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Pd(II)-catalyzed asymmetric Wacker-type cyclization for the preparation of 2-vinylchroman derivatives with biphenyl tetraoxazoline ligands

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ABSTRACT

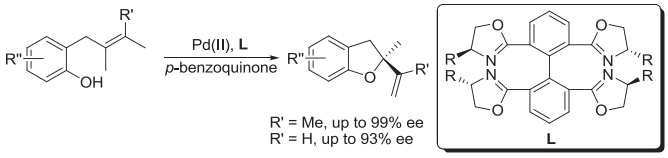
This article describes an efficient method for the preparation of chiral chroman derivatives by the Pd(II)-catalyzed asymmetric Wacker-type cyclization using a chelation-induced axially chiral tetraoxazoline ligand. Under the optimized conditions, up to 80% yield and up to 92% ee were obtained. This is the first example to utilize *o*-trisubstituted 3-butenylphenols as substrates in such transformation.

1. Introduction

In recent years, chiral chroman derivatives have attracted much attention for their broad range of biological activities.[1] For example, siccanin has potent antifungal activity[2] and rhododaurichromanic acid A has effective activity as an anti-HIV agent.[3] Vitamin E is prevalent in nature as an antioxidant,[4] nebivolol is widely used as an anti-hypertensive agent,[5] and conocurvone exhibits anti-HIV activity via the prevention of cytopathic effects and replication of HIV in human T-lymphoblastic cells.[6]

However, compared with extensive synthetic investigation, which have been performed on structurally similar dihydrobenzofuran derivatives,[7] only several syntheses concerning the construction of dihydrobenzopyran (chroman) derivatives have been reported.[8–10] Very few of these reports concern catalytic asymmetric syntheses involving allylic substitution[1,9] and Wacker-type cyclization.[4e,10]

We are interested in the development of Pd(II)-catalyzed Wacker-type oxidative cyclization for the preparation of important natural products and useful pharmaceutical intermediates including oxygen-[7n–q] and nitrogen-containing[11] heterocycles. Recently we developed an efficient catalytic asymmetric Wacker-type cyclization using biphenyl tetraoxazoline ligands **L**. Several chiral dihydrobenzofuran derivatives were prepared in good yields and excellent enantioselectivities (Scheme 1).[7n] In contrast to traditional axially chiral molecules, there is no axial chirality present in these ligands **L** because of their molecular symmetry. Yet, while the biphenyl ligands chelated with one or two metal ions, only one of the two diastereomers was produced. It is noteworthy that this untraditional chelation-induced axially chiral complex system could be applied to diverse range of substrates. Both *o*-trisubstituted and *o*-tetrasubstituted allylphenols could be converted to related products with excellent enantioselectivities. Encouraged by these results, we applied this chelation-induced axially chiral complex system to the asymmetric synthesis of chiral chroman derivatives. There are currently only a few examples involving the catalytic asymmetric synthesis of chiral chroman derivatives via Wacker-type cyclization using *o*-tetrasubstituted 3-butenylphenols,[10a] *o*-disubstituted 3-butenylphenols,[4e] and *o*-allylphenols[10b] as substrates. Herein we report the use of a new type of *o*-trisubstituted 3-butenylphenol substrate for the preparation of 2-vinylchroman derivatives.



Scheme 1. Wacker-type cyclization of *o*-allylphenols.

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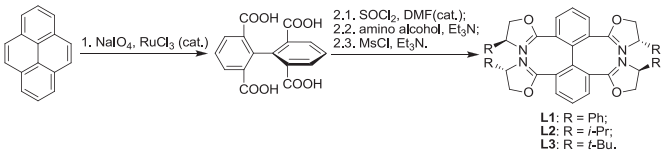
2. Results and discussion

2.1. Synthesis of ligands

Due to their molecular symmetry, we envisaged that the ligands **L** could be synthesized readily following a reported procedure (Scheme 2).[7n] The synthetic sequence involves oxidation of pyrene to 2,2′,6,6′-tetracarboxy-1,1′-biphenyl by $NaIO_4/RuCl_3$[12]; followed by oxazoline ring closure using a known process to afford the ligands **L**.[13] However, this reported method provides unsatisfactory yields of the desired product limiting the wide application of these ligands.



Scheme 2. Synthesis of ligands **L**.

In order to improve the synthesis, we optimized the preparation of ligands **L**. We were unable to obtain the high yields reported for the oxidation of pyrene using the above conditions therefore we studied the effect of catalyst, solvent, and temperature on this oxidation step (Table 1). Hydrated $RuCl_3$ was used in the reaction as the catalyst but it failed to provide an obvious increase in yield compared to when using $RuCl_3$ (entry 2 vs 1). Different mixed solvent systems were also examined (entry 1, 3, 4). $CCl_4/MeCN/H_2O$ increased yields when compared to other mixed solvents (entry 4). Temperature also plays an important role in the oxidation reaction. When the reaction temperature was increased from 40 °C to 60 °C, the yield markedly improved from 52% to 71% (entry 5 vs 4), however continual elevation of the temperature resulted in reduced yield because of purification issues (entry 6). In the second step (one-pot process) we explored the effect of the temperature and catalyst on the reaction to give ligands **L** from 2,2′,6,6′-tetracarboxy-1,1′-biphenyl (Table 2). Throughout our investigation we found that increasing the temperature of step 2.3 (Scheme 2) to reflux greatly reduced the reaction time and improved the yield of the product (entries 1, 2). The addition of a catalytic amount of DMAP to steps 2.2 and 2.3 also improved the reaction yield (entries 5–7 vs 2–4). Finally, we prepared the ligands **L** with different substituents of Ph, *i*-Pr, and *t*-Bu in yields of 63%, 61%, and 57%, respectively.

Table 1
Condition optimization for the oxidization of pyrene[a]

Entry	Catalyst	Solvent	Temp (°C)	Yield[b] (%)
1	$RuCl_3$	$CH_2Cl_2/MeCN/H_2O$	40	25
2	$RuCl_3 \cdot 3H_2O$	$CH_2Cl_2/MeCN/H_2O$	40	27
3	$RuCl_3$	$EtOAc/MeCN/H_2O$	40	23
4	$RuCl_3$	$CCl_4/MeCN/H_2O$	40	52
5	$RuCl_3$	$CCl_4/MeCN/H_2O$	60	71
6	$RuCl_3$	$CCl_4/MeCN/H_2O$	Reflux	61

[a] The reactions were catalyzed by 4 mol % Ru(III) in the presence of 9.3 equiv of $NaIO_4$ using a mixed solvent in the ratio of 3/3/5.
[b] Isolated yield.

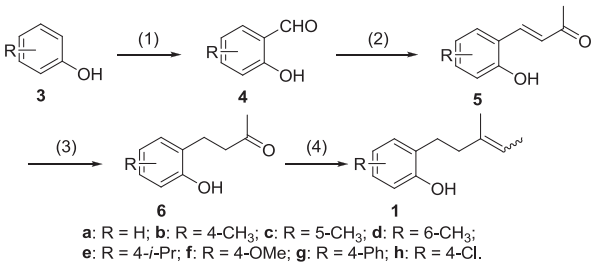
2.2. Synthesis of substrates

With the ligands **L** in hand, we prepared a series of unreported *o*-trisubstituted 3-butenylphenols substrates for the Wacker-type cyclization (Scheme 3). To a solution of phenol **3**, anhydrous $MgCl_2$, and paraformaldehyde in MeCN was added triethylamine and the reaction mixture was heated under reflux conditions for 8 h. Following purification, intermediate **4** was obtained.[14] 1 mol/L NaOH aqueous solution was added slowly to a solution of **4** in acetone at room temperature and the solution was stirred overnight. After treatment with 1 mol/L hydrochloric acid and recrystallization, a colorless solid **5** was obtained. Hydrogenation of **5** with 5% Pd/C in ethyl acetate for 6 h gave a pale yellow oil **6**. To a solution of ethyltriphenylphosphonium bromide in toluene was added *t*-BuOK at 0 °C. After stirring for 2 h at room temperature, a solution of **6** in toluene was slowly added to the solution mentioned above at 0 °C. Following stirring of the mixture overnight at room temperature and subsequent purification, substrate **1** was obtained. This method allowed for the preparation of a diverse range of substrates using readily available phenols bearing different substituents.

Table 2
Condition optimization for the ring closure of oxazoline

Entry	R	Temp[a]	Catalyst[b]	Time (d)	Yield[c] (%)
1	Ph	rt	/	5	15
2	Ph	Reflux	/	1	47
3	*i*-Pr	Reflux	/	1	45
4	*t*-Bu	Reflux	/	1	39
5	Ph	Reflux	DMAP	1	63
6	*i*-Pr	Reflux	DMAP	1	61
7	*t*-Bu	Reflux	DMAP	1	57

[a] The temperature of step 2.3.
[b] DMAP (25 mol %) was added in step 2.2.
[c] Isolated yield.



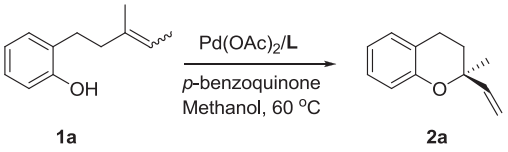
Scheme 3. Reagents and conditions: (1) $(CH_2O)_n$, anhydrous $MgCl_2$, triethylamine, MeCN, reflux; (2) acetone, NaOH aqueous solution, rt; (3) H_2 (1 atm), Pd/C, ethyl acetate, rt; (4) ethyltriphenylphosphonium bromide, *t*-BuOK, toluene, rt.

2.3. Asymmetric catalytic Wacker-type cyclization

In order to test the catalytic activity and enantioselectivity of this chelation-induced axially chiral Pd(II) complex in Wacker-type cyclization using the *o*-trisubstituted 3-butenylphenol substrates, substrate **1a** lacking any substituents on the phenyl group was selected as the model substrate (Table 3). The reaction was catalyzed by 20 mol % Pd(II)–**L** complex generated in situ by mixing $Pd(OAc)_2$ with the tetraoxazoline ligand **L** (1:1 molar ratio), in the presence of 4 equiv of *p*-benzoquinone in methanol at 60 °C for 1 day. As shown in Table 3, the catalytic efficiency was largely dependent on the substituents on the oxazoline rings. The ligand with phenyl-substituted tetraoxazoline **L1** showed remarkably higher catalytic activity and enantioselectivity compared with ligands **L2** and **L3**. No reaction occurred with the *t*-Bu-substituted tetraoxazoline ligand **L3**.

We subsequently carried out optimizations on the Wacker-type cyclization reaction of **1a** with ligand **L1** (Table 4). We discovered that the types of anions and solvents used played an important role in the catalyst system. The Pd(II) complexes formed from $Pd(OAc)_2$ and $Pd(OCOCF_3)_2$ exhibit similar catalytic efficiencies (entries 1, 2). However, the yield decreases sharply with the Pd(II) complexes bearing bromide anions (entry 3). The $Pd(OCOCF_3)_2$/**L** catalytic system (2:1 Pd/**L**) failed to give better results (entry 4). 4 Å

Table 3
Wacker-type cyclization reaction of **1a** with different ligands[a]

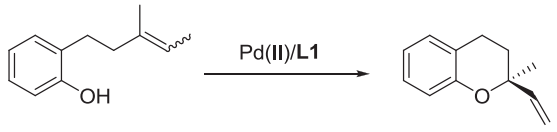


1a **2a**

Entry	Ligand	Time (d)	Yield (%)	ee (%)[b]
1	**L1**	1	67	85
2	**L2**	1	35	32
3	**L3**	1	/	/

[a] The reactions were catalyzed by 20 mol % Pd(II)–**L** complex generated in situ by mixing $Pd(OAc)_2$ with tetraoxazoline **L** (1:1 molar ratio) in the presence of 4 equiv of *p*-benzoquinone in methanol at 60 °C for 1 day. The substrate **1a** was a 1.8:1 mixture of olefin isomers. The absolute configuration of **2a** was confirmed according to specific rotation compared to relative Ref. 9a.
[b] Determined by the HPLC using chiral OD-H column.

Table 4
Condition optimization of the Wacker-type cyclization reaction of **1a** with ligand **L1**[a]



1a **2a**

Entry	Pd(II)	Solvent	Yield (%)	ee (%)[b]
1	$Pd(OAc)_2$	Methanol	67	85
2	$Pd(OCOCF_3)_2$	Methanol	69	87
3	$PdBr_2$	Methanol	30	73
4[c]	$Pd(OCOCF_3)_2$	Methanol	40	83
5[d]	$Pd(OCOCF_3)_2$	Methanol	89	73
6[e]	$Pd(OCOCF_3)_2$	Methanol	85	20
7[f]	$Pd(OCOCF_3)_2$	Methanol	Trace	/
8[g]	$Pd(OCOCF_3)_2$	Methanol	/	/
9	$Pd(OCOCF_3)_2$	Acetone	58	87
10	$Pd(OCOCF_3)_2$	Acetonitrile	61	73
11	$Pd(OCOCF_3)_2$	DMF	32	81
12	$Pd(OCOCF_3)_2$	Ethanol	42	49
13	$Pd(OCOCF_3)_2$	Toluene	28	25
14	$Pd(OCOCF_3)_2$	THF	10	3
15	$Pd(OCOCF_3)_2$	DCM	/	/

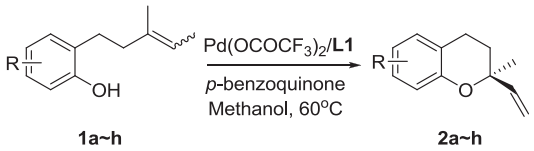
[a] The reactions were catalyzed by 20% Pd(II)–**L1** complex generated in situ by mixing Pd(II) with tetraoxazoline **L1** (1:1 molar ratio) in the presence of 4 equiv of *p*-benzoquinone at 60 °C for 1 day. The substrate **1a** was a 1.8:1 mixture of olefin isomers. The absolute configuration of **2a** was confirmed according to specific rotation compared to relative Ref. 9a.
[b] Determined by the HPLC using chiral OD-H column.
[c] $Pd(OCOCF_3)_2$/**L1**=2/1.
[d] Molecular sieves (4 Å) were added.
[e] The oxidant is O_2.
[f] The temperature of the reaction is 50 °C for 2 day.
[g] The temperature of the reaction is 40 °C for 2 day.

molecular sieves were also used. Interestingly, although the ee value decreased, an improvement in yield was observed (entry 5). When oxygen was applied to the reaction as an oxidant in place of *p*-benzoquinone, significantly lower enantioselectivity was observed (entry 6). The effect of temperature on the reaction was also examined (entries 2, 7, 8). In consideration of the decomposition of the *p*-benzoquinone at high temperatures, the temperature of the reaction was not raised above 60 °C. When the reaction temperature was reduced to 50 °C, the reaction became sluggish and only trace amounts of product were obtained. When the reaction temperature was decreased to 40 °C no reaction occurred.

The effect of solvent on the oxidative cyclization reaction was also examined (Table 4, entries 9–15). Compared with methanol, both acetone and acetonitrile were found to be efficient solvents in consideration of their effect on yield and enantioselectivity (entries 9, 10). Good enantioselectivity was obtained when using DMF, however the yield was low (entry 11). Ethanol, toluene, THF, and DCM were also examined but no ideal results were obtained (entries 12–15).

With the optimized reaction conditions in hand, we applied this methodology to a series of *o*-trisubstituted 3-butenylphenols mentioned above. The corresponding chiral chroman derivatives were obtained as expected (Table 5). As shown in Table 5, good catalytic activity and enantioselectivities were achieved regardless of the steric or electronic properties of the phenyl group on the substrates. For substrate **1a** lacking any substituent groups on the phenyl ring, 87% ee was obtained (entry 1). The pure olefin isomers were obtained using preparative HPLC with chiral OD columns and the configuration of each product was confirmed via two dimensional NMR (NOESY). Compound **1a** was used as a representative molecule to explore the effect of *Z* and *E* olefins on the outcome of the reaction. Up to 92% ee was obtained with the *E* olefin (entry 2). As these kinds of substrates are a mixture of olefin isomers and are difficult to separate, the other compounds (**1b**–**h**) were studied using the *E*/*Z* mixtures in their respective ratios. For the substrates in the order of **1b**, **1c**, and **1d** with methyl substituents at a different position of the phenyl group, the enantioselectivities increased while the yields decreased (entries 4–6). More sterically hindered *i*-Pr substituted substrate **1e** afforded comparable results (entry 7). For substrates with a 4-OMe and 4-Ph group on the phenyl ring (**1f** and **1g**, respectively) only moderate ee values were obtained (entries 8, 9). The substrate **1h** with a 4-Cl substituent also provided good enantioselectivity of 87% ee (entry 10).

Table 5
Substrate scope[a,b]

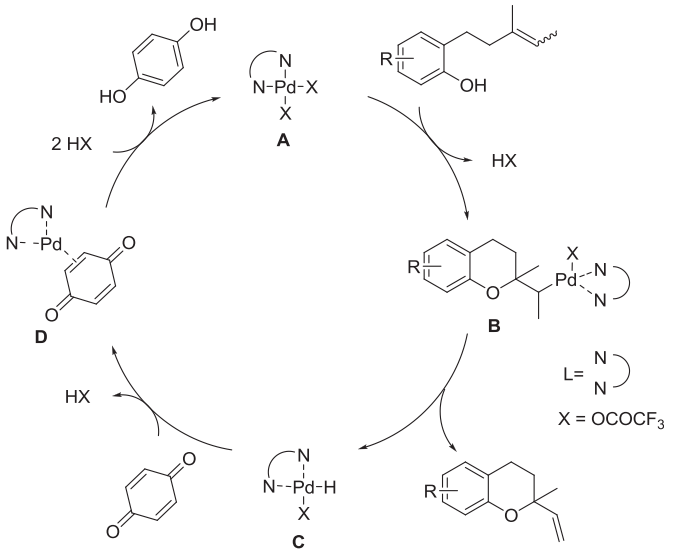


1a~h **2a~h**

Entry	Substrate	The ratio (*Z*/*E*)	Yield (%)	ee (%)
1	**1a** (R=H)	1.8:1	69	87
2	**1a** (R=H)	*E*	68	92
3	**1a** (R=H)	*Z*	70	84
4	**1b** (R=4-Me)	3.3:1	80	75
5	**1c**(R=5-Me)	4.4:1	73	80
6	**1d** (R=6-Me)	3.1:1	72	85
7	**1e** (R=4-*i*-Pr)	2.3:1	75	84
8	**1f** (R=4-OMe)	4.7:1	68	61
9	**1g** (R=4-Ph)	1.7:1	75	70
10	**1h** (R=4-Cl)	1.9:1	65	87

[a] The reactions were catalyzed by 20 mol % $Pd(OCOCF_3)_2$–**L1** complex generated in situ by mixing $Pd(OCOCF_3)_2$ with tetraoxazoline **L1** (1:1 molar ratio) in the presence of 4 equiv of *p*-benzoquinone in methanol at 60 °C for 1 day. The substrates were mixtures of olefin isomers. The absolute configuration of the **2b**–**h** was deduced by similarity to **2a**.
[b] Determined by the HPLC using chiral OD-H column.

A plausible mechanism for the asymmetric reaction is shown in Scheme 4.[7a–g,l] First, $Pd(OCOCF_3)_2$ and the ligand form the Pd(II) catalyst **A**. The substrate then reacts with **A** to form the six-membered Pd(II) intermediate **B**. Subsequently, the product and Pd(II) hydride species **C** were obtained from **B**. In the presence of *p*-benzoquinone, Pd(0) intermediate **D** was obtained. In this step, *p*-benzoquinone promotes reductive elimination from the Pd(II) hydride species **C**,[15] and the coordination of the resulting Pd(0) to *p*-benzoquinone enhances the stability of the Pd(0) species to avoid its precipitation.[15e,g] Finally, the Pd(II) catalyst **A** is regenerated with *p*-benzoquinone as the terminal oxidant.



Scheme 4. Possible mechanism for the Pd(II)-catalyzed Wacker-type cyclization.

3. Conclusion

In summary, we have applied our chelation-induced axially chiral palladium complex system to construct chiral chroman derivatives. The reaction result is dependent on the Pd(II) salt, reaction temperature, solvent, substituent groups, and especially the ligand. Under the optimized conditions, good catalytic activity and enantioselectivities were achieved, regardless of the steric or electronic properties of the phenyl group on the substrates. Both (*E*) and (*Z*) isomers of these kinds of substrates afforded high enantioselectivities, especially for (*E*) isomers, with enantioselectivity of up to 92% ee being obtained.

4. Experimental section

4.1. General

All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under nitrogen. Methanol, ethanol, acetone, MeCN, DMF, THF, toluene, and dichloromethane were dried according to published procedures. The commercially available reagents were used without further purification. TLC was run on 2×5 cm silica plate. Column chromatography was run on silica gel (200–300 mesh). ^{1}H NMR (400 MHz) spectra and ^{13}C NMR (100 MHz) spectra were obtained on a Varian MERCURY plus-400 spectrometer. HRMS was performed on a Micromass LCT TM at the Instrumental Analysis Center of Shanghai Jiao Tong University.

4.2. Procedures and analytical data

*4.2.1. Preparation of the ligands **L**.*

*4.2.1.1. 2,2′,6,6′-Tetra[(4′S)-phenyloxazolin-2′-yl]-1,1′-biphenyl (**L1**).* To a solution of pyrene (3.0 g, 0.015 mol) in MeCN (60 ml), CCl_4 (60 ml), and water (100 ml) was added $NaIO_4$ (30 g, 0.14 mol) and anhydrous $RuCl_3$ (0.12 g, 0.0006 mol). After stirring for 0.5 h, the reaction mixture was heated to 60 °C overnight (~18 h). Solvent was evaporated under reduced pressure and the residue was washed with water (30 ml) and CH_2Cl_2 (30 ml) to give a white solid. Acetone (30 ml) was added and the mixture was filtered. The acetone was evaporated under reduced pressure and the resulting yellow residue was dissolved in MeOH. CH_2Cl_2 was added to precipitate a white solid, which was filtered to give the product 2,2′,6,6′-tetracarboxy-1,1′-biphenyl as a colorless solid (3.5 g, 86% yield).

To a solution of 2,2′,6,6′-tetracarboxy-1,1′-biphenyl (3.5 g, 10.6 mmol) and DMF (2 drops) in CH_2Cl_2 (50 ml) was added another solution of $SOCl_2$ (16 ml, 0.22 mol) in CH_2Cl_2 (30 ml) at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was heated under reflux conditions for 8 h. After removal of the solvent and excess $SOCl_2$, the residue was dissolved in CH_2Cl_2 (40 ml). The mixture was added to a solution of 2-amino-2-phenylethanol (6.5 g, 47.6 mmol), DMAP (305 mg, 2.5 mmol), and triethylamine (8.0 ml, 60.4 mmol) in CH_2Cl_2 (50 ml). After stirring the mixture for 20 h at room temperature, additional triethylamine (17.5 ml, 132.1 mmol) and MsCl (4.1 ml, 52.5 mmol) were added to the mixture at 0 °C, and the reaction mixture was heated under reflux conditions overnight (~18 h). The mixture was diluted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography to give the yellowish ligand **L1** (4.9 g, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J=8.0 Hz, 4H), 7.47 (d, J=8.0 Hz, 2H), 7.27–7.21 (m, 12H), 7.11 (dd, J=1.6, 8.0 Hz, 8H), 5.18 (dd, J=8.4, 10.4 Hz, 4H), 4.40 (dd, J=8.4, 10.4 Hz, 4H), 3.91 (t, J=8.4 Hz, 4H).

*4.2.1.2. 2,2′,6,6′-Tetra[(4′S)-isopropyloxazolin-2′-yl]-1,1′-biphenyl (**L2**).* Compound **L2** was prepared from 2,2′,6,6′-tetracarboxy-1,1′-biphenyl using a similar procedure to that of **L1** (3.9 g, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J=8.0 Hz, 4H), 7.34 (d, J=7.6 Hz, 2H), 3.98 (t, J=7.6 Hz, 4H), 3.76 (dd, J=8.0, 14.8 Hz, 4H), 3.70 (dd, J=8.0, 15.6 Hz, 4H), 1.52–1.60 (m, 4H), 0.76 (d, J=6.8 Hz, 12H), 0.73 (d, J=6.4 Hz, 12H).

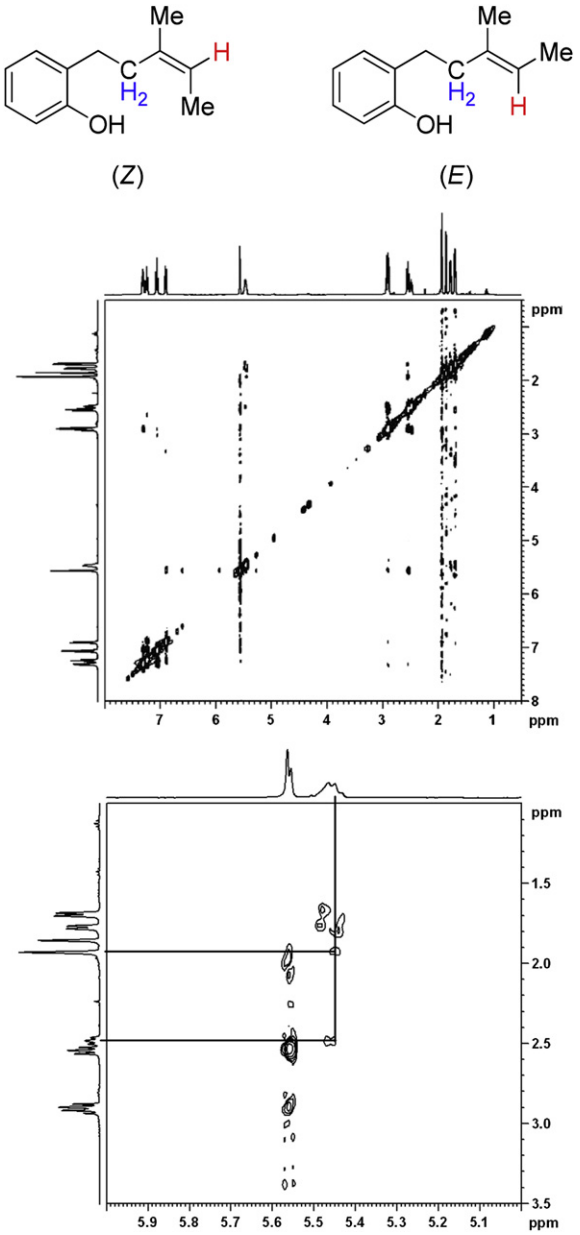
*4.2.1.3. 2,2′,6,6′-Tetra[(4′S)-tert-butyloxazolin-2′-yl]-1,1′-biphenyl (**L3**).* Compound **L3** was prepared from 2,2′,6,6′-tetracarboxy-1,1′-biphenyl using a similar procedure to that of **L1** (4.0 g, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J=8.0 Hz, 4H), 7.31 (d, J=8.0 Hz, 2H), 3.92 (dd, J=12.0, 13.2 Hz, 4H), 3.74–3.68 (m, 8H), 0.67 (s, 36H).

*4.2.2. Preparation of the substrates **1**.*

*4.2.2.1. 2-[(3-Methyl)-3-pentenyl]phenol (**1a**).* NaOH (1 mol/L) aqueous solution (60 ml, 60 mmol) was added slowly to a solution of **4a** (6 ml, 57.5 mmol) in acetone (40 ml) and the mixture was stirred at room temperature for 14 h. 1 mol/L hydrochloric acid (80 ml, 80 mmol) was added and the solution was filtered. The filtration residue was recrystallized from petroleum ether/ethyl acetate to give the white intermediate **5a** (7.4 g, 79% yield). Hydrogenation of **5a** with a hydrogen balloon using 5% Pd/C (1.4 g) in ethyl acetate (80 ml) for 6 h followed by filtration and purification by flash column chromatography, gave a pale yellow oil **6a** (7.3 g, 97% yield). To a solution of ethyltriphenylphosphonium bromide (37.4 g, 0.1 mol) in toluene (100 ml), *t*-BuOK (11.3 g, 0.1 mol) was added at 0 °C. After stirring for 2 h at room temperature, a solution of **6a** in toluene (20 ml) was slowly added to the red solution mentioned above at 0 °C. The mixture was stirred overnight at room temperature, and quenched by the addition of saturated NH_4Cl solution. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography to give the substrate **1a**[8c] (5.3 g, 68% yield). ^{1}H NMR (data for 1.8:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.93 and 1.85; 400 MHz, $CDCl_3$): δ 7.36–7.19 (m, 2H), 7.36–7.19 (m, 2H), 7.08–7.02 (m, 1H), 7.08–7.02 (m, 1H), 6.90 (d, J=8.1 Hz, 1H), 6.90 (d, J=8.1 Hz, 1H), 5.57 (m, 1H), 5.55 (m, 1H), 5.52–5.43 (m, 1H), 5.52–5.43 (m, 1H), 2.95–2.88 (m, 2H), 2.95–2.88 (m, 2H), 2.59–2.55 (m, 2H), 2.55–2.51 (m, 2H), 1.94–1.92 (m, 3H), 1.86–1.84 (m, 3H), 1.73–1.69 (m, 3H), 1.68–1.63 (m, 3H).

We confirmed the configuration of each isomer of **1a** (ratio of 1.8:1) according to two dimensional NMR (NOESY) (Scheme 5). From Scheme 5, we can find that the minor isomer shows H–H interactions between the alkenyl H (δ=5.52–5.43) and the allyl H

(δ=2.55–2.51), while the major isomer lacks these interactions. The minor isomer is therefore *E* configuration and the major one is *Z* configuration.



Scheme 5. The two dimensional NMR (NOESY) spectra of **1a** (*Z*/*E*=1.8:1).

*4.2.2.2. 4-Methyl-2-[(3-methyl)-3-pentenyl]phenol (**1b**).* To a solution of phenol **3b** (2.6 g, 24.0 mmol), anhydrous $MgCl_2$ (3.5 g, 36.8 mmol), and paraformaldehyde (5.0 g, 166.5 mmol) in MeCN (100 ml) was added triethylamine (12.8 ml, 91.8 mmol). The reaction mixture was heated under reflux conditions for 8 h. Hydrochloric acid (5%) was added and the mixture extracted with ether and dried over Na_2SO_4. Solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography to give the intermediate **4b** (2.8 g, 86% yield). 1 mol/L NaOH aqueous solution (23 ml, 23 mmol) was added slowly to a solution of **4b** (2.8 g, 20.6 mmol) in acetone (15 ml) and the mixture was stirred at room temperature for 14 h. Hydrochloric acid (1 mol/L, 30 ml, 30 mmol) was added and a light yellow deposition was obtained. The solution was filtered and the filtration residue **5b** was dissolved in ethyl acetate. Hydrogenation using 5% Pd/C (500 mg) for 6 h and filtration by kieselguhr gave a pale yellow oil **6b**. To a solution of ethyltriphenylphosphonium bromide (14.5 g, 38.9 mmol) in toluene (60 ml), *t*-BuOK (4.4 g, 38.9 mmol) was added at 0 °C. The mixture was stirred for 2 h at room temperature and a solution of **6b** in toluene (10 ml) was slowly added to the blood red solution mentioned above at 0 °C. The mixture was stirred overnight at room temperature, then quenched by the addition of saturated NH_4Cl solution. The mixture was extracted with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography to give the substrate **1b** (1.8 g, 45% yield). ^{1}H NMR (data for 3.3:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.76 and 1.70; 400 MHz, $CDCl_3$): δ 7.00–6.86 (m, 2H), 7.00–6.86 (m, 2H), 6.70–6.65 (m, 1H), 6.70–6.65 (m, 1H), 5.34–5.25 (m, 1H), 5.34–5.25 (m, 1H), 5.00–4.59 (m, 1H), 5.00–4.59 (m, 1H), 2.71–2.56 (m, 2H), 2.71–2.56 (m, 2H), 2.39–2.24 (m, 2H), 2.39–2.24 (m, 2H), 2.28 (s, 3H), 2.28 (s, 3H), 1.80–1.74 (m, 3H), 1.72–1.68 (m, 3H), 1.62–1.51 (m, 3H), 1.62–1.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 136.1, 131.1, 131.0, 130.2, 127.8, 127.7, 127.6, 120.2, 119.2, 115.4, 115.2, 40.2, 32.2, 29.4, 28.9, 23.9, 20.8, 16.2, 13.7, 13.4; HRMS (ESI) calcd for $C_{13}H_{17}O$ $[M-H]^-$: 189.1279, found 189.1274.

*4.2.2.3. 5-Methyl-2-[(3-methyl)-3-pentenyl]phenol (**1c**).* Compound **1c** was prepared from **3c** by a similar procedure with **1b** (1.60 g, overall 35% yield). ^{1}H NMR (data for 4.4:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.58 and 1.51; 400 MHz, $CDCl_3$): δ 7.02–6.94 (m, 1H), 7.02–6.94 (m, 1H), 6.71–6.63 (m, 1H), 6.71–6.63 (m, 1H), 6.59 (s, 1H), 6.59 (s, 1H), 5.31–5.22 (m, 1H), 5.31–5.22 (m, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 2.69–2.61 (m, 2H), 2.69–2.61 (m, 2H), 2.34–2.21 (m, 2H), 2.34–2.21 (m, 2H), 2.28 (s, 3H), 2.28 (s, 3H), 1.68–1.62 (m, 3H), 1.60–1.56 (m, 3H), 1.53–1.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 137.4, 136.1, 130.3, 130.1, 125.5, 121.7, 120.1, 119.2, 116.2, 40.1, 32.2, 29.0, 28.5, 23.8, 21.2, 16.7, 13.6, 13.4; HRMS (ESI) calcd for $C_{13}H_{17}O$ $[M-H]^-$: 189.1279, found 189.1267.

*4.2.2.4. 6-Methyl-2-[(3-methyl)-3-pentenyl]phenol (**1d**).* Compound **1d** was prepared from **3d** by a similar procedure with **1b** (640 mg, overall 14% yield). ^{1}H NMR (data for 3.1:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.62 and 1.54; 400 MHz, $CDCl_3$): δ 7.03–6.97 (m, 2H), 7.03–6.97 (m, 2H), 6.83–6.77 (m, 1H), 6.83–6.77 (m, 1H), 5.34–5.25 (m, 1H), 5.34–5.25 (m, 1H), 4.78–4.62 (m, 1H), 4.78–4.62 (m, 1H), 2.75–2.59 (m, 2H), 2.75–2.59 (m, 2H), 2.39–2.21 (m, 2H), 2.39–2.21 (m, 2H), 2.27 (s, 3H), 2.27 (s, 3H), 1.78–1.63 (m, 3H), 1.78–1.63 (m, 3H), 1.63–1.52 (m, 3H), 1.63–1.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 152.3, 136.3, 136.2, 129.1, 129.0, 128.5, 128.4, 128.2, 123.8, 123.7, 120.9, 120.8, 120.5, 119.4, 40.3, 32.4, 29.7, 29.2, 24.1, 16.3, 16.3, 13.9, 13.6; HRMS (ESI) calcd for $C_{13}H_{17}O$ $[M-H]^-$: 189.1279, found 189.1274.

*4.2.2.5. 4-Isopropyl-2-[(3-methyl)-3-pentenyl]phenol (**1e**).* Compound **1e** was prepared from **3e** by a similar procedure with **1b** (1.6 g, overall 31% yield). ^{1}H NMR (data for 2.3:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.74 and 1.68; 400 MHz, $CDCl_3$): δ 6.97–6.91 (m, 2H), 6.97–6.91 (m, 2H), 6.71–6.67 (m, 1H), 6.71–6.67 (m, 1H), 5.31–5.22 (m, 1H), 5.31–5.22 (m, 1H), 4.65–4.53 (m, 1H), 4.65–4.53 (m, 1H), 2.89–2.77 (m, 1H), 2.89–2.77 (m, 1H), 2.71–2.56 (m, 2H), 2.71–2.56 (m, 2H), 2.36–2.34 (m, 2H), 2.36–2.34 (m, 2H), 1.76–1.73 (m, 3H), 1.69–1.67 (m, 3H), 1.61–1.57 (m, 3H), 1.52–1.47 (m, 3H), 1.24–1.20 (m, 6H), 1.24–1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 141.5, 136.0, 128.5, 128.4, 124.9, 120.2, 119.2, 115.3, 115.2, 40.1, 33.6, 32.1, 29.5, 28.9, 24.5, 23.8, 16.2, 13.6, 13.4; HRMS (ESI) calcd for $C_{15}H_{21}O$ $[M-H]^-$: 217.1592, found 217.1581.

*4.2.2.6. 4-Methoxy-2-[(3-methyl)-3-pentenyl]phenol (**1f**).* Compound **1f** was prepared from **3f** by a similar procedure with **1b** (1.2 g, overall 24% yield). ^{1}H NMR (data for 4.7:1 mixture of olefin isomers based on the relative integration of peaks at δ 2.32 and 2.26; 400 MHz, $CDCl_3$): δ 6.72–6.67 (m, 2H), 6.72–6.67 (m, 2H), 6.65–6.60 (m, 1H), 6.65–6.60 (m, 1H), 5.31–5.23 (m, 1H), 5.31–5.23 (m, 1H), 4.51–4.44 (m, 1H), 4.51–4.44 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.69–2.62 (m, 2H), 2.69–2.62 (m, 2H), 2.33 (t, J=8.1 Hz, 2H), 2.26 (t, J=8.2 Hz, 2H), 1.74–1.72 (m, 3H), 1.68–1.66 (m, 3H), 1.60–1.56 (m, 3H), 1.52–1.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 148.0, 147.9, 136.0, 135.9, 130.2, 120.3, 119.2, 116.3, 116.2, 116.1, 112.0, 56.1, 40.0, 32.0, 29.5, 29.1, 23.8, 16.2, 13.7, 13.4. HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $[M-H]^-$: 206.1307, found 206.1233.

*4.2.2.7. 4-Phenyl-2-[(3-methyl)-3-pentenyl]phenol (**1g**).* Compound **1g** was prepared from **3g** by a similar procedure with **1b** (1.1 g, overall 18% yield). ^{1}H NMR (data for 1.7:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.76 and 1.70; 400 MHz, $CDCl_3$): δ 7.57–7.27 (m, 7H), 7.57–7.27 (m, 7H), 6.83 (d, J=7.6 Hz, 1H), 6.83 (d, J=7.6 Hz, 1H), 5.34–5.25 (m, 1H), 5.34–5.25 (m, 1H), 5.00–4.80 (m, 1H), 5.00–4.80 (m, 1H), 2.80–2.64 (m, 2H), 2.80–2.64 (m, 2H), 2.41–2.29 (m, 2H), 2.41–2.29 (m, 2H), 1.78–1.75 (m, 3H), 1.71–1.68 (m, 3H), 1.62–1.58 (m, 3H), 1.54–1.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 153.4, 141.3, 135.9, 134.2, 129.4, 129.3, 128.9, 127.0, 126.8, 126.1, 126.0, 125.9, 120.4, 119.4, 115.9, 115.8, 40.1, 32.1, 29.5, 29.0, 23.9, 16.2, 13.7, 13.5; HRMS (ESI) calcd for $C_{18}H_{19}O$ $[M-H]^-$: 251.1436, found 251.1434.

*4.2.2.8. 4-Chloro-2-[(3-methyl)-3-pentenyl]phenol (**1h**).* Compound **1h** was prepared from **3h** by a similar procedure with **1b** (450 mg, overall 9% yield). ^{1}H NMR (data for 1.9:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.72 and 1.66; 400 MHz, $CDCl_3$): δ 7.10–6.99 (m, 2H), 7.10–6.99 (m, 2H), 6.68 (d, J=8.4 Hz, 1H), 6.68 (d, J=8.4 Hz, 1H), 5.31–5.22 (m, 1H), 5.31–5.22 (m, 1H), 2.68–2.53 (m, 2H), 2.68–2.53 (m, 2H), 2.34–2.21 (m, 2H), 2.34–2.21 (m, 2H), 1.74–1.71 (m, 3H), 1.67–1.65 (m, 3H), 1.60–1.56 (m, 3H), 1.51–1.47 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 152.4, 135.6, 130.8, 130.2, 130.1, 127.2, 126.9, 125.5, 120.6, 119.6, 116.7, 39.7, 31.7, 29.2, 28.6, 23.8, 16.1, 13.6, 13.4; HRMS (ESI) calcd for $C_{12}H_{14}ClO$ $[M-H]^-$: 209.0733, found 209.0718.

4.2.3. General procedure for Pd(II)-catalyzed asymmetric oxidative cyclization. In the nitrogen atmosphere, 20 mol % of the catalyst $Pd(OCOCF_3)_2$ and 20 mol % of ligand **L1** were stirred in 2 ml MeOH to coordinate for 0.5 h at room temperature. Then 4 equiv of *p*-benzoquinone was added to the mixture. At last, the substrate **1** dissolved in 4 ml MeOH was added to the solution mentioned above for 24 h at 60 °C. After removal of the solvent, the residue was purified by flash column chromatography to afford the products **2**.

*4.2.3.1. 2-Methyl-2-vinylchroman (**2a**).*[8c,9a] Colorless oil. $[\alpha]_D^{20}$ −19 (*c* 0.55, $CHCl_3$, ee=83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (t, J=7.5 Hz, 1H), 7.02 (d, J=7.5 Hz, 1H), 6.86 (d, J=7.5 Hz, 1H), 6.82 (m, 1H), 5.85 (dd, J=10.5, 17.0 Hz, 1H), 5.18 (dd, J=1.0, 17.5 Hz, 1H), 5.06 (dd, J=1.0, 11.0 Hz, 1H), 2.78–2.64 (m, 2H), 1.96–1.79 (m, 2H), 1.43 (s, 3H).

*4.2.3.2. 2,6-Dimethyl-2-vinylchroman (**2b**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, J=7.5 Hz, 1H), 6.84 (s, 1H), 6.76 (d, J=8.4 Hz, 1H), 5.85 (dd, J=10.4, 17.2 Hz, 1H), 5.18 (dd, J=1.2, 17.2 Hz, 1H), 5.06 (dd, J=1.2, 10.8 Hz, 1H), 2.74–2.59 (m, 2H), 2.25 (s, 3H), 1.95–1.77 (m, 2H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 141.6, 129.9, 129.1, 128.2, 121.2, 116.8, 114.1, 76.7, 32.0, 27.4, 22.7, 20.7; HRMS (EI) calcd for $C_{13}H_{16}O$ $[M]^+$: 188.1201, found 188.1200.

*4.2.3.3. 2,7-Dimethyl-2-vinylchroman (**2c**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (d, J=8.0 Hz, 1H), 6.70 (s, 1H), 6.65 (d, J=7.6 Hz, 1H), 5.86 (dd, J=10.8, 17.6 Hz, 1H), 5.18 (dd, J=1.2, 17.2 Hz, 1H), 5.07 (dd, J=1.2, 10.8 Hz, 1H), 2.68–2.64 (m, 2H), 2.28 (s, 3H), 1.94–1.77 (m, 2H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 141.6, 137.4, 129.3, 120.9, 118.5, 117.4, 114.0, 76.8, 32.0, 27.3, 22.4, 21.3; HRMS (EI) calcd for $C_{13}H_{16}O$ $[M]^+$: 188.1201, found 188.1199.

*4.2.3.4. 2,8-Dimethyl-2-vinylchroman (**2d**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (dd, J=2.0 Hz, 8.0 Hz, 1H), 6.88 (s, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.87 (dd, J=10.8, 17.2 Hz, 1H), 5.19 (dd, J=1.2, 16.8 Hz, 1H), 5.07 (dd, J=1.2, 10.8 Hz, 1H), 2.86–2.77 (m, 1H), 2.76–2.62 (m, 2H), 1.96–1.79 (m, 2H), 1.42 (s, 3H), 1.21 (d, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 141.9, 128.6, 127.1, 126.0, 120.9, 119.4, 113.6, 76.9, 32.1, 27.7, 23.0, 16.5; HRMS (EI) calcd for $C_{13}H_{16}O$ $[M]^+$: 188.1201, found 188.1204.

*4.2.3.5. 6-Isopropyl-2-methyl-2-vinylchroman (**2e**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (dd, J=2.0, 8.0 Hz, 1H), 6.88 (s, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.87 (dd, J=10.8, 17.2 Hz, 1H), 5.19 (dd, J=1.2, 16.8 Hz, 1H), 5.07 (dd, J=1.2, 10.8 Hz, 1H), 2.86–2.77 (m, 1H), 2.76–2.62 (m, 2H), 1.96–1.79 (m, 2H), 1.42 (s, 3H), 1.21 (d, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 141.8, 140.3, 127.2, 125.5, 121.0, 116.7, 114.0, 76.7, 33.4, 32.1, 27.3, 24.5, 22.9; HRMS (EI) calcd for $C_{15}H_{20}O$ $[M]^+$: 216.1514, found 216.1513.

*4.2.3.6. 6-Methoxy-2-methyl-2-vinylchroman (**2f**).*[1] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, J=8.9 Hz, 1H), 6.71–6.67 (m, 1H), 6.58 (d, J=6.4 Hz, 1H), 5.85 (dd, J=11.2, 17.6 Hz, 1H), 5.17 (dd, J=1.6, 17.6 Hz, 1H), 5.06 (dd, J=1.2, 10.4 Hz, 1H), 3.74 (s, 3H), 2.71–2.66 (m, 2H), 1.93–1.77 (m, 2H), 1.42 (s, 3H); HRMS (EI) calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1150, found 204.1148.

*4.2.3.7. 6-Phenyl-2-methyl-2-vinylchroman (**2g**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56–7.25 (m, 7H), 6.93 (d, J=8.8 Hz, 1H), 5.88 (dd, J=10.8, 18.0 Hz, 1H), 5.21 (dd, J=1.2, 17.2 Hz, 1H), 5.10 (dd, J=1.2, 10.4 Hz, 1H), 2.79–2.72 (m, 2H), 2.00–1.81 (m, 2H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 141.4, 141.3, 128.8, 128.2, 126.9, 126.7, 126.3, 121.7, 117.3, 114.2, 77.2, 32.0, 27.4, 22.9; HRMS (EI) calcd for $C_{18}H_{18}O$ $[M]^+$: 250.1358, found 250.1352.

*4.2.3.8. 6-Chloro-2-methyl-2-vinylchroman (**2h**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07–6.99 (m, 2H), 6.79 (d, J=8.8 Hz, 1H), 5.82 (dd, J=10.8, 17.2 Hz, 1H), 5.14 (dd, J=1.2, 17.2 Hz, 1H), 5.07 (dd, J=1.2, 10.4 Hz, 1H), 2.70–2.63 (m, 2H), 1.95–1.75 (m, 2H), 1.42(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 141.0, 129.1, 127.5, 124.6, 123.2, 118.3, 113.4, 31.5, 27.4, 22.7; HRMS (EI) calcd for $C_{12}H_{13}ClO$ $[M]^+$: 208.0655, found 208.0656.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.077.

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