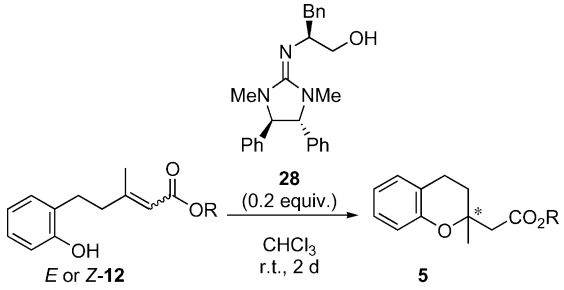
Table 3. Effect of solvent on the intramolecular oxa-Michael addition of *E*-**12b**.



entry	solvent	yield (%)[a]	*ee* (%)[b]
1[c]	$CHCl_3$	51	28
2	PhH	39	33
3	PhMe	50	26
4	PhCl	87	30
5	THF	22	24
6	EtOH	47	6
7	DMF	3	7
8	MeCN	79	12
9	none	45	14

[a] Isolated non-optimized yield. [b] Estimated by chiral HPLC analysis. [c] The data of entry 11 in Table 2.

Table 4. Effects of ester functionality and substrate geometry on the intramolecular oxa-Michael addition of **12**.



entry	*E* or *Z*	R	yield (%)[a]	*ee* (%)[b] (config.)
1	*E*	H	0	–
2	*E*	Me	58	32 (*S*)
3	*E*	Et	51	28 (*S*)
4	*E*	*t*Bu	7	6[c]
5	*Z*	Me	75	71 (*R*)
6	*Z*	Et	61	70 (*R*)

[a] Isolated non-optimized yield. [b] Estimated by chiral HPLC analysis. [c] The absolute configuration was not determined.

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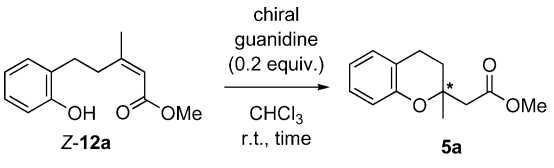
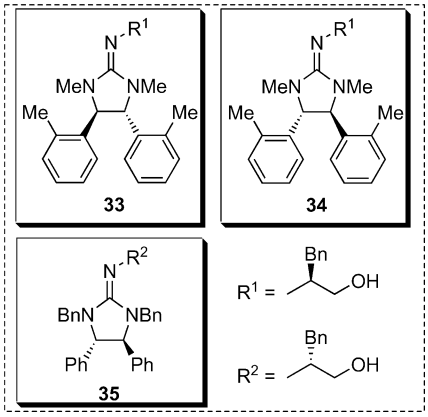
Table 5. Oxa-Michael addition of *Z*-**12a** with modified chiral guanidines.



entry	chiral guanidine	time (d)	yield (%)[a]	*ee* (%)[b] (config.)
1	**33**	2	83	76 (*R*)
2[c]	**33**	2	41	80 (*R*)
3	**34**	2	53	29 (*R*)
4	**35**	7	39	23 (*S*)

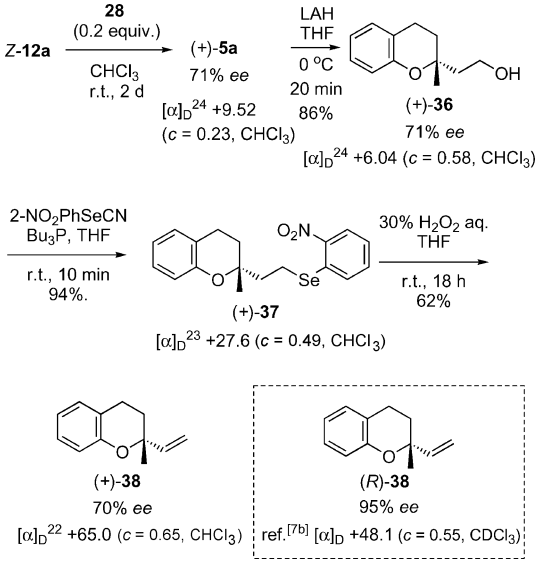


[a] Isolated non-optimized yield. [b] Estimated by chiral HPLC analysis. [c] The reaction was carried out at 0 °C.

4); in the latter case the yield after 7 days was only 39% (entry 4). Thus, the introduction of methyl groups on the phenyl pendants of the imidazolidine ring could play an important role in rate acceleration.

The absolute configurations of the chromane products **5** were determined by conversion into a known vinylchromane **38**[7b] (Scheme 5). (+)-Chromane methyl ester (+)-**5a** with 71% *ee*, synthesized from methyl ester *Z*-**12a** with chiral guanidine **28** on a preparative scale, was reduced with $LiAlH_4$ to produce alcohol (+)-**36** in 86% yield. Successive reactions with 2-nitrophenyl selenocyanate[16] and 30% H_2O_2 afforded the vinylchromane (+)-**38** with specific rotation $[\alpha]_D$ = +65.0. It is reported that (+)-vinylchromane **38** has an *R* configuration. Thus, the absolute configuration of (+)-**5a** was determined to be *R*.[17] The *ee* of our chromane (+)-**38** was estimated to be 70% by chiral HPLC, whereas the $[\alpha]_D$ of (+)-vinylchromane with 95% *ee* was reported to be +48.1.[7b] Unfortunately, the reason for this discrepancy is not clear.

In the guanidine-catalyzed Michael reaction of iminoacetate and α,β-unsaturated carbonyl compounds,[15] we pointed out the crucial role of effective hydrogen-bond formation between the catalyst and the electrophile for asymmetric induction in the adduct. Thus, it is reasonable to similarly speculate that the transition-state structure of the intramolecular oxa-Michael addition of *Z*-**12a** catalyzed by guanidine **33** (also **28**) to give (*R*)-**5a** is as shown in Figure 3. The 3D structure of guanidine **33** (also **28**) derived by X-ray crystallography[15] shows that the two NMe groups positioned between the vicinal aryl pendants and the benzyl group occupy the less hindered open space of the imidazoline ring. Substrate *Z*-**12a** can approach the guanidine by avoiding the NMe group to form hydrogen bonds between not only the O^1–H of the substrate and the guanidine N^1 atom, but also the C=O^2 of the substrate and the O^3–H of the guanidine. In the 15-membered-ring transition-state structure, the activated O^1 atom preferentially attacks the electrophilic β-position of the ester function from the *re* face to build the (*R*)-chromane skeleton (*R*)-**5a**. This effective hydrogen-bonding network is also supported by theoretical calculations.[18] On the other hand, in the alternative transition-state structure, which corresponds to *si*-face at-



Scheme 5. Determination of the absolute configuration of (+)-chromane methyl ester (+)-**5a**.

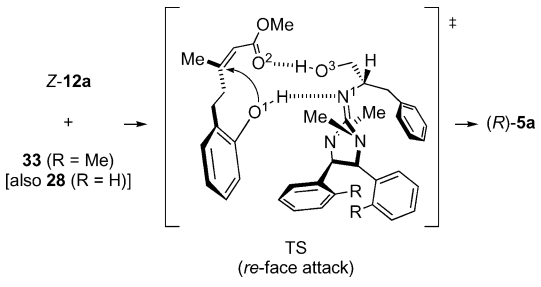


Figure 3. Supposed transition-state structure of guanidine **33** (also **28**) catalyzed oxa-Michael addition.

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tack leading to enantiomeric (*S*)-**5a**, only a single hydrogen bond between O^1–H of the substrate and the guanidine N^1 atom is possible.

Conclusions

We have examined the asymmetric construction of the 2,2-disubstituted chromane skeleton from phenols carrying an α,β-unsaturated ester function by intramolecular oxa-Michael addition and found that 6-*exo*-*trig*-type cyclization could be effectively catalyzed by modified guanidines when *Z* unsaturated esters were used as the substrates. Satisfactory construction of a quaternary chiral center with acceptable asymmetric induction was observed in reactions catalyzed with (4*S*,5*S*)-2-[(*R*)-1-hydroxymethyl-2-phenylethylimino]-1,3-dimethylimidazolidines carrying phenyl or *o*-tolyl pendants at the 4- and 5-positions. In addition, the latter pendant was responsible for remarkable rate acceleration. To the best of our knowledge, this is the first report of the asymmetric construction of a quaternary carbon center in the chromane skeleton catalyzed by an organocatalyst such as chiral guanidines with higher basicity than cinchona alkaloids. We are exploring the application of this strategy to the enantioselective synthesis of the biologically important natural 2,2-disubstituted chromanes.

Experimental Section

General: Melting points were determined with a Yanagimoto MP-SI micro melting point hot-stage instrument and are uncorrected. IR spectra were recorded with a JASCO FT/IR-300E spectrometer. Specific rotation $[\alpha]_D$ was measured with a JASCO DIP-140 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM ECP 400 and GSX-500α spectrometers in $CDCl_3$ unless otherwise stated. MS (EI) and HRMS (EI) were performed with a JASCO MS-GCMATE spectrometer, MS (FAB) with a JEOL JMS-AX500 or JMS-AX505 spectrometer, and HRMS (FAB) with a JEOL JMX-HX 110 spectrometer, respectively. For column chromatography silica gel 60 or 60N (spherical, 70–230 mesh, Kanto) was used.

Synthesis of the Substrates

(3*E*)-4-(2-Hydroxyphenyl)but-3-en-2-one (7):[13] Aqueous 10% NaOH solution (13.6 mL, 37.9 mmol) was added dropwise to a solution of 2-hydroxybenzaldehyde (**6**) (1.74 mL, 16.3 mmol) in acetone (4.00 mL, 54.5 mmol). The mixture was stirred at room temp. for 4 d, after which the pH of the mixture was adjusted to 13 by addition of H_3PO_4 (0.4 mL) and then washed with chloroform (16 mL). Acidification of the aqueous layer with 10% HCl (11.5 mL, pH ≈ 6.1) gave a yellow solid (1.95 g), which was recrystallized from benzene/AcOEt to afford yellowish needles; yield 1.53 g (58%); m.p. 139–140 °C (ref.[13] m.p. 139 °C). IR (Nujol): $\tilde{\nu}_{max}$ = 3355, 1638 cm^{-1}. ^{1}H NMR (400 MHz): δ = 2.41 (s, 3 H, Me), 5.95 (br. s, 1 H, OH), 6.85 (dd, *J* = 8.0, 1.0 Hz, 1 H, ArH), 6.89 (d, *J* = 16.5 Hz, 1 H, ArCHC*H*), 6.96 (ddd, *J* = 7.6, 7.5, 1.0 Hz, 1 H, ArH), 7.26 (ddd, *J* = 8.0, 7.5, 1.6 Hz, 1 H, ArH), 7.51 (dd, *J* = 7.9, 1.7 Hz, 1 H, ArH), 7.84 (d, *J* = 16.5 Hz, 1 H, ArC*H*CH) ppm. ^{13}C NMR (100 MHz): δ = 26.8, 116.6, 120.6, 121.5, 127.6, 129.6, 131.9, 140.9, 156.1, 201.2 ppm. MS (FAB): *m*/*z* = 163 $[M + H]^+$.

(3*E*)-4-{2-[(2-Methoxyethoxy)methoxy]phenyl}but-3-en-2-one (8):[19] *N*,*N*-Diisopropylethylamine (0.830 mL, 4.77 mmol) was added to a suspension of **7** (500 mg, 3.09 mmol) in CH_2Cl_2 (4.0 mL) under ice-cooling and Ar and the mixture was stirred for 3 min. 2-Methoxyethoxymethyl chloride (0.600 mL, 5.26 mmol) was added to the mixture and the whole was stirred at room temp. for 4 h. The reaction mixture was diluted with CH_2Cl_2 (15 mL), washed with water (2 × 10 mL), aq. 10% NaOH (10 mL), water (2 × 10 mL), and brine (10 mL), and dried with $MgSO_4$. The organic layer was evaporated in vacuo to afford a yellow oil which was used directly in the next step; yield 675 mg (87%). IR (neat): $\tilde{\nu}_{max}$ = 1670 cm^{-1}. ^{1}H NMR (400 MHz): δ = 2.39 (s, 3 H, COMe), 3.37 (s, 3 H, OMe), 3.55–3.58 (m, 2 H, OCH_2CH_2O), 3.84–3.87 (m, 2 H, OCH_2CH_2O), 5.36 (s, 2 H, OCH_2O), 6.74 (d, *J* = 16.5 Hz, 1 H, ArCHC*H*), 7.02 (dd, *J* = 7.7, 7.7 Hz, 1 H, ArH), 7.21 (d, *J* = 8.4 Hz, 1 H, ArH), 7.34 (ddd, *J* = 8.4, 7.7, 1.6 Hz, 1 H, ArH), 7.56 (dd, *J* = 7.7, 1.6 Hz, 1 H, ArH), 7.91 (d, *J* = 16.5 Hz, 1 H, ArC*H*CH) ppm. ^{13}C NMR (100 MHz): δ = 27.2, 58.9, 67.8, 71.4, 93.5, 114.8, 121.9, 123.8, 127.6, 127.8, 131.7, 138.3, 155.9, 198.8 ppm.

4-{2-[(2-Methoxyethoxy)methoxy]phenyl}butan-2-one (9): A mixture of ketone **8** (3.92 g, 15.7 mmol) and 5% Pd/C (333 mg) in AcOEt (156 mL) was stirred at room temp. under H_2 for 2 h. The mixture was then filtered through a Celite pad and the filtrate was concentrated in vacuo. The resulting yellow oil (4.26 g) was purified by column chromatography (silica gel 60N, *n*-hexane/AcOEt = 2:1) to afford a colorless oil; yield 3.87 g (98%): IR (neat): $\tilde{\nu}_{max}$ = 1718 cm^{-1}. ^{1}H NMR (400 MHz): δ = 2.15 (s, 3 H, COMe), 2.73 (t, *J* = 7.6 Hz, 2 H, $ArCH_2CH_2$), 2.89 (t, *J* = 7.6 Hz, 2 H, $ArCH_2CH_2$), 3.38 (s, 3 H, OMe), 3.56–3.58 (m, 2 H, OCH_2CH_2O), 3.81–3.83 (m, 2 H, OCH_2CH_2O), 5.30 (s, 2 H, OCH_2O), 6.93 (ddd, *J* = 7.3, 7.3, 1.5 Hz, 1 H, ArH), 7.10–7.19 (m, 3 H, 3 × ArH) ppm. ^{13}C NMR (100 MHz): δ = 24.8, 29.8, 43.7, 58.9, 67.6, 71.5, 93.3, 113.8, 121.6, 127.4, 129.7, 129.9, 155.0, 208.3 ppm. MS (FAB): *m*/*z* = 275 $[M + Na]^+$. HRMS (FAB): calcd. for $C_{14}H_{20}O_4Na$ 275.1259; found 275.1266.

Ethyl 5-{2-[(2-Methoxyethoxy)methoxy]phenyl}-3-methylpent-2-enoate (11b): Triethyl phosphonoacetate (**10b**, 2.30 mL, 11.6 mmol) was added to a suspension of NaH (478 mg, 60% oil suspension, 12.0 mmol) in THF (15 mL) under ice-cooling and Ar. The mixture was stirred at room temp. for 1 h and a solution of **9** (727 mg, 2.88 mmol) in THF (21 mL) was added under ice-cooling. The whole mixture was stirred at room temp. for 7 h, and then water (150 mL) was added and extracted with AcOEt (1 × 200 mL, 2 × 100 mL). The organic layer was washed with water (5 × 20 mL) and brine (20 mL), dried with K_2CO_3, and the solvent evaporated in vacuo to afford a pale yellowish oil (1.62 g). This crude product was purified by column chromatography (silica gel 60N, *n*-hexane, *n*-hexane/AcOEt = 6:1 to 1:3, AcOEt) to afford an *E*/*Z* mixture as a colorless oil; yield 967 mg, (quant.; *E*/*Z* = 84:16). IR (ATR): $\tilde{\nu}_{max}$ = 1712 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.26 *Z* (t, *J* = 7.1 Hz, 0.6 H, CH_2CH_3), 1.28 *E* (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.89 *Z* (d, *J* = 1.3 Hz, 0.6 H, Me), 2.22 *E* (d, *J* = 1.3 Hz, 3 H, Me), 2.38–2.42 *E* (m, 2 H, $ArCH_2CH_2$), 2.77–2.81 *E* and *Z* (m, 2.4 H, $ArCH_2CH_2$), 2.87–2.89 *Z* (m, 0.4 H, $ArCH_2CH_2$), 3.39 *E* and *Z* (s, 3.6 H, OMe), 3.56–3.58 *E* and *Z* (m, 2.4 H, OCH_2CH_2O), 3.82–3.85 *E* and *Z* (m, 2.4 H, OCH_2CH_2O), 4.12 *Z* (q, *J* = 7.1 Hz, 0.4 H, CH_2CH_3), 4.15 *E* (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 5.30 *E* (s, 2 H, OCH_2O), 5.31 *Z* (s, 0.4 H, OCH_2O), 5.67–5.70 *E* and *Z* (m, 1.2 H, CH), 6.91 *E* and *Z* (ddd, *J* = 7.2, 7.2, 1.6 Hz, 1.2 H, ArH), 7.11–7.17 *E* and *Z* (m, 3.6 H, 3 × ArH) ppm. MS (FAB): *m*/*z* = 322 $[M]^+$. HRMS (FAB): calcd. for $C_{18}H_{26}O_5$ 322.1780; found 322.1770.

Deprotection of 11b: Aqueous 10% HCl solution (2.80 mL, 8.06 mmol) was added to a solution of ethyl ester **11b** (296 mg,

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0.92 mmol) in EtOH (6.5 mL) at room temp. under Ar and the mixture was heated at reflux for 1.5 h. After being quenched with water (80 mL), the aqueous mixture was extracted with AcOEt (100 mL, 2 × 50 mL) and the combined organic solutions were washed with water (3 × 40 mL) and brine (40 mL), and dried with $MgSO_4$. After evaporation of the solvent, a crude yellowish oil (210 mg) was purified by column chromatography (silica gel 60, *n*-hexane/AcOEt = 6:1) to give *E*-**12b** and *Z*-**12b** as a colorless oil, respectively.

Ethyl (2*E*)-5-(2-Hydroxyphenyl)-3-methylpent-2-enoate (*E*-12b): Yield 157 mg (73%). IR (ATR): $\tilde{\nu}_{max}$ = 3422, 1685 cm^{-1}. ^1H NMR (400 MHz): δ = 1.27 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.21 (d, J = 1.2 Hz, 3 H, Me), 2.42–2.46 (m, 2 H, $ArCH_2CH_2$), 2.77–2.81 (m, 2 H, $ArCH_2CH_2$), 4.16 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 5.72 (m, 1 H, CH), 6.00 (br. s, 1 H, OH), 6.76 (d, J = 7.7 Hz, 1 H, ArH), 6.91 (ddd, J = 7.5, 7.3, 1.1 Hz, 1 H, ArH), 7.04–7.09 (m, 2 H, 2 × ArH) ppm. ^{13}C NMR (100 MHz): δ = 14.2, 19.0, 28.4, 40.9, 59.8, 115.2, 115.6, 120.5, 127.3, 127.5, 130.0, 153.8, 160.2, 167.4 ppm. MS (FAB): m/z = 235 $[M + H]^+$. HRMS (FAB): calcd. for $C_{14}H_{19}O_3$ 235.1334; found 235.1313.

Ethyl (2*Z*)-5-(2-Hydroxyphenyl)-3-methylpent-2-enoate (*Z*-12b): Yield 21.8 mg (10%). IR (ATR): $\tilde{\nu}_{max}$ = 3422, 1686 cm^{-1}. ^1H NMR (400 MHz): δ = 1.29 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.02 (d, J = 1.5 Hz, 3 H, Me), 2.63–2.76 (m, 4 H, CH_2CH_2), 4.22 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 5.77 (q, J = 1.5 Hz, 1 H, CH), 6.82 (ddd, J = 7.5, 7.3, 1.3 Hz, 1 H, ArH), 6.93 (dd, J = 8.1, 1.3 Hz, 1 H, ArH), 7.08 (dd, J = 7.5, 1.6 Hz, 1 H, ArH), 7.15 (ddd, J = 7.9, 7.5, 1.6 Hz, 1 H, ArH), 7.76 (br. s, 1 H, OH) ppm. ^{13}C NMR (100 MHz): δ = 14.2, 26.1, 30.8, 35.4, 60.4, 115.8, 116.5, 119.9, 126.0, 128.1, 129.8, 155.2, 161.6, 167.4 ppm. MS (FAB): m/z = 234 $[M]^+$. HRMS (FAB): calcd. for $C_{14}H_{18}O_3$ 234.1256; found 234.1272.

Typical Procedure for the Intramolecular Oxa-Michael Addition

Ethyl (2-Methylchroman-2-yl)acetate (5b, Table 1, Entry 3): TMG (0.090 mL, 0.72 mmol) was added to a solution of ester *E*-**12b** (56.2 mg, 0.24 mmol) in chloroform (0.28 mL) at room temp. under Ar. After stirring at room temp. for 2 d, the mixture was diluted with chloroform (5 mL) and quenched with 10% HCl (2 mL). The organic layer was washed with water (2 × 2 mL) and brine, and dried with $MgSO_4$. The organic layer was concentrated in vacuo to afford a yellowish oil (57.4 mg). The resulting crude oil was purified by column chromatography (silica gel 60, *n*-hexane/AcOEt = 7:1) to afford a colorless oil; yield 38.2 mg (76%). IR (ATR): $\tilde{\nu}_{max}$ = 1735 cm^{-1}. ^1H NMR (400 MHz): δ = 1.26 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.46 (s, 3 H, Me), 1.88–2.08 (m, 2 H, $ArCH_2CH_2$), 2.62 (d, J = 14.0 Hz, 1 H, CH_2CO_2Et), 2.65 (dd, J = 14.0 Hz, 1 H, CH_2CO_2Et), 2.74–2.82 (m, 2 H, $ArCH_2CH_2$), 4.15 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 6.78 (dd, J = 8.2, 1.2 Hz, 1 H, ArH), 6.83 (ddd, J = 7.5, 7.3, 1.1 Hz, 1 H, ArH), 7.05–7.10 (m, 2 H, 2 × ArH) ppm. ^{13}C NMR (100 MHz): δ = 14.2, 21.9, 25.0, 30.7, 43.9, 60.4, 74.6, 117.3, 120.1, 120.8, 127.3, 129.4, 153.2, 170.4 ppm. MS (FAB): m/z = 234 $[M]^+$. HRMS (FAB): calcd. for $C_{14}H_{18}O_3$ 234.1256; found 234.1267. HPLC: (1) (CHIRALCEL OD-H; λ = 275 nm; eluent: *n*-hexane; flow rate: 1.0 mL/min): t_R for *R* isomer: 24.19, t_R for *S* isomer: 32.25 min; (2) (CHIRALCEL OD-H; λ = 275 nm; eluent: *n*-hexane/*i*PrOH = 95:5; flow rate: 1.0 mL/min): t_R for *R* isomer: 4.83, t_R for *S* isomer: 5.27 min.

Ethyl [(2*S*)-2-Methylchroman-2-yl]acetate [(*S*)-5b, Table 4, Entry 3]: Ethyl ester (*S*)-**5b** was obtained as a colorless oil from *E*-**12b** (44.3 mg, 0.19 mmol) by using chiral guanidine **28** (15.3 mg, 0.038 mmol, 0.20 equiv.); yield 22.6 mg (51%, 28% *ee*); $[\alpha]_D^{24}$ = –2.41 (c = 1.29, $CHCl_3$).

Methyl (2-Methylchroman-2-yl)acetate (5a): Methyl ester **5a** was obtained as a colorless oil from *E*-**12a** (25.9 mg, 0.12 mmol) using TMG (0.003 mL, 0.03 mmol); yield 27.6 mg (quant.). IR (ATR): $\tilde{\nu}_{max}$ = 1736 cm^{-1}. ^1H NMR (400 MHz): δ = 1.45 (s, 3 H, Me), 1.92 (ddd, J = 13.9, 6.4, 6.4 Hz, 1 H, $ArCH_2CH_2$), 2.05 (ddd, J = 13.7, 6.6, 6.6 Hz, 1 H, $ArCH_2CH_2$), 2.64 (d, J = 14.0 Hz, 1 H, CH_2CO_2Me), 2.69 (d, J = 15.0 Hz, 1 H, CH_2CO_2Me), 2.73–2.86 (m, 2 H, $ArCH_2CH_2$), 3.69 (s, 3 H, OMe), 6.78 (d, J = 8.1 Hz, 1 H, ArH), 6.84 (ddd, J = 7.3, 7.3, 1.1 Hz, 1 H, ArH), 7.05–7.11 (m, 2 H, 2 × ArH) ppm. ^{13}C NMR (100 MHz): δ = 22.0, 25.0, 30.7, 43.8, 51.6, 74.6, 117.4, 120.1, 120.8, 127.4, 129.4, 153.2, 170.9 ppm. MS (FAB): m/z = 220 $[M]^+$. HRMS (FAB): calcd. for $C_{13}H_{16}O_3$ 220.1099; found 220.1114. HPLC (CHIRALCEL OD-H; λ = 275 nm; eluent: *n*-hexane/*i*PrOH = 95:5; flow rate: 1.0 mL/min): t_R for *R* isomer: 5.79, t_R for *S* isomer: 7.09 min.

Methyl [(2*R*)-2-Methylchroman-2-yl]acetate [(*R*)-5a, Table 4, Entry 5]: Methyl ester (*R*)-**5a** was obtained as a colorless oil from *Z*-**12a** (24.9 mg, 0.11 mmol) using chiral guanidine **28** (9.0 mg, 0.023 mmol); yield 18.7 mg (75%, 71% *ee*). $[\alpha]_D^{24}$ = +9.52 (c = 0.23, $CHCl_3$).

Determination of Absolute Configuration of Chromane Methyl Ester (+)-5a

(+)-2-(2-Methylchroman-2-yl)ethanol [(+)-36]: A solution of (+)-chromane methyl ester (+)-**5a** (53.9 mg, 0.25 mmol, 71% *ee*) in THF (1.4 mL) was added dropwise to a solution of $LiAlH_4$ (20.8 mg, 0.50 mmol) in THF (0.2 mL) under ice-cooling and Ar. The whole mixture was stirred at 0 °C for 20 min, quenched with methanol (1.0 mL) and then aq. 30% Rochelle salt, and the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic solutions were washed with brine (3 mL), dried with $MgSO_4$, and the solvents evaporated in vacuo. The resulting crude oil (42.7 mg) was purified by column chromatography (silica gel 60, *n*-hexane/AcOEt = 4:1) to afford a colorless oil; yield 40.4 mg (86%, 71% *ee*). $[\alpha]_D^{24}$ = +6.04 (c = 0.58, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 3364 cm^{-1}. ^1H NMR (400 MHz): δ = 1.34 (s, 3 H, Me), 1.75–2.03 (m, 4 H, CH_2CH_2OH), 2.23 (br. s, 1 H, OH), 2.74–2.88 (m, 2 H, $ArCH_2CH_2$), 3.82–3.98 (m, 2 H, $ArCH_2CH_2$), 6.77 (d, J = 8.1 Hz, 1 H, ArH), 6.85 (dd, J = 7.3, 1.1 Hz, 1 H, ArH), 7.06–7.11 (m, 2 H, 2 × ArH) ppm. HPLC (CHIRALCEL OD-H; λ = 275 nm; *n*-hexane/*i*PrOH = 95:5; flow rate: 1.0 mL/min): t_R for major isomer: 9.62, t_R for minor isomer: 18.68 min.

(+)-2-Methyl-2-{2-[(2-nitrophenyl)seleno]ethyl}chromane [(+)-37]: Tributylphosphane (0.08 mL, 0.32 mmol) was added to a solution of (+)-**36** (31.9 mg, 0.17 mmol, 71% *ee*) and 2-nitrophenyl selenocyanate (78.8 mg, 0.35 mmol) in THF (0.4 mL) at room temp. under Ar. The whole was stirred at room temp. for 10 min, quenched with ethanol (10 mL), and the solvents evaporated in vacuo. The resulting crude oil (206 mg) was purified by column chromatography (silica gel 60, *n*-hexane/AcOEt = 20:1) to afford a colorless oil; yield 58.7 mg (94%). $[\alpha]_D^{23}$ = +27.6 (c = 0.49, $CHCl_3$). IR (ATR): $\tilde{\nu}_{max}$ = 1508, 1330 cm^{-1}. ^1H NMR (400 MHz): δ = 1.39 (s, 3 H, Me), 1.77–2.19 (m, 4 H, CH_2CH_2Se), 2.75–2.84 (m, 2 H, $ArCH_2CH_2$), 2.95–3.17 (m, 2 H, $ArCH_2CH_2$), 6.85–6.89 (m, 2 H, 2 × ArH), 7.06–7.08 (m, 1 H, ArH), 7.13–7.17 (m, 1 H, ArH), 7.26 (ddd, J = 7.7, 7.7, 1.3 Hz, 1 H, ArH), 7.34 (ddd, J = 8.1, 7.1, 1.6 Hz, 1 H, ArH), 7.43 (dd, J = 8.2, 1.4 Hz, 1 H, ArH), 8.28 (dd, J = 8.2, 1.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz): δ = 19.8, 21.8, 24.0, 31.3, 38.2, 75.8, 117.2, 120.1, 120.9, 125.2, 126.4, 127.4, 128.7, 129.6, 133.3, 133.6, 146.7, 153.5 ppm. MS (EI): m/z = 377 $[M]^+$. HRMS (EI): calcd. for $C_{18}H_{19}NO_3Se$ 377.0530; found 377.0545.

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(+)-2-Ethenyl-2-methylchromane [(+)-38]:[7b] A solution of (+)-**37** (50.7 mg, 0.13 mmol) and aq. 30% H_2O_2 (0.16 mL, 1.55 mmol) in THF (0.4 mL) was stirred at room temp. for 18 h, diluted with water (5 mL), and extracted with AcOEt (3 × 5 mL). The combined organic solutions were washed with brine (3 mL), dried with $MgSO_4$, and the solvents evaporated in vacuo. The resulting crude oil (158 mg) was purified by column chromatography (silica gel 60, *n*-hexane) to afford a colorless oil; yield 14.6 mg (62%, 70% *ee*). IR (ATR): $\tilde{\nu}_{max}$ = 1582 cm^{-1}. $[\alpha]_D^{22}$ = +65.0 (*c* = 0.65, $CHCl_3$). ^1H NMR (400 MHz): δ = 1.43 (s, 3 H, Me), 1.79–1.95 (m, 2 H, $ArCH_2CH_2$), 2.64–2.76 (m, 2 H, $ArCH_2CH_2$), 5.07 (dd, *J* = 10.8, 1.3 Hz, 1 H, $CHCH_2$), 5.18 (dd, *J* = 17.3, 1.2 Hz, 1 H, $CHCH_2$), 5.85 (dd, *J* = 17.2, 10.8 Hz, 1 H, $CHCH_2$), 6.82 (ddd, *J* = 7.3, 7.3, 1.1 Hz, 1 H, ArH), 6.85 (dd, *J* = 8.2, 0.9 Hz, 1 H, ArH), 7.02 (d, *J* = 7.3 Hz, 1 H, ArH), 7.08–7.12 (m, 1 H, ArH) ppm. HPLC (CHIRALCEL OD-H; λ = 275 nm; *n*-hexane/*i*PrOH = 99.9:0.1; flow rate: 1.0 mL/min): t_R for minor isomer: 5.49, t_R for major isomer: 5.75 min.

Supporting Information (see also the footnote on the first page of this article): Additional experimental procedures and spectroscopic data, including NOE experiments for substrates **12a**, **12c**, and **12d** and chromanes (*S*)-**5a**, (*R*)-**5b**, **5c**, (±)-**36**, and (–)-**36**.

Acknowledgments

This work was partially supported by the Ministry of Education, Culture, Sports, Science and Technology, Japan (Grant-in-Aid for Scientific Research, 19590002).

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[18] The relative energy of the transition state that leads to (*R*)-**5a** was estimated to be 31.5 kcal/mol, which is 5.5 kcal/mol lower than that of (*S*)-**5a**. The theoretical calculation was performed by PM3 using the CAChe MOPAC2002 program. The results of these calculations will be published in the near future.
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Received: January 25, 2008
Published Online: April 11, 2008

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