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Synthesis of Chiral Chromans by the Pd-Catalyzed Asymmetric Allylic Alkylation (AAA): Scope, Mechanism, and Applications

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Abstract: The Pd-catalyzed asymmetric allylic alkylation (AAA) of phenol allyl carbonates serves as an efficient strategy to construct the allylic C−O bond allowing access to chiral chromans in up to 98% ee. The effect of pH and the influence of olefin geometry, as well as substitution pattern on the ee and the absolute configuration of the chiral chromans were explored in detail. These observations suggest a mechanism involving the cyclization of the more reactive π-allyl palladium diastereomeric intermediate as the enantiodiscriminating step (Curtin−Hammett conditions). This methodology led to the enantioselective synthesis of the vitamin E core, the first enantioselective total synthesis of (+)-clusifoliol and (−)-siccanin, and the synthesis of an advanced intermediate toward (+)-rhododaurichromanic acid A.

Introduction

Chiral chromans or closely related chromens are a class of compounds possessing significant biological properties (Figure 1). For example, vitamin E (**1**)[1] and its analogues trolox (**2**)[2] and MDL-73404 (**3**)[3] are important lipophilic antioxidants. MDL-73404 (**3**) also exhibits cardioprotective effects during a myocardial infarction. Conocurvone (**4**), a naphthoquinone trimer isolated from a *Conospermum* sp. in 1993,[4] prevents the cytopathic effects and replication of HIV in human T-lymphoblastic cells (CEM-SS). Centchroman (**5**), an estrogen antagonist, is an antifertility agent.[5] Clusifoliol (**6**) was a component isolated from *Peperomia* species which have been used to treat malignant tumors.[6] Daurichromenic acid (**7**) and rhododaurichromanic acid A (**8**) have also shown potent anti-HIV activity.[7] Nebivolol (**9**) is an anti-hypertensive agent.[8] Siccanin (**10**) is a potent antifungal agent and used clinically in Asia.[9] Prior to our work, there were no asymmetric total syntheses of centchroman (**5**), clusifoliol (**6**), rhododaurichromenic acid (**7**), rhododaurichromanic acid A (**8**), and siccanin (**10**). Therefore, it is important to develop general methodologies[10] to construct chiral chromans or chromens, which could potentially lead to natural products of this general type, and/or their analogues with more desirable pharmacological features.

The Pd-catalyzed asymmetric allylic alkylations (AAA) are powerful tools in organic synthesis.[11] Our initial studies of the Pd-catalyzed AAA of phenols in an *intermolecular* fashion led to the enantioselective formation of the allylic C−O bond, which was followed by cyclization to provide chiral chromans (Scheme 1).[12] However, this strategy has two aspects yet to improve. First, this reaction generally gave a small amount of regioisomers, resulting from the competitive attack at the primary allylic terminus. Furthermore, the ee of this reaction is generally lower than 90%. To address these issues, Pd-catalyzed *intramolecular* asymmetric allylic alkylation of phenol allyl carbonates could potentially afford chiral chromans in one step (Scheme 2)

(1) *Vitamin E*; Machlin, L. J., Ed.; Marcel Dekker: New York, 1980.
(2) Terao, K.; Niki, E. *J. Free Rad. Biol. Med.* **1986**, *2*, 193−201.
(3) Grisar, J. M.; Petty, M. A.; Bolkenius, F. N.; Dow, J.; Wagner, J.; Wagner, E. R.; Haegele, K. D.; Jong, W. D. *J. Med. Chem.* **1991**, *34*, 257−260.
(4) (a) Decosterd, L. A.; Parsons, I. C.; Gustafson, K. R.; Cardellina II, J. H.; McMahon, J. B.; Cragg, G. M.; Murata, Y.; Pannell, L. K.; Steiner, J. R.; Clardy, J.; Boyd, M. R. *J. Am. Chem.. Soc.* **1993**, *115*, 6673−6679. (b) Laatsch, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 422−424.
(5) Sankaran, M. S.; Prasad, M. R. N. *Contraception* **1974**, *9*, 279−289.
(6) (a) Seeram, N. P.; Jacobs, H.; McLean, S.; Reynolds, W. F. *Phytochemistry* **1998**, *49*, 1389−1391. (b) Tanaka, T.; Asai, F.; Iinuma, M. *Phytochemistry* **1998**, *49*, 229−232.
(7) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559−1563.
(8) (a) De Cree, J.; Geukens, H.; Leempoels, J.; Verhaegen, H. *Drug Dev. Res.* **1986**, *8*, 109−117. (b) Van de Water, A.; Janssen, W.; Van Nueten, J.; Xhonneux, R.; De Cree, J.; Verhaegen, H.; Reneman, R. S.; Janssen, P. A. J. *J. Cardiovasc. Pharmacol.* **1988**, *11*, 552−563.
(9) Isabashi, K. *J. Antibiot. Ser. A* **1962**, *15*, 161−167.
(10) For approaches leading to chiral chromans or chromenes, see: (a) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron*, **2000**, *56*, 6339−6344. (b) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799. (c) Cohen, N.; Lopresti, R. J.; Saucy, G. *J. Am. Chem. Soc.* **1979**, *101*, 6710−6716. (d) Mizuguchi, E.; Suzuki, T.; Achiwa, K. *Synlett* **1994**, 929−930. (e) Mizuguchi, E.; Suzuki, T.; Achiwa, K. *Synlett* **1996**, 743−744. (f) Mizuguchi, E.; Achiwa, K. *Synlett* **1995**, 1255−1256. (g) Tietze, L. F.; Gorlitzer, J. *Synthesis* **1997**, 877−878. (h) Solladie, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097−6098. (i) Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527−532. (j) Gassman, P. G.; Amick, D. R. *J. Am. Chem. Soc.* **1978**, *100*, 7611−7619. (k) Inoue, S.; Ikeda, H.; Sato, S.; Horie, K.; Ota, T.; Miyamoto, O.; Sato, K. *J. Org. Chem.* **1987**, *52*, 5495−5497. (l) Hubscher, v. J.; Barner, R. *Helv. Chim. Acta* **1990**, *73*, 1068−1086. (m) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *101*, 6071−6072. (n) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063−5064.
(11) (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943. (b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1−14. (c) Helmchen, G. Pfaltz, A. *Acc. Chem. Res.***2000**, *33*, 336−345 (d) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. "Comprehensive Asymmetric Catalysis", Vol. II, pp 833−884, Springer-Verlag: Berlin Heidelberg, 1999.
(12) Trost, B. M.; Toste, D. F. *J. Am. Chem. Soc.* **1998**, *120*, 9074−9075.

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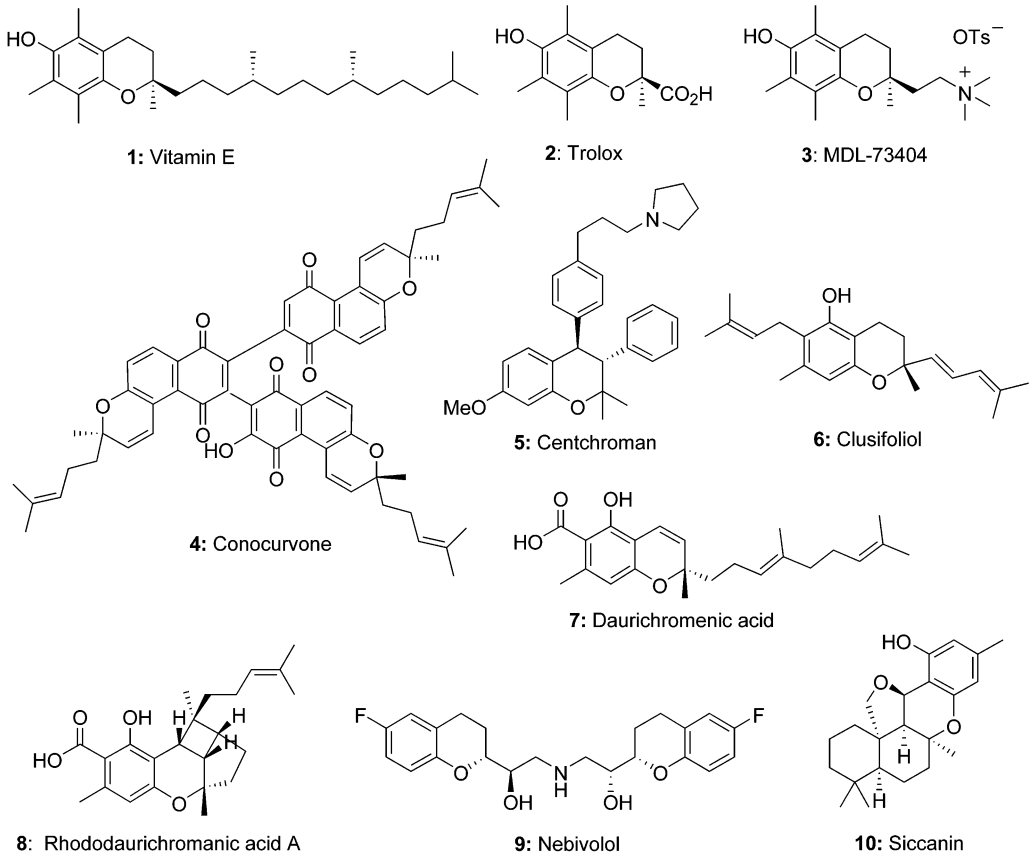
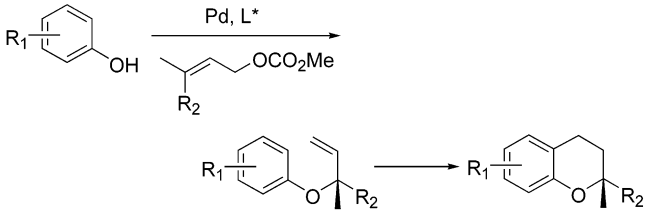


Figure 1. Representative chiral chromans and chromens.

Scheme 1. Pd-Catalyzed Intermolecular Allylic Alkylation of Phenols To Access Chiral Chromans

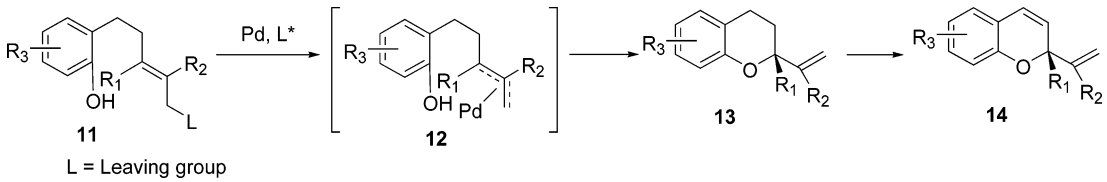


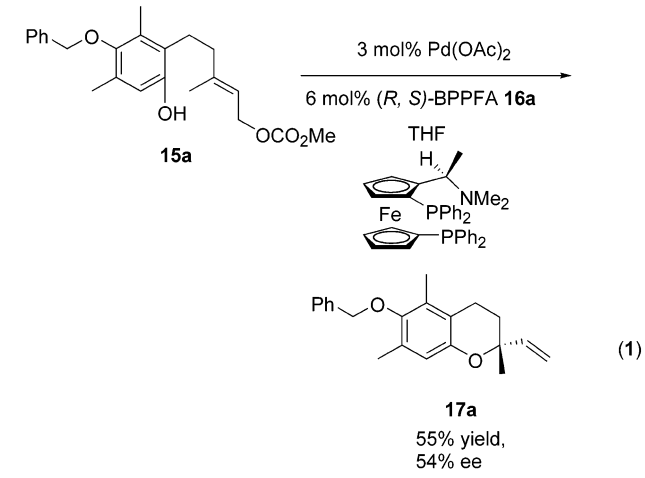
without the complication of regioselectivity. In this reaction, a chiral Pd complex catalyzes the ionization of the leaving group such as carbonate to form π-allyl palladium intermediate **12**, which could be attacked by phenol intramolecularly to form chiral chroman **13**. A subsequent oxidation of chroman **13** will lead to chiral chromen **14**.

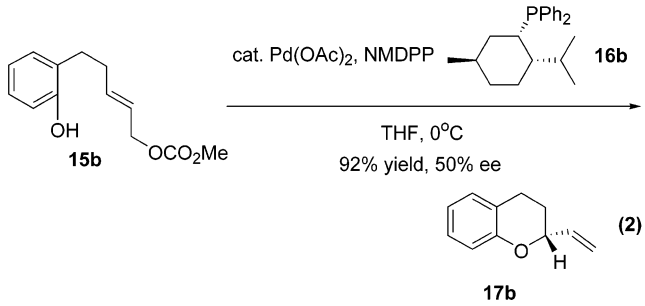
Prior to our investigation, two groups have examined this approach to chiral vinylchromans. After screening a large variety of chiral phosphine ligands and reaction conditions, Achiwa and co-workers showed that optically active vinylchromans such as **17a** could be obtained with moderate enantiomeric excess (54% ee) using BFFPA ligand (eq 1).[13] Furthermore, they proposed that the asymmetric induction derives from the chiral recognition of the enantiotopic faces of the substrate during the ionization event. Sinou's group also screened a considerable number of chiral phosphine ligands for this transformation. They obtained up to 50% ee when they employed a chiral monophosphine ligand (NMDPP) (eq 2).[14] It should be noted that only 7% ee of the desired chroman *ent*-**17b** was obtained employing the Trost ligand **16c** and substrate **15b** (eq 3). Different from the Achiwa's proposal, the Sinou group presumed that the nucleophilic attack on the π-allyl palladium intermediates was the enantiodiscriminating step.

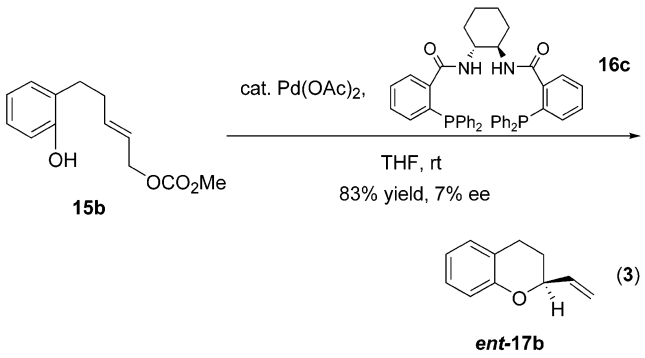
Despite the low ee of the Pd-catalyzed AAA reaction employing the Trost ligand **16c** reported by Sinou's group, our group started investigating this reaction in the context of the asymmetric synthesis of the core of vitamin E (**1**). We were pleased to discover that trans-allyl carbonate **15a** could undergo a Pd-catalyzed intramolecular cyclization to generate chiral vinyl chroman **17a** in 96% yield and 84% ee (eq 4).[15] It should be noted that a tetrasubstituted stereogenic center is constructed in this reaction. Since then, we have explored the scope and studied the factors that dictate the enantioselectivity of this reaction, such as the choice of chiral ligand and additive, the olefin geometry of the starting material, and reaction condi-

Scheme 2. Projected Synthesis of Chiral Chromans and Chromens via Pd-Catalyzed AAA Reactions

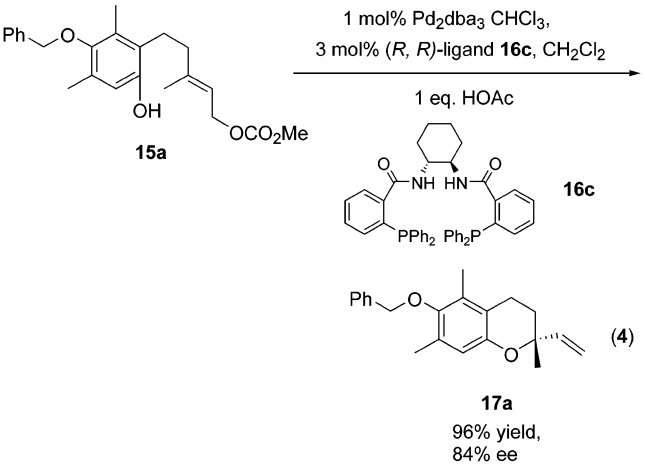




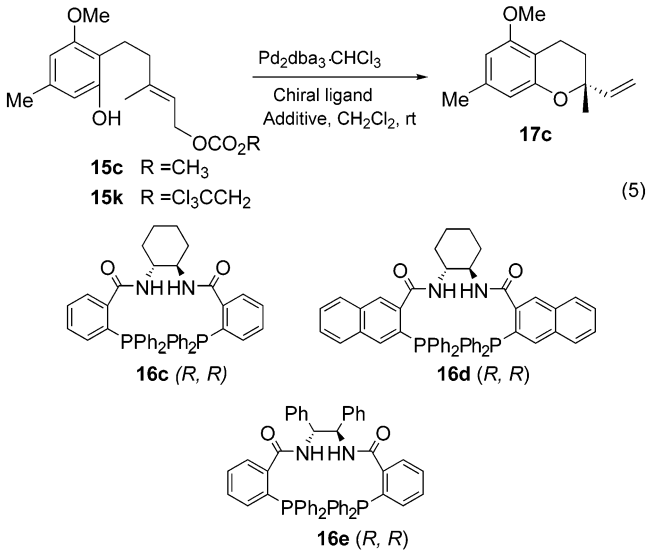




tions.[16] In light of these results, a mechanistic working model is proposed to accommodate all of our observations.



Synthesis of Substrates. Following the protocol depicted in Scheme 3 , trans trisubstituted allyl carbonate **15c** can be easily



prepared on a multigram scale.[14,15] The key step in this synthetic sequence is the olefination of ketone **22**. Three different conditions have been examined (a−c). The Horner−Wardsworth−Emmons reaction using *n*-butyllithium as a base afforded allylic ester **23** with a better *E* to *Z* ratio (11:1) than the case in which sodium hydride was used (7:1). Still's protocol using trifluoroethyl phosphonoacetate[17] gave a 4.6 to 1 ratio of allylic esters still favoring the *E* isomer **23**. Fortunately, trans allylic alcohol **24** can be crystallized, whereas the cis allylic alcohol is an oil. The separation of the trans and cis allylic alcohols is crucial for a good enantioselectivity because the trans and cis allyl carbonates will give opposite enantiomers using the same chiral ligand, as revealed in the later experiments.

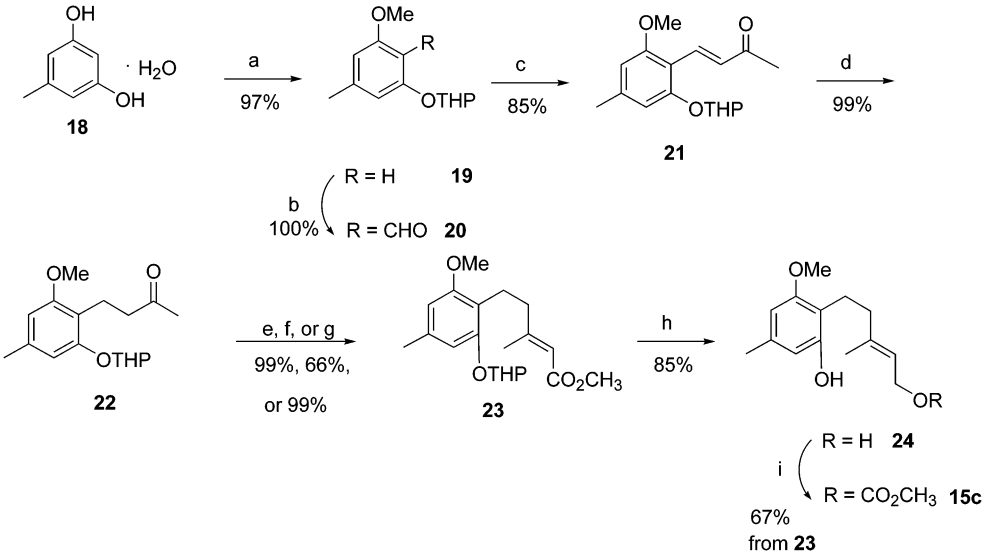
To have access to either trans or cis trisubstituted allyl carbonates without the complication of isolation of the geometrical isomers, a different route was developed involving a Negishi coupling[18] of alkyl iodide **29** and vinyl iodide **30**[19] or **32**[20] as a key step (Schemes 4 and 5). The Negishi coupling strategy is also applied to the preparation of substrates **15d**, **15d′**, **15e**, and **15e′**. It should be noted that the monodemethylation of **33** was achieved using lithium propylthiolate in HMPA. To our surprise, the conditions using sodium ethyl thiolate in DMF afforded allyl ethyl sulfide. Under these thermal basic conditions, allyl alcohol and DMF presumably generated allyl formate, which was displaced by ethyl thiolate to give allyl sulfide.

The syntheses of trans-disubstituted allyl carbonate **15g** and cis-disubstituted allyl carbonate **15g′** are also straightforward (Schemes 6 and 7).[21] This strategy is utilized to prepare all trans- and cis-disubstituted allyl carbonates shown in Table 6.

Pd-Catalyzed Asymmetric Allylic Alkylations (AAA). In the comprehensive studies of conditions for the Pd-catalyzed

(13) Mizuguchi, E.; Achiwa, K. *Chem. Pharm. Bull.* **1997**, *45*, 1209−1211.
(14) Labrosse, J.-R.; Poncet, C.; Lhoste, P.; Sinou, D. *Tetrahedron: Asymmetry* **1999**, *10*, 1069−1078.
(15) Trost, B. M.; Asakawa, N. *Synthesis* **1999**, 1491−1494.
(16) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276−9277.
(17) Still, W. C.; Gennart, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.
(18) Negishi, E.; Liou, S.-Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, *4*, 261−264.
(19) Wang, Q.; Wei, H.; Schlosser, M. *Eur. J. Org. Chem.* **1947**, *12*, 3263−3268.
(20) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *Bull. Soc. Chim. Fr.* **1993**, *130*, 358−370.
(21) Chandrasekhar, S.; Reddy, M. V. *Tetrahedron* **2000**, *56*, 6339−6344.

Scheme 3. First Generation Synthesis of Trans Trisubstituted Allyl Carbonate **15c**[a]



[a] Reagents and conditions: (a) i. $(MeO)_2SO_2$, K_2CO_3, acetone; ii. $NaSC_2H_5$, DMF; iii. TsOH, DHP, THF. (b) nC_4H_9Li, TMEDA, THF then DMF. (c) $Ph_3P{=}CHC(O)CH_3$, $PhCH_3$ (d) i. $NaBH_4$, CH_3OH; ii. H_2 (1 atm), 5% PtO_2, EtOAc, iii. TPAP, NMO, 4 Å MS, CH_2Cl_2. (e) $(MeO)_2P(O)CH_2CO_2Me$, nC_4H_9Li, THF, E/Z 11:1. (f) $(CF_3CH_2O)_2P(O)$ $CH_2CO_2CH_3$, $KN(TMS)_2$, THF, E:Z 4.6:1. (g) $(MeO)_2P(O)$ $CH_2CO_2CH_3$, NaH, THF, E:Z 7:1. (h) i. DIBAL-H, THF, −78°; ii. TsOH, MeOH. iii. MeOCOCl, pyridine, CH_2Cl_2.

Table 1. Effects of Ligands and Additives on the Pd-Catalyzed AAA Reaction of **15c**

entry	Pd (%)	ligand (%)	additvie (equiv)	[C] (M)	time (h)	yield (%)	ee (%)[a]
1	4	**16c** (6)	None	0.2	1	95	−14
2	4	**16c** (6)	Et_3N (1)	0.2	1	96	−22
3	4	**16c** (6)	AcOH (1)	0.01	1.3	99	75
4	4	**16c** (6)	AcOH (1)	**0.2**	**1**	**94**	**84**
5	2	**16c** (3)	AcOH (1)	0.3	1	96	74
6	1	**16c** (1.5)	AcOH (1)	0.5	3	73	72
7	4	**16c** (6)	AcOH (0.5)	0.2	1	95	73
8	4	**16c** (6)	$PhCO_2H$ (1)	0.2	1	98	75
9	4	**16c** (6)	H_3PO_4 (0.5)	0.2	1	99	−5
10	4	**16c** (6)	nBu_4NOAc (1)	0.2	1	99	66
11	4	**16c** (6)	nBu_4NCl (1)[b]	0.2	1	40	63
12	4	**16c** (6)	nBu_4NCl (0.3)	0.2	1	24	33
13	4	**16d** (6)	AcOH (1)	0.2	1	99	69
14	4	**16e** (6)	AcOH (1)	0.2	1	95	64

[a] Measured by chiral GC. [b] With 1 equiv of HOAc.

Table 2. Effects of Additives on the Pd-Catalyzed AAA Reactions of Substrate **15k**

entry	Pd (%)	ligand **16c** (%)	additive (equiv)	[C] (M)	yield (%)	ee (%)[a]
1	4	6	none	0.2	>95	−16
2	4	6	Et_3N (1)	0.1	>95	−21
3	4	6	$PhCO_2H$ (1)	0.2	>95	76
4	2	3	$PhCO_2H$ (1)	0.1	>95	76
5[b]	2	3	$PhCO_2H$ (1)	0.1	>95	75
6	4	6	AcOH (1)	0.2	>95	75
7	4	6	AcOH (0.5)	0.2	>95	75
8	4	3	AcOH (1)	0.2	>95	75
9	2	3	AcOH (0.5)	0.1	>95	76
10	2	3	AcOH (1)	0.1	>95	75

[a] Measured by chiral GC. [b] Performed at 40 °C.

asymmetric allylic alkylation, it was found that the best reaction conditions were identical for both di- and trisubstituted trans allyl carbonates among all the examined cases. Taking a trisubstituted allyl carbonate **15c** as an example, the effects of additive, concentration, catalyst loading, ligands, leaving group, solvent, and temperature were systematically studied and the results are summarized in Tables 1−4.

Table 3. Influence of Solvents on the Pd-Catalyzed AAA Reaction of **15c**[a]

entry	Pd (%)	ligand **16c** (%)	solvent	yield (%)	ee (%)[b]
1	4	6	DMSO	>95	58
2	4	6	THF	12	43
3	4	6	Toluene	87	62
4	4	6	$ClCH_2CH_2Cl$	81	78
5	**4**	**6**	**CH_2Cl_2**	**94**	**84**
6	4	6	CH_3CN	72	70
7	4	6	HOAc	10	52

[a] The reaction of eq 5 using substrate **15c** was performed with $(dba)_3Pd_2{\cdot}CHCl_3$, ligand **16c** and 1 equiv of HOAc, at 0.2 M for 1 h in the stated solvent. [b] Measured by chiral GC.

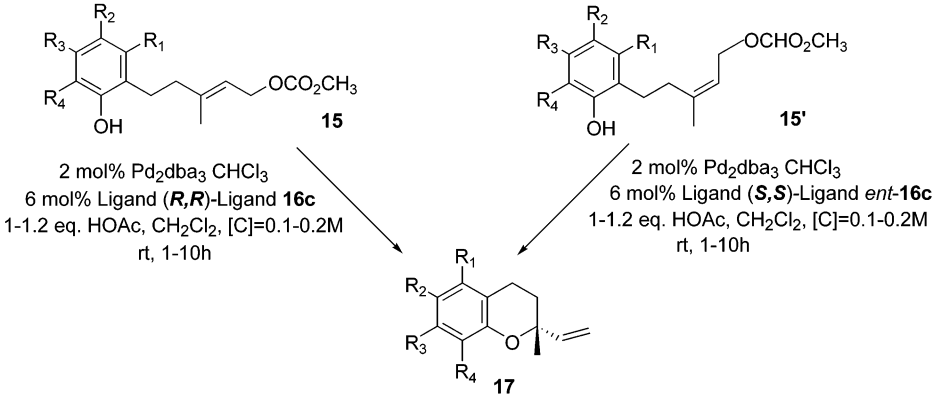
Table 4. Effect of Temperature on the Pd-Catalyzed AAA Reaction of **15c**[a]

entry	*T* (°C)	time (h)	yield (%)	ee (%)[b]
1	0	1	58	72
2	rt	1	94	84
3	40	1	92	85
4[c]	45	1	95	82

[a] The reaction was performed as in Table 3 using compound **16c** as ligand, methylene chloride as solvent at the stated temperature. [b] Measured by chiral GC. [c] In sealed tube.

Equation 5 and Table 1 show our studies on the influence of ligand and additive on the yield and ee of the reaction. Without any additive and in the presence of 2 mol % Pd_2dba_3 chloroform complex and 6 mol % ligand **16c**, substrate **15c** gave 95% yield but only 14% ee favoring the formation of *S* chroman (***ent*-17c)** (entry 1). The addition of 1 equiv of triethylamine slightly improved the ee and still favored the formation of *S* chroman. Interestingly, the ee was dramatically enhanced when 1 equiv of acetic acid was added (entries 3−7). Moreover, the absolute configuration of chroman was reversed to *R.* After the optimization of substrate concentration and catalyst loading, *R* chroman **17c** was obtained in 94% yield and 84% ee (entry 4). To explore the influence of different acids, we have also screened benzoic acid which gave similar results (entry 8), and phosphoric acid

Table 5. Pd-Catalyzed AAA Reactions of Trans and Cis Trisubstituted Allyl Carbonates



Entry	(*E*)-Substrate	Yield%	ee%[a]	Entry	(*Z*)-Substrate	Yield%	ee%[a]
1	**15c**, R_2, R_4 = H R_1 = OMe, R_3 =Me	94	84	6	**15c'**, R_2, R_4 = H R_1 = OMe, R_3 =Me	75	97
2	**15d**, R_1,R_2,R_3, R_4 = H	62	73	7	**15d'**, R_1,R_2,R_3, R_4 = H	68	95
3	**15e**, R_2 = OMe R_1,R_3,R_4 = H	83	80	8	**15e'**, R_2 = OMe R_1,R_3,R_4 = H	69	98
4	**15a**, R_1,R_3 = Me R_2,R_4 = OMe	96	84[b]				
5	**15f**, R_2,R_3 = Me R_1,R_4 = OMe	100	80				

[a] The ee's of products were determined by chiral GC unless otherwise noted. [b] The ee's of products were determined by chiral HPLC.

which gave lower ee's but still good yield (entry 9). Entry 10 clearly demonstrates an acetate ion effect on improving the ee compared to the additive free case (entry 1). Meanwhile, it suggests that the acid may have a synergistic effect on the improvement of ee. In entry 12, tetrabutylammonium chloride was employed to speed up Pd $\pi-\sigma-\pi$ equilibration. Although the ee was low, it was higher than entry 1, and the reaction favored the formation of the *R* enantiomer. We also observed that the standard ligand **16c** (*R*, *R*) was superior to **16d** or **16e**, despite the similar yields obtained for all ligands in the presence of acetic acid (entries 13 and 14).

To probe whether a better leaving group could improve the reaction outcome, Troc group was employed as shown in eq 5 and Table 2. It is again noted that substrate **15k** favored the formation of *S* chroman ***ent*-17c** in the presence of triethylamine or in the absence of any additive (entries 1 and 2). Reactions with acetic or benzoic acid as additive gave similar yield and ee compared to the carbonate substrate **15c**.

We have also screened a number of solvents (Table 3). Dichloromethane and 1,2-dichloroethane are most suitable for high yields and higher ee's. The temperature profile shown in Table 4 shows that room temperature to 45 °C gave better ee's and yields than lower temperature such as 0 °C.

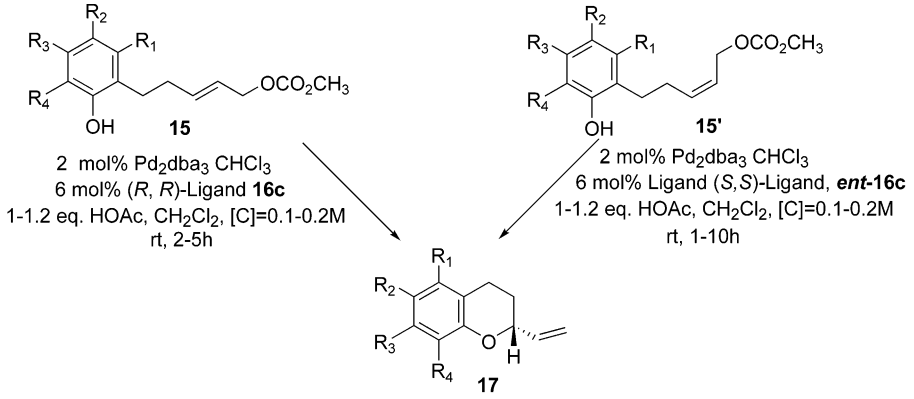
The optimized reaction conditions were employed for various tri- and disubsituted allyl carbonates (Tables 5 and 6).[22] The impact of the olefin geometry of the substrates on the reaction was also studied. Interestingly, we observed that trans- and cis trisubstituted allyl carbonates **15c** and **15c′** both led to *R* chroman **17c** using ligands of opposite chirality (entries 1 and 6, Table 5). Furthermore, the cis-allyl carbonate **15c′** afforded chiral vinyl chroman **17c** in substantially higher ee (97%) than the trans-counterpart **15c** (84% ee). Similar observations were also made for substrates **15d**, **15d′**, **15e**, and **15e′** (entries 2, 7, 3 and 8, Table 5).

Trans disubstituted allyl carbonates, **15g**, **15b**, **15h**, and **15i** in the presence of (*R*, *R*)-ligand **16c**, and their cis disubstituted counterparts **15g′**, **15b′**, **15h′**, and **15i′** in the presence of (*S*, *S*)-ligand, favored the formation of the same chroman enantiomer, namely, **17g′**, **17b′**, **17h′**, and **17i′** respectively (Table 6). More interestingly, the trans series gave much higher ee than the cis counterparts, which is opposite to the trend we observed for the trisubstituted allyl carbonates. Moreover, the para substituents seem to have little effect over the ee's of the reaction for the trans series. In contrast, the substituent effect on the cis disubstituted cases on the ee of the reaction is much more pronounced.

Determination of Absolute Configuration of Vinyl Chromans. The absolute configuration of these compounds was established by comparing with known compounds from the literature (such as **17a** and **17b**),[13] or derivatization (vide infra, such as **17c** and **17f**). The absolute configuration of other chroman products was determined by comparing the sign of the optical rotation, the retention time order on chiral GC or chiral HPLC for both enantiomers with that of **17a**, **17b**, **17c**, and **17f**, whose absolute configuration and chiral HPLC/GC retention time order for both enantiomers have been established.

The method of assigning absolute configuration of an α-oxy-α,α-disubstituted acetic acid employing phenylglycine methyl

Table 6. Pd-Catalyzed AAA Reactions of Trans and Cis Disubstituted Allyl Carbonates



Entry	(***E***)-Substrate	Yield%	ee%[a]	Entry	(***Z***)-Substrate	Yield%	ee%[a]
1	**15g**, R_2, = F R_1,R_3,R_4 = H	95	80	6	**15g'**, R_2, = F R_1,R_3,R_4 = H	93	57
2	**15b**, R_1,R_2,R_3, R_4 = H	99	84	7	**15b'**, R_1,R_2,R_3, R_4 = H	67	34
3	**15h**, R_2 = Me R_1,R_3,R_4 = H	97	87	8	**15h'**, R_2 = Me R_1,R_3,R_4 = H	72	48
4	**15i**, R_2 = OMe R_1,R_3,R_4 = H	82	89	9	**15i'**, R_2 = OMe R_1,R_3,R_4 = H	84	18
5	**15j**, R_1,R_3 = H R_2 = Me,R_4 = OMe	82	82				

[a] The ee's of products were determined by chiral HPLC.

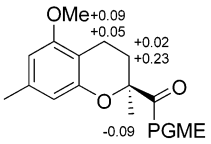


Figure 2. $\Delta\delta$ values ($\delta_{(S)} - \delta_{(R)}$) for 10-(*S*)-PGME amide **43** and 10-(*R*)-PGME amide **44**.

ester (PGME) was developed by Kusumi and Yabuuchi.[23] Applying this method, we were able to assign the absolute configuration of chroman **17c** and **17f**. For example, chiral chroman **17c** was converted to aldehyde **41** via a sequence of dihydroxylation and oxidative cleavage reactions. The resulting aldehyde **41** was further oxidized to carboxylic acid **42**,[24] which was then coupled with (*S*)-PGME and (*R*)-PGME, respectively, to afford two diasteromeric amides **43** and **44** (Scheme 8). The $\Delta\delta$ values ($\delta_{(S)} - \delta_{(R)}$) were calculated by subtracting the proton chemical shifts of 10-(*S*)-PGME amide **43** with the chemical shifts of the corresponding protons of 10-(*R*)-PGME amide **44**. The comparison with the described model allowed us to determine that chroman **17c** has the *R* configuration (Figure 2).

Mechanistic Discussion

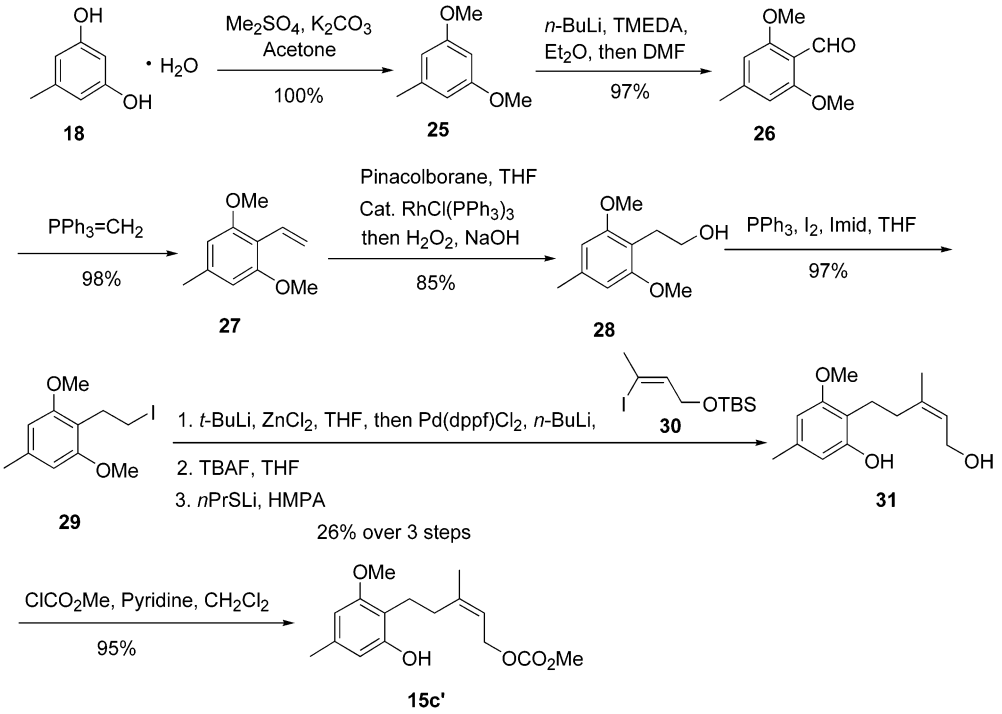
There are at least two possible mechanisms for the catalytic asymmetric allylic alkylation (AAA) of phenol allyl carbonates.[11b] The first mechanism assumes that the diastereomeric π-allyl palladium intermediates do not interconvert fast enough prior to cyclization, i.e., the kinetically formed π-allyl palladium complex was immediately captured by nucleophile. In this scenario, the ionization leading to the more reactive π-allyl palladium intermediate is the enantiodiscriminating step. The second plausible mechanism envisions that the interconversion of diastereomeric Pd π-allyl intermediates is fast relative to the nucleophilic attack, and the asymmetric induction is determined by the reaction rate of the two diastereomeric intermediates (Curtin-Hammett conditions). The mechanistic picture is more complex if the rate of interconversion and nucleophilic attack is comparable.

The addition of 1.5 equiv of triethylamine led to a dramatic drop of both ee (8%) and yield (34%) (entry 2, Table 1). If the ionization of leaving group is the enantiodiscriminating step, the presence of base should speed up the cyclization so that the full $\pi-\sigma-\pi$ equilibration does not occur. Therefore, the ee should increase. The observation that ee decreases suggests that the enantiodiscriminating step is most likely not the ionization of carbonate, as proposed by the Achiwa group.[13]

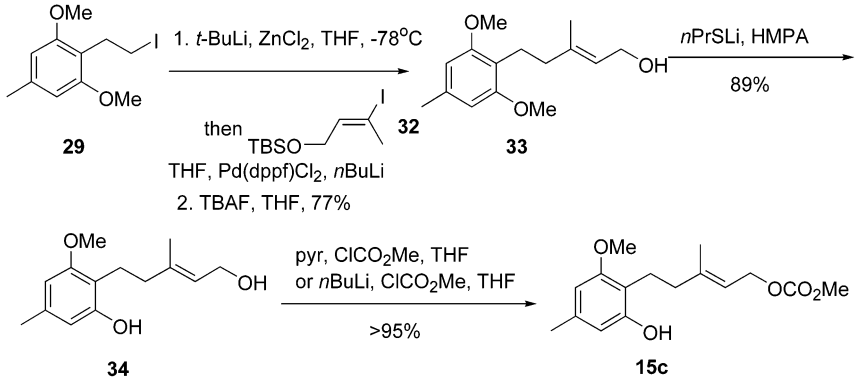
Our studies summarized in Tables 5 and 6 provide further evidence to support the second mechanism (Curtin−Hammett conditions). Three important observations help to elucidate the mechanistic picture. First, both trans- and the corresponding cis-allyl carbonates lead to the same chiral chroman as the major enantiomer using ligands of opposite chirality. Second, trisubstituted cis-allyl carbonates (**15c′**, **15d′**, and **15e′**) afford chiral chromans in substantially higher ee than their trans-counterparts (**15c**, **15d**, and **15e**). Third, disubstituted trans-allyl carbonates (such as **15g**, **15b**, **15h**, and **15i**) afford chiral vinyl chromans

(22) Compound **15a** and **15f** were prepared according to Achiwa's procedure. See ref 13.
(23) Yabuuchi, T.; Kusumi, T. *J. Org. Chem.* **2000**, *65*, 397−404.
(24) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

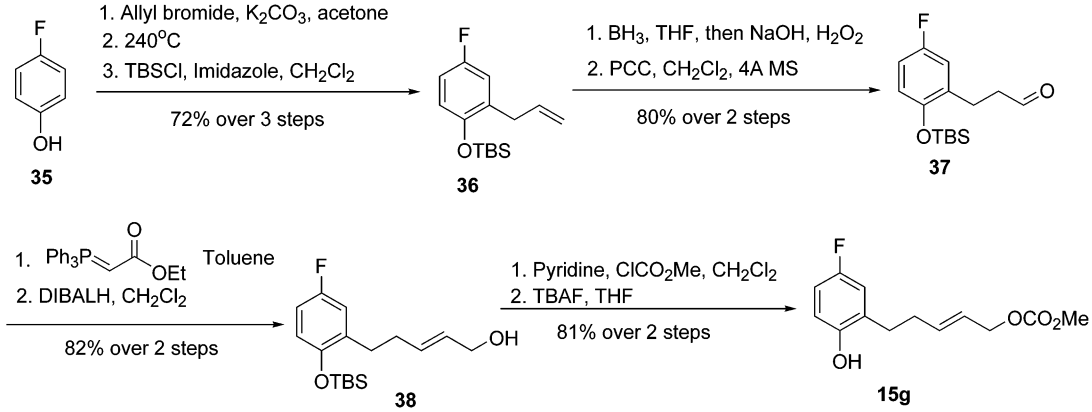
Scheme 4. Synthesis of Cis Trisubstituted Allyl Carbonate **15c′**



Scheme 5. Second Generation of Trans Trisubstituted Allyl Carbonate **15c**



Scheme 6. Synthesis of Trans Disubstituted Allyl Carbonate **15g**

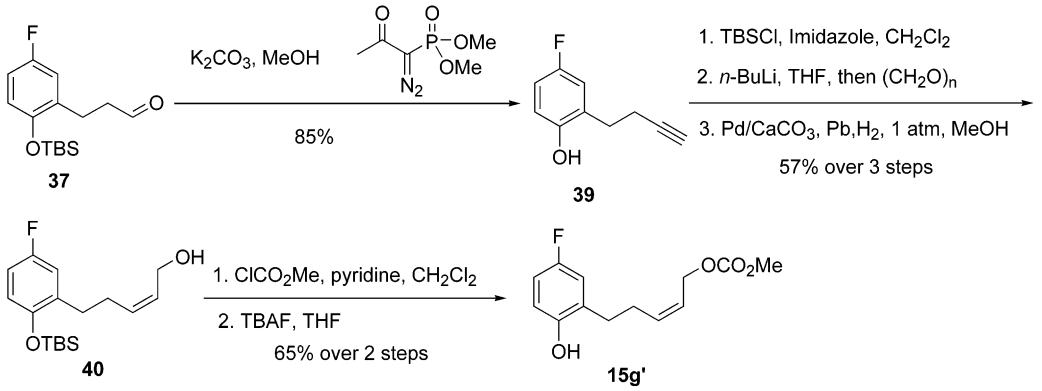


in substantially higher ee's than the cis-counterpart (such as **15g′**, **15b′**, **15h′**, and **15i′**).

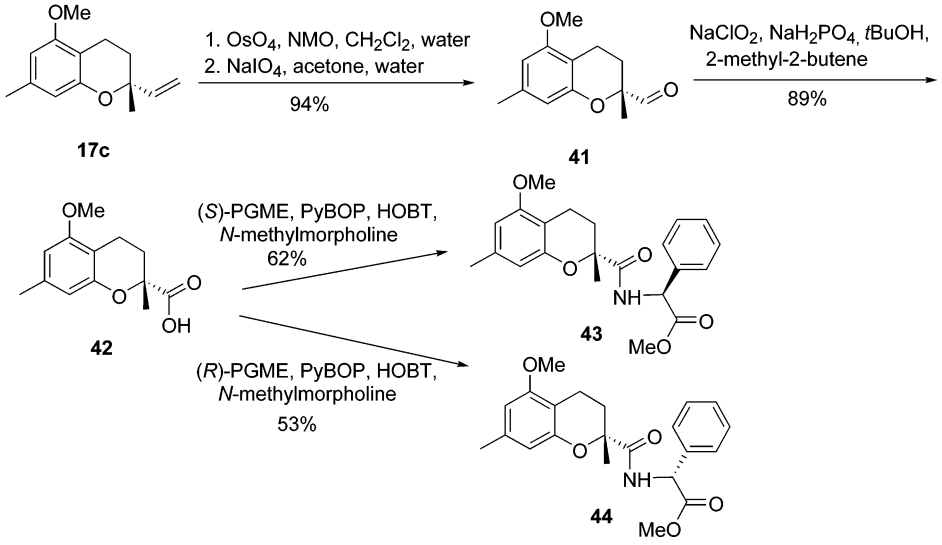
The first observation can be rationalized by the mechanistic proposal shown in Schemes 9 and 10. On the basis of our working model,[25] the (*R*, *R*)-ligand **16c** can be exemplified by the simplified cartoon picture. The flaps and walls of the chiral scaffold represent the phenyl groups of the triarylphospine moiety. The trans-allyl carbonate (**15c**, **15d**, or **15e**) generates *syn*-π-allyl palladium complex **46** kinetically via a "matched" ionization ("matched" indicates that the leaving group departs

(25) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545−4554.

Scheme 7. Synthesis of Cis Disubstituted Allyl Carbonate **15g′**



Scheme 8. Preparation of Diastereomeric Amides **43** and **44**

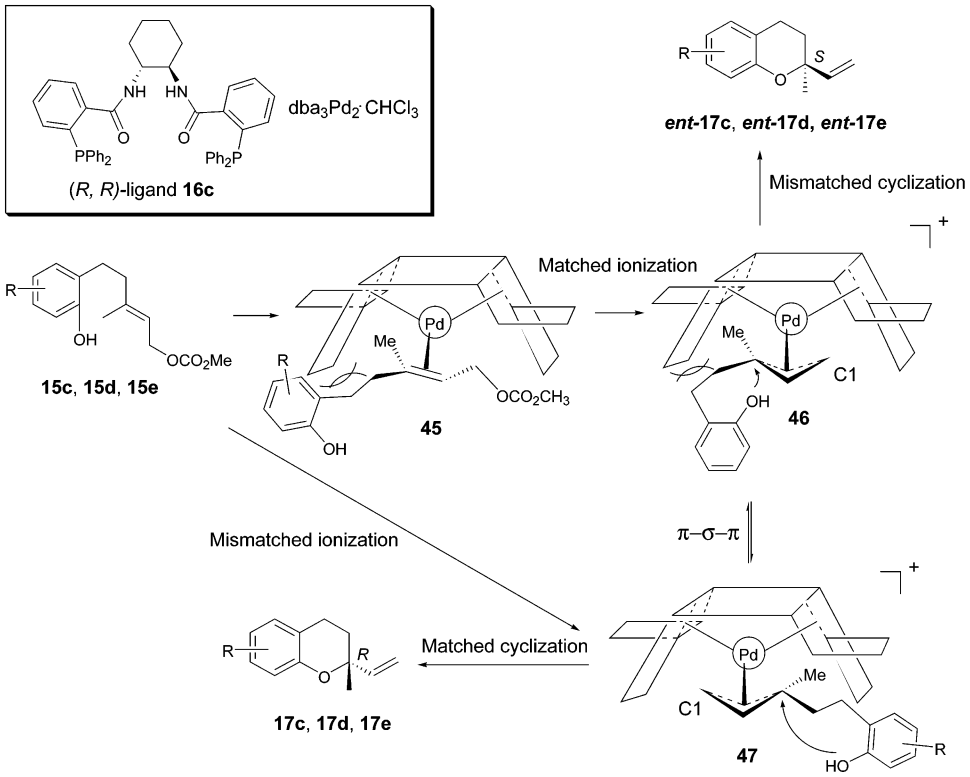


under the flap of the chiral pockets (Scheme 9). To the extent cyclization occurs at this stage, the product is *S* enantiomer ***ent*-17c**, ***ent*-17d**, or ***ent*-17e**. Intermediate **46** invokes a disfavored steric interaction between the large substituent bearing the phenol nucleophile and the wall of the chiral scaffold, i.e., the nucleophilic attack would occur from the more hindered left front quadrant. Therefore, the cyclization of intermediate **46** is a "mismatched" event. The equilibration of intermediate **46** leads to **47** via a $\pi-\sigma-\pi$ process through C1. Intermediate **47** is considerably less encumbered because the large substituent is under the right front flap and therefore better accommodated. Furthermore, the nucleophilic attack from under the flap is not blocked, in contrast to the cyclization of intermediate **46**. Therefore, the cyclization of the less sterically encumbered intermediate **47** is a "matched" event, in which **17c**, **17d**, or **17e** is obtained as the major enantiomer. The observed ee then depends on the rate difference of cyclization from the two diastereomeric complexes, **46** and **47**, compared to the rate of their interconversions. To the extent that a "mismatched" ionization occurs then **47** forms directly and should lead to high ee in its cyclization.

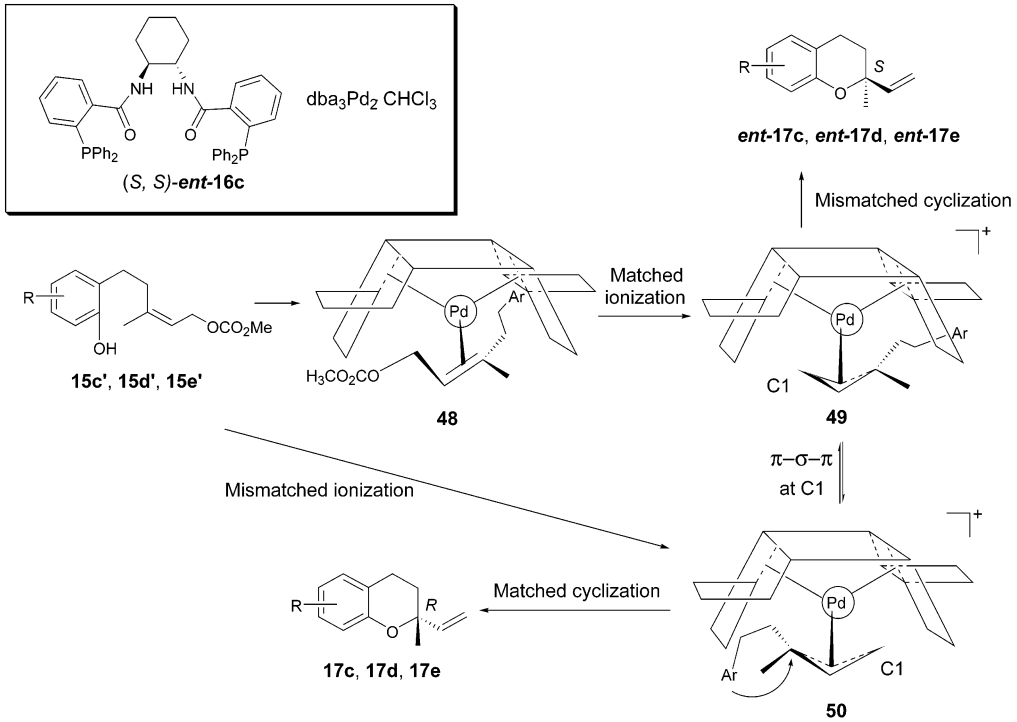
The Curtin−Hammett situation also applies to the case of cis-trisubstituted allyl carbonates **15c′**, **15d′**, and **15e′** (Scheme 10). The "matched" ionization of carbonate **15c′**, **15d′**, or **15e′** led to *anti*-π-allyl palladium intermediate **49** as the kinetic product which could subsequently undergo a $\pi-\sigma-\pi$ process at C1 to form **50**. Apparently, the nucleophilic attack involving intermediate **49** is less favored due to the steric interaction between the right front wall and the incoming nucleophile (mismatched cyclization). Therefore, intermediate **50** is more reactive toward cyclization under the left front flap to form *R* chroman **17c**, **17d**, or **17e** (matched cyclization).

To address the second observation that cis trisubstituted allyl carbonates (**15c′**, **15d′**, and **15e′**) gave substantially higher ee's than the trans counterparts (**15c**, **15d**, and **15e**), we may consider the reactivity difference of intermediate **46** and **47** vs **49** and **50**. While the steric stress between the large arylethyl moiety and the wall in **46** destabilizes it and enhances its propensity to undergo $\pi-\sigma-\pi$ isomerization to **47**, that same interaction favors a conformation of this moiety that facilitates cyclization. Thus, cyclization versus $\pi-\sigma-\pi$ becomes somewhat competitive. Since cyclization via **46** vs **47** gives mirror image products, the net result is a diminished ee. On the other hand, the arylethyl moiety is nicely accommodated in **49** in the extended conformation which cannot cyclize. Adopting the required conformation for cyclization requires this moiety to encounter a severe steric interaction with a "wall" of the ligand. Isomerization to diastereomeric complex **50** places this moiety into a conformation favorable to cyclization as well as bringing the nucleophile toward the sterically less congested flap-therefore enhancing the rate of cyclization. The decreased rate of cyclization for diastereomer **49** and the increased rate for **50** then lead to a

Scheme 9. Working Model for the Pd-Catalyzed Intramolecular AAA Reaction of Trans Trisubstituted Allyl Carbonates



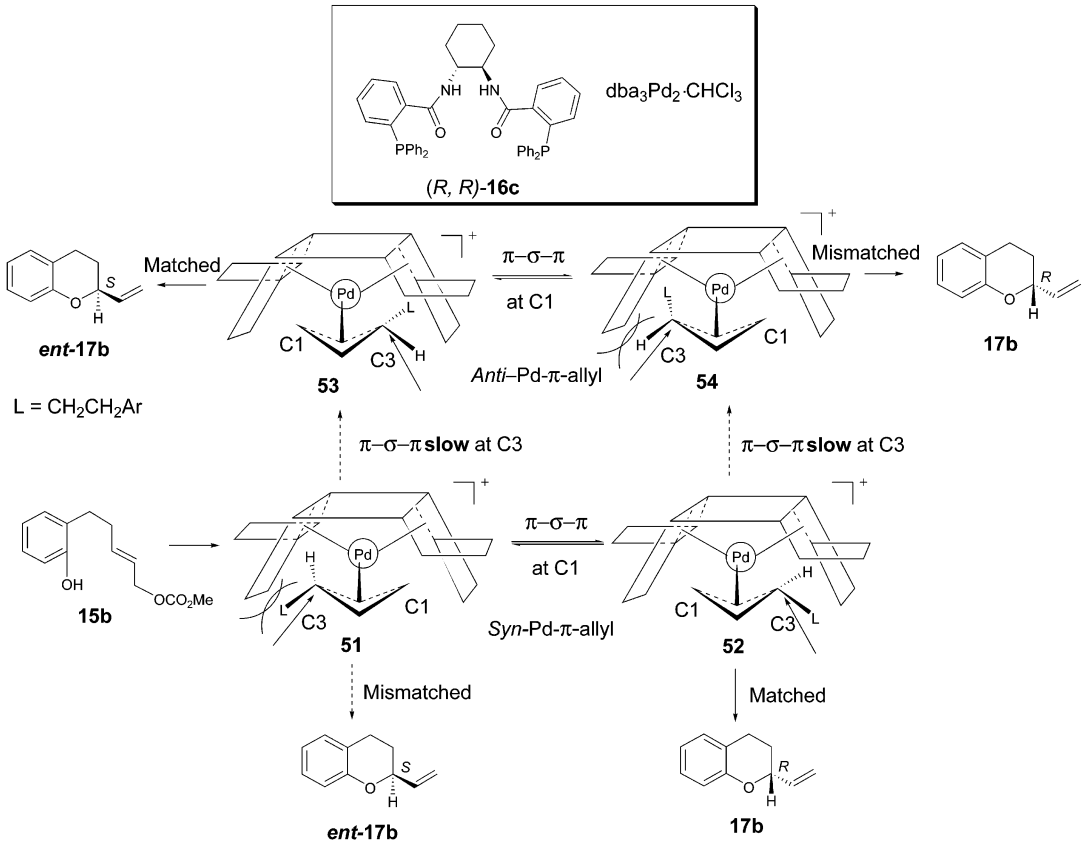
Scheme 10. Working Model for the Pd-Catalyzed Intramolecular AAA Reaction of Cis Trisubstituted Allyl Carbonates



larger rate difference and a higher ee. In general, cis allyl carbonates **15c′**, **15d′**, and **15e′** all gave higher ee's than their trans counterparts.

Interestingly, the Pd-catalyzed intramolecular AAA reaction of cis disubstituted allyl carbonates gave much lower ee than their trans counterparts (Table 6), as opposed to what we observed for the trisubstituted substrates in Table 5. As shown in Scheme 11, the "matched" ionization of trans disubstituted allyl carbonate **15b** kinetically generates *syn*-π-allyl palladium complex **51**, which can undergo $\pi-\sigma-\pi$ isomerization at C1 to form **52**. The nucleophile then preferentially approaches π-allyl intermediate **52** under the flap of the front right quadrant (matched cyclization), which is sterically more favorable than intermediate **51** (mismatched cyclization). Consequently, the formation of the *R* enantiomer **17b** is favored. It is known that *syn*-π-allylpalladium complexes are more stable than the cor-

Scheme 11. Working Model for the Pd-Catalyzed AAA Reaction of Trans Disubstituted Allyl Carbonate **15b**



responding anti complexes.[26] Therefore, the conversion of *syn*-π-allyl complexes **51** and **52** to *anti*-π-allyl complexes **53** and **54** at C3 is thermodynamically disfavored. Therefore, the mechanistic picture for trans disubstituted allyl carbonates is essentially the same as that of the trans trisubstituted allyl carbonates, which accounts for similar ee's for the trans tri- and disubstituted allyl carbonate series.

Conversely, the "matched" ionization of cis allyl carbonate **15b′** leads to *anti*-π-allylpalladium complex **55**, which could isomerize to **56** through $\pi-\sigma-\pi$ at C1 (Scheme 12). Steric factors leads to preferential nucleophilic attack via intermediate **56** over **55** to give the *R* isomer **17b**. Meanwhile, the conversion of *anti*-π-allylpalladium complex **55** to the syn complex **57** is thermodynamically favored, and **57** can undergo a "matched" cyclization leading to the *S* isomer ***ent*-17b**. Such a $\pi-\sigma-\pi$ isomerization at a secondary carbon is still kinetically accessible albeit slower than at a primary carbon. On the other hand, although *syn*-π-allylpalladium complex **58** can be formed, either via $\pi-\sigma-\pi$ isomerization of *anti*-π-allylpalladium complex **56**, or via such an isomerization of *syn*-π-allylpalladium complex **57** at C1, **58** could only undergo a "mismatched" cyclization to the *R* enantiomer **17b**. Therefore, the likely pathway leading to **17b** is **15b′** to **55** to **56** to **17b**. The facile $\pi-\sigma-\pi$ process from **55** to the thermodynamically more favored *syn* complex **57**[27] followed by a "matched" cyclization leading to ***ent*-17b** becomes a competitive pathway with respect to the pathway leading to **17b** with the net effect of diminished ee's.

In contrast to the disubstituted cases, the $\pi-\sigma-\pi$ equilibration at C3 of trisubstituted π-allyl palladium complex is disfavored.[28] Thus, the *syn-anti* interconversion of the substituted terminus does not occur as already outlined in Schemes 9 and 10, only two of the four possible diastereomeric complexes need to be considered and can nicely account for the selectivity differences.

Therefore, the enantioselectivity of the Pd-catalyzed intramolecular AAA reaction of phenols is presumably governed by the $\pi-\sigma-\pi$ equilibration of diastereomeric Pd complexes (Curtin−Hammett conditions). The kinetically generated π-allylpalladium intermediate via the "matched" ionization is less reactive, and will isomerize to the more reactive intermediate via the $\pi-\sigma-\pi$ process. For trisubstituted substrates, such an isomerization can only occur at one allyl terminus; however, for disubstituted substrates, the isomerization can occur at both allyl termini.

Finally, the unusual acetic acid effect to enhance both the yield and ee of the Pd-catalyzed AAA reaction may have wide implications for various reactions.[29] The effect of pH alone does not seem to account for all the improvement of ee, as suggested by the fact that the use of phosphoric acid as an additive led to low ee. As demonstrated by entry 10 of Table 1, tetraalkylammonium acetate improved the yield and ee of the reaction

(26) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642−2643.

(27) (a) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215−3216. (b) Ohta, T.; Hosokawa, T.; Murahashi, S. I.; Miki, K.; Kasai, N. *Organometallics* **1985**, *4*, 2080−2085.

(28) (a) Faller, J. W.; Incorvia, M. *J. Organomet. Chem.* **1969**, *19*, P13−P14. (b) Faller, J. W.; Mattina, M. J. *Inorg. Chem.* **1972**, *11*, 1296−1297. (c) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3452−457. (d) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591−2594.

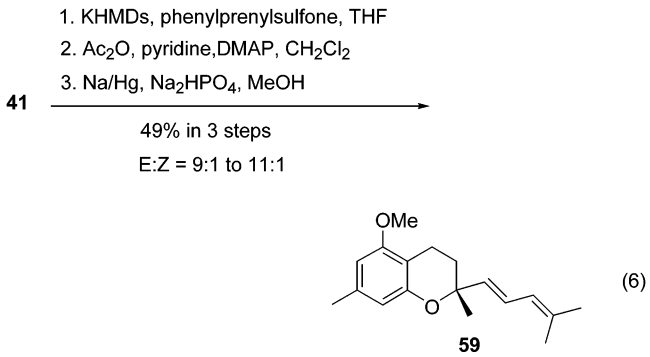
(29) For another example of acetic acid effect on the Pd-catalyzed asymmetric reaction, see: Trost, B. M.; Fandrick, D. R. **2003**, *125*, 11 836−11 837.

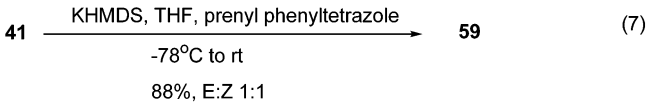
compared to the additive-free case. Thus, the acetate ion seems to play a critical role in improving the enantioselectivity. The addition of tetrabutylammonium chloride (entry 12 of Table 1) was employed to speed up the $\pi-\sigma-\pi$ equilibration of π-allyl palladium complex, and it did give higher ee than entry 1, albeit still considerably lower than in the case of acetate. In light of these results, the acetate or chloride ion may help facilitate the $\pi-\sigma-\pi$ process of π-allylpalladium intermediates as required. The potential bidentate nature of acetate may account for its enhanced effectiveness compared to chloride. The acidity of acetic acid may synergistically contribute to the high enantioselectivity by slowing down the cyclization, thus allow the π-allylpalladium intermediates to reach full equilibrium prior to cyclization. The protonation of the methoxide formed from the ionization of methyl carbonate by acetic acid, can avoid the deprotonation of phenol to give phenoxide, a much more reactive nucleophile for cyclization than neutral phenol.

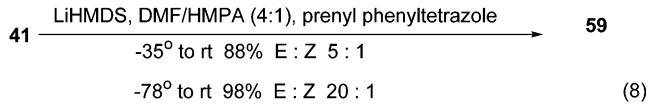
Synthesis of Clusifoliol and Des-Carboxy Daurichromenic Acid A MOM Ether. To demonstrate the utility of this methodology, we chose vitamin E,[15] nebivolol, (+)-clusifoliol, (+)-rhododaurichromanic acid A, and (−)-siccanin as targets. Prelimimary reports describe a part of our work on the first enantioselective total syntheses of (+)-clusifoliol[16] and (−)-siccanin.[30] We report the details of the synthesis of (+)-clusifoliol and herein a synthesis of descarboxydaurichromenic acid A MOM ether **59**, a possible intermediate toward the total synthesis of daurichromenic acid (**7**), a precursor of (+)-rhododaurichromanic acid A (**8**) (Scheme 13).

Clusifoliol **6** was isolated from *Peperomia clussifolia*. Its structure has been established as 3,4-dihydro-2,7-dimethyl-6-(3-methyl-2-butenyl)-2-(4-methyl-1,3-pentadienyl)-2*H*-1-benzopyran-5-ol by spectroscopic methods. In one of the papers, the authors claimed no optical rotation[6b] whereas, in the other one, a significant value (+160° in EtOH) was reported.[6a]

As shown in Scheme 14, clusifoliol **6** can be derived from a Julia olefination[31] and a subsequent prenylation of chroman **17c**, by the Pd-catalyzed asymmetric allylic alkylation with excellent ee and yield. Chiral chroman **17c** can be easily converted to aldehyde **41** via a dihydroxylation followed by an oxidative cleavage (Scheme 8). The one-pot protocol of dihydroxylation/oxidative cleavage[32] only gave trace amount of desired aldehyde accompanied with decomposition of the starting material. The resulting aldehyde **41** then reacted with phenyl prenyl sulfone to give the trans olefin in good yield and selectivity (9:1 to 11:1) via a Julia olefination protocol, but three steps are required (eq 6). The modified Julia protocol using phenyltetrazole prenyl sulfone was also examined to shorten the steps. However, a 1:1 mixture of *E/Z* isomers was obtained when KHMDS was used as the base.[33] As previously reported,[34] a more polar medium with lithium as the counterion favors the desired trans diene which was obtained in 98% yield and an excellent *E/Z* ratio (20:1) initiating the reaction at −78 °C. If the initial temperature was −35 °C, then the *E*:*Z* selectivity and yield both dropped (eq 8).







Attempts to ortho metalate the methyl ether and alkylate failed.[35] Following a protocol developed by Dauben's group,[36] the sequential demethylation, O-prenylation,[37] and prenyl group rearrangement proceeded smoothly to yield the desired (+)-clusifoliol **6** (Scheme 15). The specific optical rotation, chiral HPLC eluting time, and all other spectroscopic data of our synthetic sample matched that of the authentic sample kindly provided by Dr. McLean and Dr. Jacobs. Since we have established the absolute configuration of **17c**, this synthesis allows assignment of the absolute configuration of **6** as depicted.

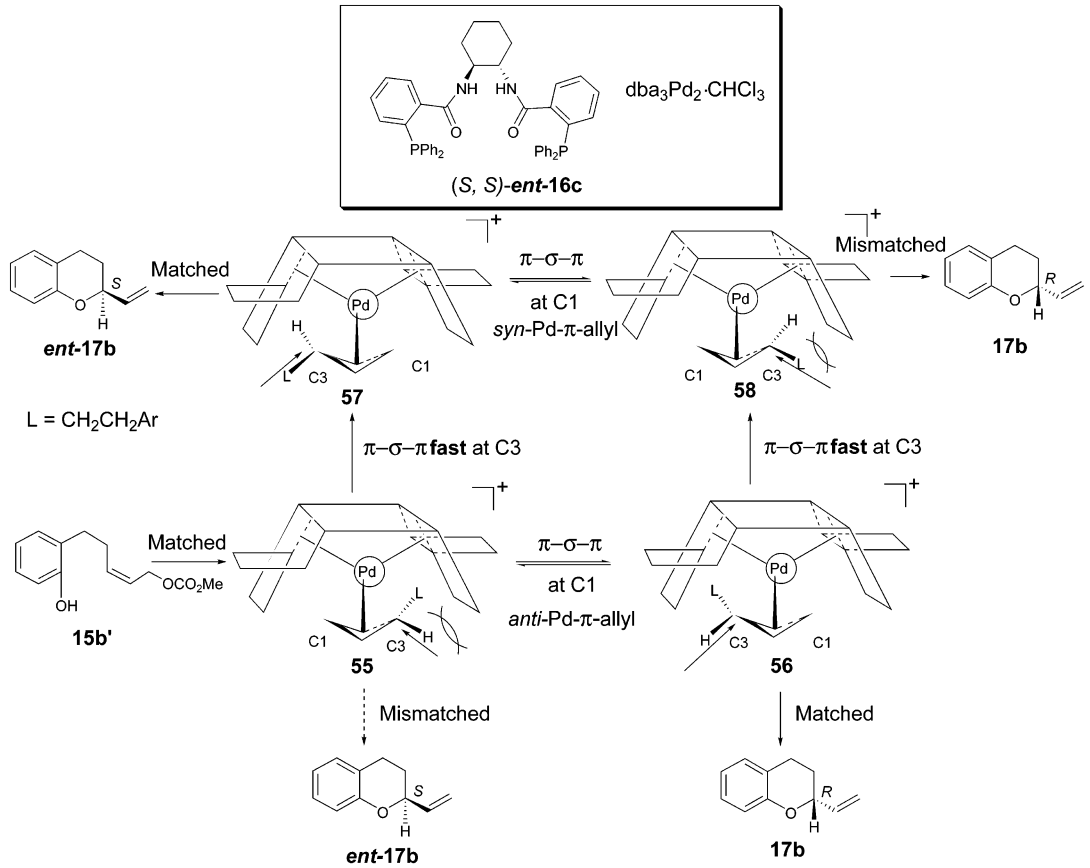
Rhododaurichromanic acid A (**8**) and daurichromenic acid (**7**) were both isolated from the leaves of *Rhododendron dauricum* by Kashiwada's group in 2001.[38] Daurichromenic acid demonstrated potent *anti*-HIV activity with an EC_{50} value of 0.00567 μg/mL and therapeutic index (TI) of 3710; whereas, rhododaurichromanic acid showed relatively potent anti-HIV activity with an EC_{50} value of 0.37 μg/mL and TI of 92.

The retrosynthetic analysis of rhododaurichromanic acid A (**8**) and daurichromenic acid (**7**) can be easily envisioned to be derived from chiral chroman **17c**, as shown in Scheme 16.[39] The key step involves a C−C bond formation between vinyl iodide **63** and vinyl chroman **17c** or its derivatives.

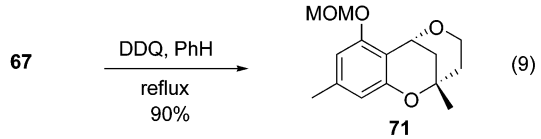
Various types of cross-coupling methods failed to unite the two building blocks, the chroman core **17c** with the side chain **63**. An alternative strategy involves the addition of side chain to chromen aldehyde **64**. Envisioning that a more easily cleavable protecting group for the phenol would be needed, the

(30) Trost, B. M.; Shen, H. C.; Surivet, J. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3943−3947.
(31) (a) Julia, M.; Righini-Tapie, A.; Verpeaux, J.-N. *Tetrahedron*, **1983**, *39*, 3283−3287. (b) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron. Lett*. **1976**, *17*, 3477−3478.
(32) Demuth, M.; Ritterskamp, P.; Weigt, E.; Schaffner, K. *J. Am. Chem. Soc.* **1986**, *108*, 4149−4154.
(33) Baudin, J. B.; Hareau, G.; Julia, S. H.; Lorne, R.; O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 356−357 and reference therein.
(34) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10 772−10 773.
(35) (a) Bates, R. W.; Gabel, C. J.; Ji, J.; Rama-Devi, T. *Tetrahedron*, **1995**, *51*, 8199−8212. (b) Trost, B. M.; Saulnier, M. G. *Tetrahedron Lett.* **1985**, *26*, 123−126.
(36) Dauben, W. G.; Cogen, J. M.; Behar, V. *Tetrahedron Lett*. **1990**, *31*, 3241−3244.
(37) Bu, X.; Zhao, L.; Li, Y. *Synthesis*, **1997**, *11*, 1246−1248.
(38) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559−1563.
(39) For the racemic total syntheses of rhododaurichromanic acids A and B, see: (a) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935−3938. (b) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481−4484.

Scheme 12. Working Model for the Pd-Catalyzed AAA Reaction of Cis Disubstituted Allyl Carbonate **15b′**



methyl ether was exchanged for MOM as shown in Scheme 17 steps a and b. The latter, **66**, was hydroborated to give a 3:1 regioisomeric mixture of alcohols, the major being the primary alcohol **67**. The MOM group may serve later as an ortho-directing group for metalation to introduce the carboxylate group to the aromatic ring. Interestingly, when alcohol **67** was submitted to DDQ oxidation, the reaction cleanly gave a tricyclic compound **71** (eq 9). Presumably the benzylic cation formed



(9)

in situ can be intramolecularly trapped by alcohol, which completely ruled out the potentially competitive elimination to afford the corresponding chromen. This observation demands the protection of the primary alcohol with TBDPS prior to DDQ oxidation. The resulting chroman silyl ether **68** underwent DDQ oxidation smoothly to give chromen **69**. The removal of the silyl group to alcohol **70** followed by oxidation using TPAP afforded chromenic aldehyde **64** (path b).

The subsequent vinyllithium addition to aldehyde **64** yielded allylic alcohol **72** as a mixture of diastereomers, both of which were converted to carbonate. The highly Pd-catalyzed regioselective reduction (2.5 mol % of π-allyl palladium chloride dimer, 10 mol % of phosphite **74** and 2 equiv of bulky L-selectride) of both diastereomers of carbonate **73** gave cleanly the desired product **62**, without scrambling or isomerization of the double bond.

The synthetic efforts toward the total synthesis of rhododaurichromanic acid A demonstrated the utility of the Pd-catalyzed AAA reaction of phenol allyl carbonates to form chiral chromans, and the subsequent oxidation leading to chiral chromens. A highly Pd-catalyzed regioselective allylic deoxygenation was developed to introduce the side chain to this natural product.

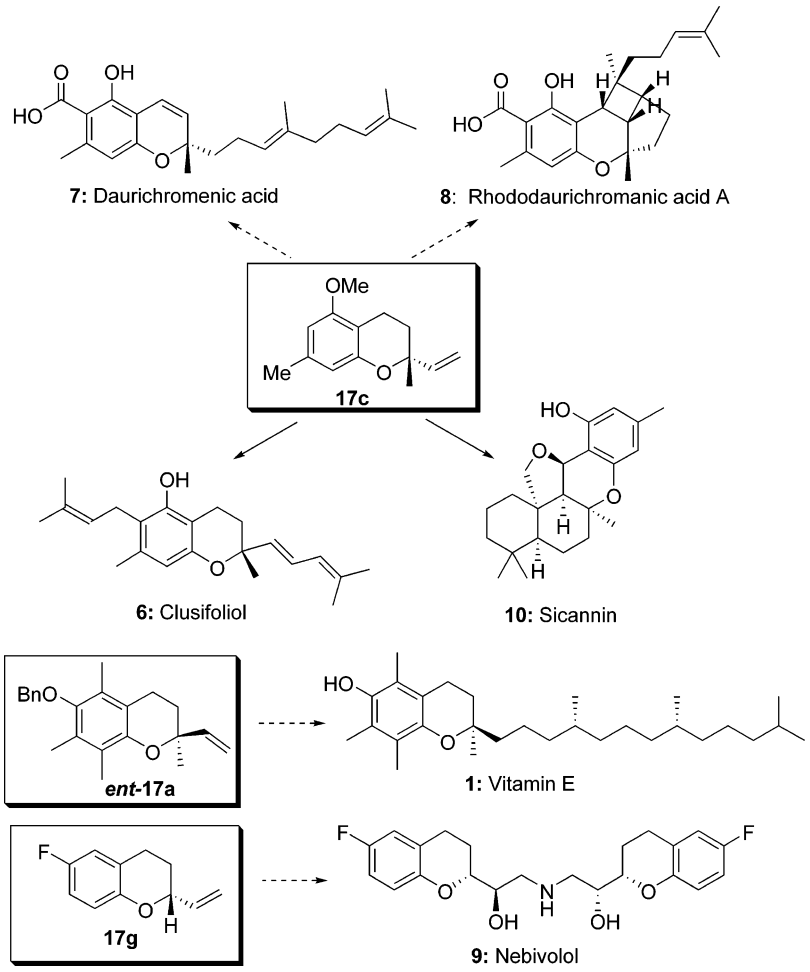
Experimental Section

General Procedure for Chroman Formation. To a degassed mixture of $Pd_2(dba)_3$·$CHCl_3$ (2 mol %) and (*R*, *R*) chiral ligand **16c** (6 mol %) or ***ent*-16c** was added dichloromethane. The solution was stirred for 10 min under argon to yield a yellow solution. To this solution was added acetic acid (1−1.2 equiv). After 5 min, a solution of carbonate in dichloromethane was added. The reaction mixture was stirred at room temperature for 1−10 h. The volatiles were removed under reduced pressure and the residue was purified directly over silica gel eluting with 1:11 of diethyl ether in petroleum ether to afford the chiral chroman.

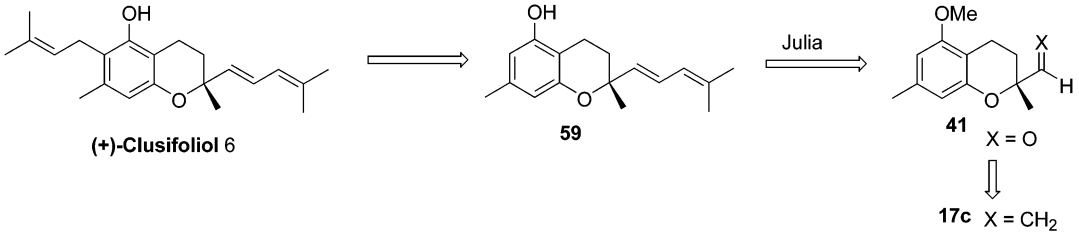
(*R*)-6-Benzyloxy-2,5,7,8-tetramethyl-2-vinyl-chroman (17a): A colorless oil. $[\alpha]_D = +49.4$ (*c* 1.20, CH_2Cl_2) (HPLC: Chiralpak OD, heptane/2-propanol); IR (neat): 1454, 1411, 1370, 1254, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70−7.33 (m, 5H), 5.86 (dd, J = 17.2, 10.8 Hz, 1H), 5.13 (dd, J = 17.2, 1.2 Hz, 1H), 5.03 (dd, J = 10.8, 1.2 Hz, 1H), 4.69 (s, 2H), 2.65−2.45 (m, 2H), 2.23 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 1.93 (m, 1H), 1.83 (m, 1H), 1.40 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.4, 147.9, 141.9, 138.1, 128.5, 128.0, 127.8, 127.7, 125.9, 122.6, 117.7, 113.3, 75.5, 74.6, 31.7, 26.9, 20.8, 12.8, 11.9, 11.8; Anal. Calcd for $C_{12}H_{14}O$: C, 81.95, H, 8.13. Found: C, 81.86; H, 8.26.

(*R*)-2-Vinylchromane (17b): a colorless oil. $[\alpha]_D = +80.3$ (*c* 0.27, CH_2Cl_2, 84% ee) (HPLC: Chiralpak OJ, 100% heptane); IR (neat):

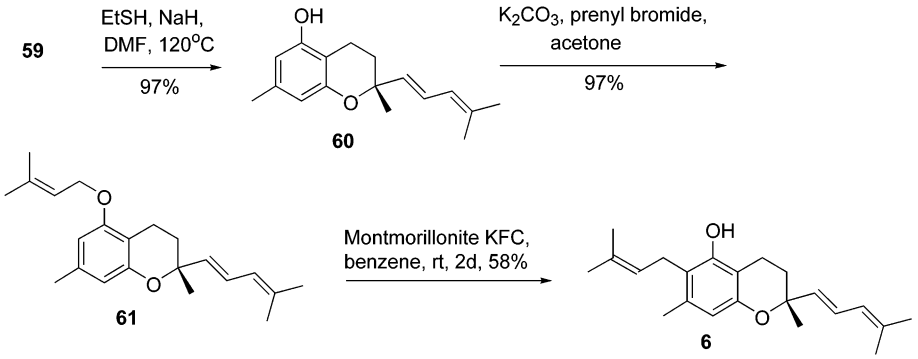
Scheme 13. Targets for the Application of Pd-Catalyzed AAA Reaction Leading to Chiral Chromans



Scheme 14. Retrosynthetic Analysis of the Total Synthesis of Clusifoliol **6**



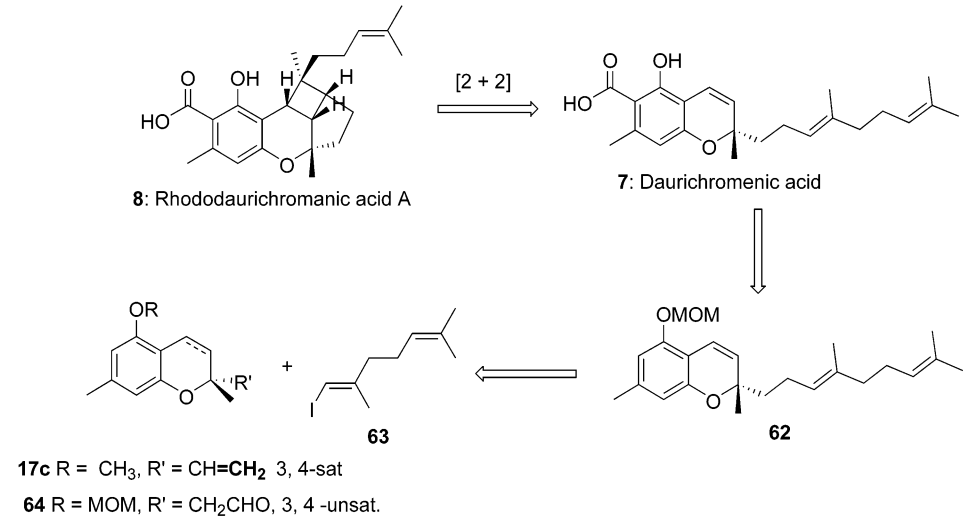
Scheme 15. Completion of Synthesis of Clusifoliol



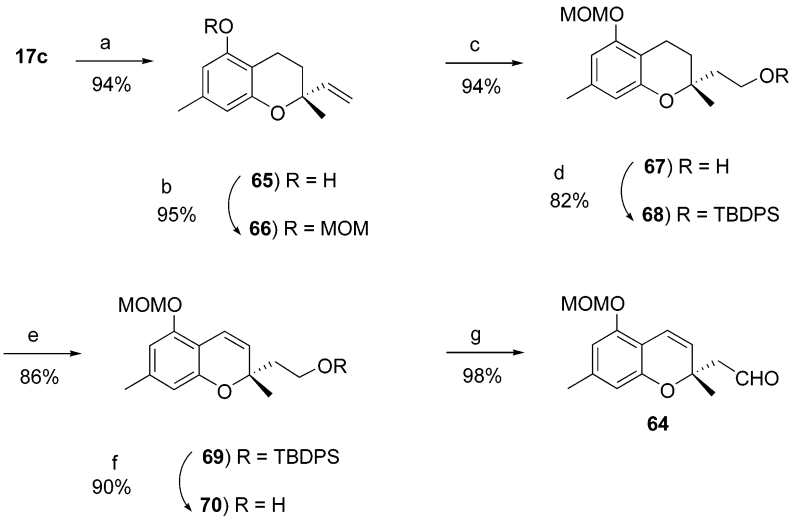
1581, 1488, 1458, 1233 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.86 (m, 1 H), 2.08 (m, 1 H), 2.86−2.73 (m, 2 H), 4.55 (m, 1 H), 5.24 (ddd, J = 10.5, 1.2, 1.2 Hz, 1 H), 5.39 (ddd, J = 17.4, 1.5, 1.5 Hz, 1 H), 6.00 (ddd, J = 17.4, 10.5, 5.4 Hz, 1 H), 6.84 (m, 2 H), 7.09 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.1, 137.5, 129.5, 127.3, 121.7, 120.1, 116.8, 116.2, 76.1, 27.4, 24.1, 20.4; HRMS Calcd for $C_{11}H_{12}O$ $[M]^+$: 160.0888; Found: 160.0888.

(*R*)-5-Methoxy-2,7-dimethyl-2-vinyl-chroman (17c): $[\alpha] = +54.0$ (c 2.18, $CHCl_3$), 97% ee; IR (neat): 2936, 1618, 1586, 1139 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.40 (s, 1H), 6.25 (s, 1H), 5.85 (dd, J =

Scheme 16. Retrosynthetic Analysis of Rhododaurichromanic Acid A (**8**) and Daurichromenic Acid (**7**)

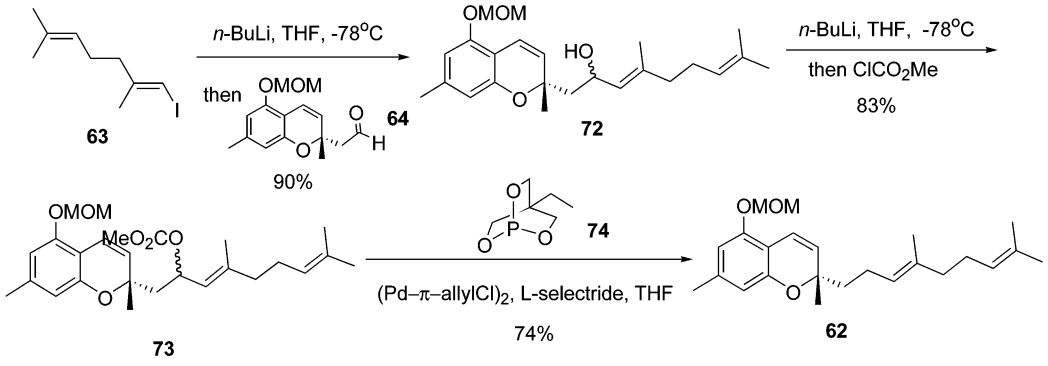


Scheme 17. Synthesis of Chromen Aldehyde **64**[a]



[a] Reagents and conditions: (a) C_2H_5SH, NaH, DMF, 120 °C. (b) *n*-C_4H_9Li, MOM-Cl, THF, 0 °C to room temperature. (c) BH_3·THF, THF, 0 °C to room temperature then H_2O_2, NaOH, rt to 50 °C. (d) TBDPS−Cl, DMAP, CH_2Cl_2, rt. (e) DDQ, PhH, reflux. (f) TBAF, THF, 0 °C. (g) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt.

Scheme 18. Synthesis of Chromene MOM Ether **62**



10.7, 17.3 Hz, 1H), 5.20 (dd, J = 1.2, 17.3 Hz, 1H), 5.07 (dd, J = 1.2, 10.7 Hz, 1H), 3.81 (s, 3H), 2.68 (td, J = 5.6, 16.8 Hz, 1H), 2.47 (ddd, J = 6.1, 9.8, 16.8 Hz, 1H), 2.31 (s, 3H), 1.93 (dd, J = 4.8, 5.8, 13.4 Hz, 1H), 1.79 (ddd, J = 5.6, 9.8, 13.4 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 154.3, 141.3, 136.9, 113.6, 110.0, 107.2, 102.6,76.1, 55.2, 31.0, 26.7, 21.6, 16.7. HRMS: Calcd for $C_{14}H_{18}O_2$ [M^+]: 218.1307. Found: 218.1303. Chromatographic separation (GC, Cyclosil B): T oven = 160 °C, t_R (*S*, minor) = 18.5 min, t_R (*R*, major) = 18.9 min.

(*R*)-2-Methyl-2-vinylchroman (17d): a colorless oil. $[\alpha]_D = +48.1$ (*c* 0.55, $CDCl_3$, 95% ee); IR (neat): 2932w, 2850m, 1649w, 1494s, 1434m, 1259m, 1218s, 1198m, 1139m, 1045m, 999m, 930m, 872w,

847w, 810m, 792w cm^{-1}; ^1H NMR (500 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 (td, J = 1.0, 7.5 Hz, 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), 2.71 (m, 2H), 1.93 (m, 1H), 1.83 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 141.2, 129.3, 127.3, 121.3, 119.7, 116.8, 113.9, 76.6, 31.7, 29.1, 27.1; Anal. Calcd for $C_{12}H_{14}O$: C, 82.72, H, 8.10. Found: C, 82.50; H, 8.29. Chromatographic separation (GC, Cyclosil B): T oven = 120 °C, $t_R(S)$ = 21.6 min, t_R (R) = 22.7 min.

(*R*)-6-Methoxy-2-methyl-2-vinylchroman (17e): $[\alpha]_D$ = +60.0 (c 1.0, $CDCl_3$, 98% ee). IR (neat): 2926s, 2854s, 1495s, 1465w, 1429w, 1374w, 1228m, 1094w, 1044w, 923w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (d, J = 9.0 Hz, 1H), 6.71 (dd, J = 3.0, 9.0 Hz, 1H), 6.59 (d, J = 3.0 Hz, 1H), 5.86 (dd, J = 11.0, 17.5 Hz, 1H), 5.20 (dd, J = 1.0, 17.5 Hz, 1H), 3.76 (s, 3H), 2.71 (m, 2H), 1.93 (m, 1H), 1.84 (m, 1H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 148.0, 141.4, 121.8, 117.3, 113.9, 113.8, 113.4, 76.3, 55.6, 31.7, 29.7, 27.1. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44, H, 7.90. Found: C, 76.19; H, 8.08. Chromatographic separation (GC, Cyclosil B): T oven = 150 °C, t_R (S, minor) = 20.5 min, t_R (R, major) = 20.8 min.

(*R*)-5,8-Dimethoxy-2,6,7-trimethyl-2-vinylchroman (17f): a colorless oil. IR (neat): 2935, 1463, 1414, 1329, 1259, 1132, 1088, 1027, 970, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.89 (dd, J = 11, 17 Hz, 1H), 5.21 (d, J = 17 Hz, 1H), 5.07 (d, J = 11 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 2.79−2.52 (m, 2H), 2.17 (s, 3H), 2.12 (s, 3H), 1.96−1.72 (m, 2H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.5, 145.2, 142.7, 141.4, 128.5, 120.1, 113.5, 113.3, 76.3, 60.1, 31.2, 26.8, 17.4, 12.2, 12.0; HRMS Calcd for $C_{16}H_{22}O_3$ [M^+]: 262.1569; Found: 262.1562; Chromatographic separation (GC, Cyclosil B): T oven = 170 °C, t_R (S, minor) = 32.4 min, t_R (R, major) = 31.6 min.

(*R*)-6-Fluoro-2-vinylchroman (17g): $[\alpha]_D$ = +62.4 (c 0.35, Et_2O, 80% ee); IR (neat): 2926s, 2853m, 1493s, 1434w, 1258m, 1217s, 1138w, 1044w, 997w, 929m, 871w, 809m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (m, 3H), 5.96 (ddd, J = 5.6, 10.4, 17.2 Hz, 1H), 5.36 (dt, J = 1.2, 17.2 Hz, 1H), 5.23 (dt, J = 1.2, 10.4 Hz, 1H), 4.51 (m, 1H), 2.84 (ddd, J = 6.4, 10.0, 16.8 Hz, 1H), 2.73 (dt, J = 4.8, 16.4 Hz, 1H), 2.05 (m, 1H), 1.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.9, 150.7, 137.6, 123.0 (d, J = 7.6 Hz), 117.8 (d, J = 8.1 Hz), 116.7, 115.5 (d, J = 9.9 Hz), 114.2 (d, J = 22.9 Hz), 76.3, 27.4, 24.6; HRMS Calcd for $C_{11}H_{11}OF$ [M^+]: 178.0794; Found: 178.0791; AD column (Flow rate: 0.4 mL/min, S isomer: 15.80 min, R isomer: 16.68 min).

(*R*)-6-Methyl-2-vinylchromane (17h): a clear oil (96%). $[\alpha]_D$ = +76.8 (c 0.69, $CHCl_3$, **17h**), 87% ee (HPLC: Chiralpak OJ, 99.7% heptane/0.3% i-PrOH). IR (neat): 1498, 1243, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.84 (m, 1 H), 2.03 (m, 1 H), 2.24 (s, 3 H), 2.82−2.69 (m, 2 H), 4.51 (m, 1 H), 5.22 (ddd, J = 10.5, 1.5, 1.5 Hz, 1 H), 5.39 (ddd, J = 17.4, 1.5, 1.5 Hz, 1 H), 5.97 (ddd, J = 17.4, 10.5, 5.4 Hz, 1 H), 6.74 (m, 2 H), 6.87 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.2, 137.6, 129.8, 127.9, 127.3, 121.4, 116.5, 116.1, 76.0, 27.5, 24.1, 20.4; HRMS Calcd for $C_{12}H_{14}O$ [M^+]: 174.1044; Found: 174.1047.

(*R*)-6-Methoxy-2-vinylchromane (17i): a colorless oil. $[\alpha]_D$ = +74.6 (c 2.19, $CHCl_3$); 89% ee (HPLC: Chiralpak OJ, 99.7% heptane/0.3% i-PrOH); IR (neat): 1496, 1425, 1269, 1269, 1221, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.82 (m, 1 H), 2.03 (m, 1 H), 2.72 (m, 1 H), 2.81 (m, 2 H), 3.74 (s, 3 H), 4.49 (m, 1 H), 5.22 (ddd, J = 10.5, 1.5, 1.5 Hz, 1 H), 5.36 (ddd, J = 17.4, 1.5, 1.5 Hz, 1 H), 5.98 (ddd, J = 17.4, 10.5, 5.4 Hz, 1 H), 6.58 (d, J = 3.0 Hz, 1 H), 6.67 (m, 1 H), 6.78 (d, J = 9.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2, 148.5, 137.6, 122.3, 117.3, 116.2, 113.9, 113.3, 76.0, 55.7, 27.5, 24.5; HRMS Calcd for $C_{12}H_{14}O$ [M^+]: 174.1045; Found: 174.1040.

(*R*)-8-Methoxy-6-methyl-2-vinylchromane (17j): a white solid (82%); mp. 35−36 °C; $[\alpha]_D$ = −62.3 (c 0.21, $CHCl_3$), 82% ee (HPLC: Chiralpak OJ, 99.7% heptane/0.3% i-PrOH). IR (neat) 1592, 1554, 1493, 1275, 1228 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.86 (m, 1 H), 2.05 (m, 1 H), 2.26 (s, 3 H), 2.79−2.70 (m, 2 H), 3.84 (s, 3 H), 4.62 (m, 1 H), 5.21 (ddd, J = 13.0, 2.0, 2.0 Hz, 1 H), 5.35 (ddd, J = 21.5, 1.5, 1.5 Hz, 1 H), 6.01 (m, 1 H), 6.74 (m, 2 H), 6.47 (s, 1 H), 6.53 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.0, 141.4, 137.3, 128.9, 122.0, 121.4, 116.4, 110.1, 76.2, 55.8, 27.0, 23.6, 20.0; HRMS Calcd for $C_{13}H_{16}O_2$ [M^+]: 204.1150; Found: 204.1045.

2-(2-Iodoethyl)-1,3-dimethoxy-5-methylbenzene (29). To alcohol **28** (35 mg, 0.18 mmol) in THF (2 mL) at 0 °C were added triphenylphosphine (56 mg, 0.21 mmol), imidazole (16 mg, 0.24 mmol) and iodine (59 mg, 0.23 mmol). The mixture was warmed to room temperature and stirred for 1 h. The mixture was washed with sodium thiosulfate solution (1 mL), and the aqueous layer was extracted with diethyl ether (2 × 15 mL). The combined organic layers were concentrated and chromatographed eluting with 2% diethyl ether in petroleum ether to afford iodide **29** (53 mg, 0.17 mmol, 97%).

IR (neat): 2934w, 2936w, 1608m, 1587s, 1463m, 1115m, 1303w, 1239m, 1117s, 1086m, 970w, 814m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (s, 2H), 3.77 (s, 6H), 3.20 (s, 4H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 138.1, 114.3, 100.5, 55.5, 27.9, 22.1, 4.7. Anal. Calcd for $C_{11}H_{15}O_2$: C, 43.16; H, 4.94. Found: C, 43.32; H, 5.09. HRMS: Calcd for $C_{11}H_{15}O_2I$: 306.0117. Found: 306.0118.

***Z*-2-(5-Hydroxy-3-methyl-pent-3-enyl)-3-methoxy-5-methyl-phenol (31).** To alkyl iodide **29** (75 mg, 0.25 mmol) and zinc chloride (55 mg, 0.41 mmol) was added THF (2 mL) to afford a colorless solution. To this solution at −78 °C was added *tert*-butyllithium (0.33 mL, 0.50 mmol, 1.5 M in pentane). After 30 min, this solution was warmed to RT and stirred for 3 h. In another flask containing Pd(dppf)Cl_2 (7.5 mg, 0.01 mmol) and 0.5 mL of THF was added *n*-butyllithium (8 uL, 0.02 mmol, 2.5 M in hexane) to result a dark purple red solution. To this solution was added vinyl iodide **30** (75 mg, 0.25 mmol) in 1 mL of THF. This solution was then transferred to the first flask containing alkyl zinc species via cannula at room temperature. The solution immediately turned brownish black but resumed the reddish color in 5 min. The solution was stirred overnight. Without workup, the mixture was purified eluting with 5% diethyl ether in petroleum ether to afford a colorless oil, which was dissolved in THF (2 mL). To this solution was added TBAF (0.16 mL, 0.16 mmol, 1 M in THF). After 2 h, without workup this mixture was directly chromatographed eluting with 5% to 50% diethyl ether in petroleum ether to afford allylic alcohol (20 mg, 0.08 mmol, 32% over 2 steps) as a colorless oil. To the resulting allylic alcohol was added lithium *n*-propyl thiolate (0.8 mL, 0.4 mmol, 0.5 M in HMPA). The resulting orange mixture was heated at 120 °C overnight. Without workup, the mixture was chromatographed eluting with 5% to 60% diethyl ether in petroleum ether to afford allylic alcohol **31** (15 mg, 0.064 mmol, 80%, 26% over three steps) as a colorless oil.

IR (neat): 3320, 2936, 1660, 1615, 1594, 1514, 1463, 1416, 1378, 1319, 1227, 1151, 1076, 1034, 978 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.50 (s, 1H), 6.28 (s, 2H), 5.46 (t, J = 7.5 Hz, 1H), 3.98 (t, J = 6.0 Hz, 2H), 3.79 (s, 3H), 2.75 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.8 Hz, 2H), 2.25 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 154.7, 143.0, 137.2, 123.2, 113.0, 109.1, 103.7, 58.8, 55.5, 31.2, 23.9, 22.4, 21.5. HRMS: Calcd for $C_{17}H_{24}O_4$ [M^+]: 292.1674. Found: 292.1675.

5-(2,6-Dimethoxy-4-methylphenyl)-2-methyl-pent-2-en-1-ol (33). To alkyl iodide **29** (124 mg, 0.405 mmol) and zinc chloride (110 mg, 0.81 mmol) was added THF (3 mL) to afford a colorless solution. To this solution at −78 °C was added *tert*-butyllithium (0.59 mL, 0.89 mmol, 1.5 M in pentane). After 30 min, this solution was warmed to RT and stirred for 3 h. In another flask containing Pd(dppf)Cl_2 (15 mg, 0.02 mmol) and 0.5 mL of THF was added *n*-butyllithium (16 uL, 0.04 mmol, 2.5 M in hexane) to result a dark purple red solution. To this solution was added vinyl iodide **32** (151 mg, 0.49 mmol) in 1.5 mL of THF. This solution was then transferred to the first flask containing alkyl zinc species via cannula at room temperature. The solution immediately turned brownish black but resumed the reddish color in 5 min. The solution was stirred overnight. Without workup,

the mixture was purified eluting with 5% diethyl ether in petroleum ether to afford a colorless oil, which was taken up in 2 mL of THF. To this solution was added TBAF (1.5 mL, 1.5 mmol, 1 M in THF). After 1 h, without workup, the mixture was purified by column eluting with 5% to 20% diethyl ether in petroleum ether to afford **33** (78 mg, 0.312 mmol, 77%) as a colorless oil.

IR (neat): 3384b, 2935s, 2850s, 1668w, 1609s, 1588s, 1464s, 1416s, 1381m, 1313s, 1241s, 1185s, 1168sa, 1124s, 1005m, 970m, 813m, 668m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.36 (s, 2H), 5.38 (t, J = 6.9 Hz, 1H), 4.12 (d, J = 7.2 Hz, 2H), 3.79 (s, 6H), 2.73 (t, J = 8.4 Hz, 2H), 2.33 (s, 3H), 2.15 (t, J = 8.4 Hz, 2H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 140.8, 136.7, 122.8, 115.5, 59.3, 55.6, 38.9, 21.9, 21.3, 16.2. HRMS: Calcd for $C_{15}H_{22}O_3$: 250.1569. Found: 250.1566.

5-(2-Hydroxy-6-methoxy-4-methylphenyl)-2-methyl-pent-2-en-1-ol (34). To allylic alcohol **33** (50 mg, 0.2 mmol) was added *n*-propyllithium thiolate (2 mL, 1.0 mmol, 0.5 M in HMPA). The resulting orange solution was heated at 120 °C for overnight. Without workup, the mixture was purified by flash chromatography eluting with 5% to 60% diethyl ether in petroleum ether to afford allylic alcohol **34** (41 mg, 0.17 mmol, 87%) as a white solid.

mp: 92−94 °C; IR (neat): 3329, 2935, 1672, 1616, 1595, 1463, 1418, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 6.31 (s, 1H), 6.28 (s, 1H), 5.42 (qt, J = 1.2, 5.8 Hz, 1H), 5.37 (s, 1H), 4.16 (br t, J = 5.8 Hz, 2H), 3.80 (s, 3H), 2.75 (dd, J = 7.6 Hz, 2H), 2.28 (s, 3H), 2.21 (dd, J = 8.3 Hz, 2H), 1.80 (s, 1H), 1.77 (d, J = 1.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.2, 1154.2, 140.9, 136.9, 122.8, 113.4, 108.9, 104.0, 59.3, 55.5, 38.6, 21.6, 21.5, 16.4. HRMS: Calcd for $C_{14}H_{19}O_2$ [M^+-OH]: 219.1385. Found: 219.1343.

2-But-3-ynyl-4-fluoro-phenol (39). To a solution of aldehyde **37** (1.72 g, 6.10 mmol) in methanol (20 mL) at room temperature were added potassium carbonate (1.68 g, 12.2 mmol) a solution of then acetyldiazophosphonate (1.41 g, 7.32 mmol) in methanol (10 mL). The solution was stirred at room temperature overnight. The mixture was filtered through a pad of diatomaceous earth and washed with diethyl ether (50 mL). The volatile fraction was removed and the residue was chromatographed eluting with 5% to 20% diethyl ether in petroleum ether to afford alkyne **39** (0.85 g, 5.18 mmol, 85%) as a colorless oil.

IR (neat): 3504b, 3301s, 2937m, 2117w, 1507s, 1436s, 1329w, 1269m, 1176s, 1092m, 870m, 810m, 764m, 711m, 639s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.78 (dd, J = 3.0, 9.0 Hz, 1H), 6.72 (td, J = 3.0, 8.4 Hz, 1H), 6.60 (dd, J = 4.8, 8.7 Hz, 1H), 5.95 (bs, 1H), 2.74 (d, J = 7.2 Hz, 2H), 2.41 (td, J = 2.7, 7.2 Hz, 2H), 1.92 (t, J = 2.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 155.2, 128.5 (d, J = 7.3 Hz), 116.7 (d, J = 23.1 Hz), 116.1 (d, J = 8.5 Hz), 113.6 (d, J = 23.1 Hz), 84.0, 69.2, 29.5, 25.5. HRMS: Calcd for $C_{10}H_9FO$: 164.0637. Found: 164.0638.

***Z*-5-[2-(*tert*-Butyldimethylsilyloxy)-5-fluorophenyl]-pent-2-en-1-ol (40).** To alkyne phenol **39** (0.81 g, 4.94 mmol) in 5 mL of dichloromethane at room temperature were added imidazole (0.89 g, 5.93 mmol) and TBSCl (673 mg, 9.88 mmol). The reaction mixture was stirred overnight and directly chromatographed eluting with 5% diethyl ether in petroleum ether to afford silyl phenol ether (1.14 g, 4.10 mmol, 83%). To a solution of the silyl phenol ether (1.14 g, 4.10 mmol) in THF (15 mL) at −78 °C was added *n*-butyllithium (3.1 mL, 4.92 mmol, 1.6 M in hexane). After 30 min at this temperature, to this dark solution was added paraformaldehyde (185 mg, 6.15 mmol, dried in a vacuum overnight). The mixture was slowly warmed to room temperature over 1 h and stirred at room temperature for an additional 1 h. The mixture was concentrated and directly chromatographed eluting with 5% to 20% diethyl ether in petroleum ether to afford propargyl alcohol (1.06 g, 3.44 mmol, 84%). To a solution of propargyl alcohol (554 mg, 1.80 mmol) in methanol (5 mL) was added Lindlar catalyst (100 mg). This mixture was stirred under 1 atm of hydrogen at room temperature for 18 h then chromatographed directly eluting with 5% to 25% diethyl ether in petroleum ether to afford cis allylic alcohol **40** (450 mg, 1.45 mmol, 81%) as a yellow oil.

IR (neat): 3374b, 2959s, 2933s, 2860s, 1614w, 1495s, 1423m, 1362w, 1257s, 1214s, 1145m, 1022m, 899m, 840m, 804m, 780m, 692w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.84 (dd, J = 3.5, 9.5 Hz, 1H), 6.79 (td, J = 3.0, 8.0 Hz, 1H), 6.71 (dd, J = 5.0, 9.0 Hz, 1H), 4.08 (d, J = 6.5 Hz, 2H), 2.65 (t, J = 7.0 Hz, 2H), 2.38 (q, J = 7.5 Hz, 2H), 1.43 (bs, 1H), 1.04 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 156.0, 149.4, 134.5 (d, J = 7.1 Hz), 131.5, 129.3, 118.9 (d, J = 8.0 Hz), 116.6 (d, J = 22.5 Hz), 112.9 (d, J = 22.4 Hz), 58.4, 30.5, 27.4, 25.7, 18.1, −4.28. HRMS: Calcd for $C_{17}H_{27}O_2FSi$ (M^+): 310.1764. Found: 310.1783.

(*R*)-5-Methoxy-2,7-dimethyl-chroman-2-carboxyaldehyde (41). To a solution of (*R*)-5-methoxy-2.7-dimethyl-2-vinyl-chroman **17c** (0.20 g, 0.92 mmol) in 3.5 mL of dichloromethane was added *N*-methylmorphonline-*N*-oxide (0.3 g, 2.56 mmol) and aqueous osmium tetraoxide (0.27 mL, 4% in water, 0.043 mmol). The solution was stirred for 5 h at room temperature and diluted with water (10 mL) and dichloromethane (20 mL). The organic layer was dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed with 1:1 to 1:5 of petroleum ether in diethyl ether. The resulting brown oil (contaminated with osmium residue) was resuspended in acetone (4 mL) and a solution of sodium periodate (0.4 g, 1.87 mmol) in water (1 mL) was added. After a white precipitate was formed the reaction mixture was stirred at room temperature for additional 20 min. The mixture was filtered through a pad of diatomaceous earth, and the filtrate was partitioned between water (5 mL) and dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with brine (20 mL) and dried over magnesium sulfate. The residue was separated by flash chromatography eluting with 5% to 25% diethyl ether in petroleum ether to afford aldehyde **41** as a colorless oil (0.19 g, 0.86 mmol, 94%).

$[\alpha]_D$ = +16.3 (*c* 0.47, Et_2O); IR (film): 2935, 1738, 1619, 1587, 1463, 1146, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.65 (s, 1H), 6.44 (s, 1H), 6.27 (s, 1H), 3.78 (s, 3H), 2.64 (td, J = 6.4, 17.3 Hz, 1H), 2.47 (ddd, J = 6.6, 9.2, 16.1 Hz, 1H), 2.30 (s, 3H), 2.22 (m, 1H), 1.77 (ddd, J = 6.6, 9.5, 15.8 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 157.5, 153.5, 137.4, 110.0, 107.1, 103.4, 80.0, 55.3, 27.2, 21.5, 21.2, 16.1. HRMS: Calcd for $C_{13}H_{16}O_3$: 220.1099. Found: 220.1093.

(*R*)-5-Methoxy-2,7-dimethyl-2-(4-methyl-penta-1,3-dienyl)-chroman (59). Method A. To a solution of prenyl phenyl sulfone (0.38 g, 1.82 mmol) in distilled THF (4 mL) at −78 °C was added potassium bis(trimethylsilyl)amide (1.25 mL, 2.0 mmol, 1.6 M in hexanes) resulting in formation of an orange solution was formed. After 30 min, to the above solution was slowly added (*R*)-5-methoxy-2,7-dimethyl-chroman-2-carbaldehyde (0.40 g, 1.82 mmol) in 3 mL of THF (including rinsing solvent). The reaction solution turned light yellow from orange. The reaction mixture was stirred at −78 °C for 1 h and quenched with 8 mL of water. The aqueous fraction was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with magnesium sulfate and concentrated in vacuo before silica gel chromatography eluting with 5% to 50% diethyl ether in petroleum ether to afford the sulfone alcohol. The sulfone alcohol was then diluted with 10 mL of dicholomethane and treated with pyridine (3.2 mL) and acetic anhydride (1.3 mL) followed by a few crystals of DMAP at room temperature. After being stirred overnight, the solution was diluted with 200 mL of diethyl ether and washed with 1N HCl (3 × 30 mL) and brine. The organic fraction was then dried with magnesium sulfate and concentrated. The residue was chromatographed eluting with 5−40% diethyl ether in petroleum ether to afford the corresponding acetate. The acetate was then dissolved in 20 mL of distilled methanol, and to this solution was added sodium bibasic phosphate (2 g) and sodium amalgam (1.5 g, amalgam in mercury) at 0 °C under argon (be careful about the pressure build-up). The solution was stirred for 30 min and filtered through a diatomaceous earth pad on a filtration funnel. The

filtrate was concentrated in vacuo and the residue was chromatographed eluting with 5% to 20% diethyl ether in petroleum ether to afford 5-methoxy-2,7-dimethyl-2-(4-methyl-penta-1,3-dienyl)-chroman **59** (243 mg, 0.89 mmol, 49%, *E/Z* = 15:1 to 9:1) as a light yellow oil.

Method B.[35] To lithium bis(trimethylsilyl)amide (22 mg, 0.13 mmol) was added 5-prenylsulfonyl-1-phenyltetrazole (30 mg, 0.11 mmol) in 0.5 mL of a mixture of DMF and HMPA (4:1) at −78 °C resulting in a yellow solution. Immediately to this mixture was added a solution of(*R*)-5-methoxy-2,7-dimethylchroman-2-carbaldehyde (10 mg, 0.045 mmol) in 0.5 mL of a mixture of DMF and HMPA (4:1). The resulting solution was slowly warmed to room temperature over 2 h. Without workup, this mixture was directly chromatographed eluting with 2−5% diethyl ether in petroleum ether to afford desired 5-methoxy-2,7-dimethyl-2-(4-methyl-penta-1,3-dienyl)-chroman **59** (12 mg, 0.044 mmol, 98%, *E/Z* = 20:1) as a light yellow oil.

$[\alpha]_D$ = -5.0 (*c* 1.27, $CHCl_3$); IR (film): 2929, 1618, 1585, 1352, 1115 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.42 (dd, *J* = 10.8, 15.1 Hz, 1H), 6.39 (s, 1H), 6.24 (s, 1H), 5.79 (d, *J* = 10.8 Hz, 1H), 5.62 (d, *J* = 15.1 Hz, 1H), 3.81 (s, 3H), 2.65 (td, *J* = 5.8, 16.8 Hz, 1H), 2.51 (ddd, *J* = 6.1, 9.3, 15.6 Hz, 1H), 2.30 (s, 3H), 1.93 (td, *J* = 5.8, 13.4 Hz, 1H), 1.82 (m, 1H), 1.76 (s, 3H), 1.71 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4, 154.3, 136.8, 135.3, 134.0, 125.2, 124.5, 110.1, 107.3, 102.5, 75.9, 55.2, 31.8, 26.7, 25.9, 21.6, 18.2, 16.8. HRMS: Calcd for $C_{18}H_{24}O_2$: 272.1776. Found: 272.1776.

(*R*)-2,7-Dimethyl-2-(4-methylpenta-1,3-dienyl)-chroman-5-ol (60). To a flask containing 3 mL of anhydrous DMF (from a newly opened bottle, quality is important) at 0 °C was added sodium hydride (153 mg, 60%) followed by the addition of ethanethiol (0.26 mL). The solution was warmed to room temperature and stirred for 30 min before the addition of diene **59** (119 mg, 0.44 mmol) in 4 mL of anhydrous DMF. The solution was heated at 120 °C for 18 h. To the mixture was added 20 mL of water and extracted with diethyl ether (3 × 50 mL). The combined organic fractions were dried with magnesium sulfate and concentrated in vacuo. The residue was chromatographed eluting with 5% to 20% diethyl ether to afford phenol **60** (110 mg, 0.43 mmol, 97%) as a pale yellow oil.

$[\alpha]_D$ = −10.1 (*c* 1.2, $CHCl_3$); IR (film): 3419b, 2925s, 2857m, 1627m, 1586s, 1516w, 1436s, 1415s, 1352m, 1312m, 1274s, 1254s, 1130m, 1088s, 1051m, 996m, 872w, 822w, 739w cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.29 (dd, *J* = 10.8, 15.3 Hz, 1H), 6.24 (s, 1H), 5.67 (d, *J* = 10.8 Hz, 1H), 5.50 (d, *J* = 15.6 Hz, 1H), 4.48 (s, 1H), 2.46 (m, 1H), 2.13 (s, 3H), 1.80 (m, 2H), 1.65 (s, 3H), 1.59 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 153.4, 137.3, 135.6, 133.7, 125.5, 124.4, 110.1, 107.2, 105.7, 76.0, 31.7, 29.7, 26.9, 25.9, 21.2, 18.3, 16.7. HRMS: Calcd for $C_{17}H_{22}O_2$: 258.1620. Found: 258.1618.

(*R*)-2,7-Dimethyl-5-(3-methyl-but-2-enyloxy)-2-(4-methylpenta-1,3-dienyl)-chroman (61). To a solution of phenol **60** (20 mg, 0.078 mmol) in acetone (2 mL) were added potassium carbonate (50 mg, 0.36 mmol) and 4-bromo-2-methyl-2-butene (26 mg, 20 μL, 0.17 mmol). The reaction mixture was heacted under reflux for 2 h. Without workup, the solution was chromatographed eluting with 5% to 10% diethyl ether in petroleum ether to afford ether **61** (25 mg, 0.077 mmol, 99%) as a colorless oil.

$[\alpha]_D$ = −15.7 (*c* 1.1, $CDCl_3$, 29.4 °C) IR (film): 2964s, 2926s, 2857s, 1617m, 1585s, 1434s, 1414s, 1381s, 1352m, 1259s, 1235m, 1097s, 1013m, 959w, 810m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.38 (dd, *J* = 11.0, 15.0 Hz, 1H), 6.35 (s, 1H), 6.23 (s, 1H), 5.76 (dd, *J* = 1.0, 11.0 Hz, 1H), 5.60 (d, *J* = 16.0 Hz, 1H), 5.48 (m, 1H), 4.47 (d, *J* = 6.5 Hz, 2H), 2.63 (dt, *J* = 5.5, 11.0 Hz, 1H), 2.52 (ddd, *J* = 6.0, 9.0, 11.0 Hz, 1H), 2.27 (s, 3H), 1.89 (m, 1H), 1.79 (m, 1H), 1.78 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9, 154.4, 137.0, 136.7, 135.3, 134.2, 125.2, 124.6, 123.9, 120.3, 110.0, 103.8, 75.9, 64.9, 31.9, 26.8, 25.9, 25.8, 21.6, 18.3, 18.2, 17.0. HRMS: Calcd for $C_{22}H_{30}O_2$: 326.2246. Found: 326.2247.

Clusifoliol (6).[36] To prenyl ether **61** (12 mg, 0.037 mmol) in 1.5 mL of distilled benzene was added montmorillonite KFC (24 mg, in two portions, Aldrich) at room temperature. The reaction mixture was stirred at room temperature for 2 d. Without workup, the mixture was purified by flash chromatography eluting with 5% diethyl ether in petroleum ether to afford the desired natural product clusifoliol (3,4-dihydro-2,7-dimethyl-6-(3-methyl-2-butenyl)-2-(4-methyl-1,3-pentadienyl)-2*H*-1-benzo-pyran-5-ol) **6** (7 mg, 0.021 mmol, 58%) as a colorless oil which turned pale brown over 1 d in freezer.

$[\alpha]_D$ = +0.68 (*c* 0.9, EtOH); $[\alpha]_D$ = +0.62 (*c* 0.7, EtOH, authentic sample); IR (film): 3420, 2925, 2855, 1660, 1619, 1592, 1446, 1417, 1259, 1101, 1071, 985, 961 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ (Experimental value) 6.33 (dd, *J* = 15.0, 11.0 Hz, 1H), 6.17 (s, 1H), 5.76 (d, *J* = 11.0 Hz, 1H), 5.55 (d, *J* = 15.5 Hz, 1H), 5.14 (tm, *J* = 7.0 Hz, 1H), 4.46 (bs, 1H), 3.36 (dd, *J* = 7.0, 14.0 Hz, 1H), 3.25 (dd, *J* = 7.0, 14.5 Hz, 1H), 2.62 (ddd, *J* = 5.5, 5.5, 16.5 Hz, 1H), 2.49 (ddd, *J* = 6.0, 9.5, 16.5 Hz, 1H), 2.21 (s, 3H), 1.91 (ddd, *J* = 6.0, 6.0, 12.5 Hz, 1H), 1.77 (s, 3H), 1.73 (m, 1H), 1.73 (s, 3H), 1.66 (s, 3H), 1.66 (s, 3H), 1.41 (s, 3H); (Literature value) 6.36 (dd, *J* = 10.6, 15.4 Hz, 1H), 6.14 (s, 1H), 5.76 (d, *J* = 10.6 Hz, 1H), 5.55 (d, *J* = 15.5 Hz, 1H), 5.14 (t, *J* = 7.1 Hz, 1H), 3.36 (dd, *J* = 7.1, 14.9 Hz, 1H), 3.25 (dd, *J* = 7.1, 14.9 Hz, 1H), 2.62 (ddd, *J* = 5.6, 5.6, 16.3 Hz, 1H), 2.49 (ddd, *J* = 6.2, 9.7, 16.3 Hz, 1H), 2.20 (s, 3H), 1.91 (ddd, *J* = 5.9, 5.9, 13.3 Hz, 1H), 1.77 (s, 3H), 1.73 (m, 1H), 1.73 (s, 1H), 1.64 (s, 3H), 1.64 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (Literature value) 152.1 (152.2), 151.1 (151.2), 135.2 (135.1), 135.0 (135.0), 134.1 (134.2), 130.3 (130.3), 125.0 (125.1), 124.5 (124.5), 123.2 (123.3), 120.0 (120.0), 107.7 (107.7), 105.9 (105.9), 76.0 (75.9), 31.5 (31.4), 27.4 (27.5), 26.0 (26.0), 25.9 (25.9), 24.9 (25.0), 19.5 (19.3), 18.3 (18.2), 18.0 (17.9), 17.0 (17.2). Chiral HPLC separation (AD column): flow rate 1 mL/min, t_R (*S*, minor) = 3.52 min, t_R (*R*, major) = 4.79 min, ee = 97%. HRMS: Calcd for $C_{22}H_{30}O_2$: 326.2246. Found: 326.2245.

(*R*)-*tert*-Butyl-[2-(5-Methoxymethoxy-2,7-dimethyl-2*H*-chromen-2-yl)-diphenylsilane (69). To a solution of chroman **68** (15 mg, 0.03 mmol) in 0.8 mL of benzene at room temperature was added DDQ (17 mg, 0.75 mmol). The resulting blue solution was heated under reflux for 2 h. Without workup, the mixture was directly purified by flash chromatography eluting with 5% diethyl ether in petroleum ether to afford chromen **69** (12 mg, 0.024 mmol, 80%) as a light brown oil.

$[\alpha]_D$ = −0.03 (*c* 0.68, $CDCl_3$); IR (neat): 3072w, 2929s, 2857s, 1618m, 1571w, 1464m, 1428m, 1388w, 1325w, 1156m, 1112s, 1056s, 1112s, 1060s, 1008m, 823m, 739m, 702s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (m, 4H), 7.40 (m, 6H), 6.60 (d, *J* = 6.0 Hz, 1H), 6.42 (s, 1H), 6.25 (s, 1H), 5.48 (d, *J* = 6.0 Hz, 1H), 5.15 (s, 2H), 3.85 (bs, 2H), 3.47 (s, 3H), 2.24 (s, 3H), 2.05 (m, 1H), 1.97 (m, 1H), 1.27 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.4, 152.7, 135.5, 135.1, 134.8, 129.6, 127.7, 127.4, 117.0, 111.0, 108.8, 107.4, 94.6, 78.6, 60.0, 56.1, 43.2, 29.7, 26.8, 29.7, 19.1. HRMS: Calcd for $C_{31}H_{38}O_4Si$ [M^+]: 502.2539. Found: 502.2540.

(*R*)-2-(5-Methoxymethoxy-2,7-dimethyl-2*H*-chromen-2-yl)-ethanol (70). To silyl ether **69** (48 mg, 0.127 mmol) in THF (3 mL) at room temperature was added TBAF (0.25 mL, 0.25 mmol, 1 M in THF). The solution was stirred at room temperature for 20 h and directly chromatographed eluting with 5% to 40% diethyl ether in petroleum ether to afford alcohol **70** (30 mg, 0.114 mmol, 90%) as a pale brown oil.

$[\alpha]_D$ = −6.3 (*c* 1.7, $CDCl_3$, 20.0 °C); IR (film): 3448b, 1915s, 1855m, 1616m, 1571m, 1458m, 1386m, 1325w, 1202w, 1156s, 1108s, 1058s, 1009m, 924w, 828w, 778w cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.71 (d, *J* = 9.9 Hz, 1H), 6.46 (s, 1H), 6.31 (s, 1H), 5.52 (d, *J* = 9.6 Hz, 1H), 5.16 (s, 2H), 3.87 (t, *J* = 5.7 Hz, 2H), 3.49 (s, 3H), 2.25 (s, 3H), 2.01 (t, *J* = 6.0 Hz, 2H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 139.9, 126.9, 117.8, 110.9, 108.6, 107.8, 104.1, 94.6, 78.5, 59.4, 56.1, 42.9, 29.7, 26.2. HRMS: Calcd for $C_{15}H_{20}O_4$ [M^+]: 264.1368. Found: 264.1362.

(*R*)-(5-Methoxymethoxy-2,7-dimethyl-2*H*-chromen-2-yl)-acetaldehyde (64). To a solution of alcohol **70** (60 mg, 0.23 mmol) in 2 mL of dichloromethane was added 4Å molecular sieves and *N*-methyl morpholine *N*-oxide (40 mg, 0.34 mmol) at 0 °C. The mixture was then stirred at room temperature for 30 min. At 0 °C to this mixture was added tetrapropylammonium perruthenate (4 mg, 0.011 mmol) resulting in a dark brown solution. After 1 h at room temperature-,without workup, the mixture was directly chromatographed eluting with 5% to 20% diethyl ether in petroleum ether to afford aldehyde **64** as a yellow oil (58 mg, 0.22 mmol, 98%).

$[\alpha]_D = +44.4$ (*c* 0.5, $CDCl_3$, 21.6 °C); IR (film): 2959m, 2928m, 2859w, 2741w, 1996w, 1724s, 1616s, 1571m, 1453m, 1386m, 1302w, 1233w, 1203w, 1156s, 1110s, 1059s, 1006m, 940w, 923w, 829w, 777w cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.87 (t, $J = 2.4$ Hz, 1H), 6.75 (d, $J = 10.2$ Hz, 1H), 6.48 (s, 1H), 6.34 (s, 1H), 5.57 (d, $J = 9.9$ Hz, 1H), 5.17 (s, 2H), 3.49 (s, 3H), 2.72 (d, $J = 2.4$ Hz, 2H), 2.26 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 152.9, 152.8, 140.3, 125.4, 118.6, 110.9, 108.4, 108.0, 94.7, 76.1, 56.2, 53.6, 26.6, 21.9. HRMS: Calcd for $C_{15}H_{18}O_4$ [M^+]: 262.1205. Found: 262.1195.

(*R*)-2-(4,8-Dimethyl-nona-3,7-dienyl)-5-methoxymethoxy-2,7-dimethyl-2*H*-chromene (62). To a solution of vinyl iodide **63** (30 mg, 0.12 mmol) in THF (1 mL) at −78 °C was added *n*-butyllithium (93 μL, 0.15 mmol, 1.6 M in hexane). After 30 min, to this colorless clear solution was added a solution of aldehyde **64** (15 mg, 0.057 mmol) in THF (0.5 mL). The resulting mixture turned pale yellow and was warmed to room temperature from −78 °C over 10 h. The mixture was quenched with water and chromatographed eluting with 5% to 50% diethyl ether in petroleum ether to afford allylic alcohol **72** (20 mg, 0.515 mmol, 90%, dr = 2:1) as a slightly brown oil. The reaction was repeated to afford another 20 mg of allylic alchol **72**. To a solution of allylic alcohol **72** (40 mg, 0.103 mmol) in THF (2 mL) was added *n*-butyllithium (78 μL, 0.124 mmol) at −78 °C. After 10 min, to this solution was added methyl chloroformate (12 mg, 10 μL). The resulting solution was stirred for 2 h at −78 °C and warmed to room temperature. Without workup, the mixture was purified by flash column chromatography eluting with 5% to 15% diethyl ether in petroleum ether to afford allylic carbonate **73** (38 mg, 0.086 mmol, 83%) as a colorless oil. To a solution of allylic carbonate **73** (26 mg, 0.059 mmol) in THF (2 mL) were added π-allyl palladium chloride dimer (1 mg, 0.0029 mmol) and phosphite **74** (1.6 mg, 0.012 mmol). To this solution at 0 °C was added L-selectride (0.12 mL, 0.12 mmol, 1 M in THF). The resulting dark yellow solution was warmed to room temperature and stirred for an additional 20 min. The reaction mixture was directly chromatographed eluting with 5% diethyl ether in petroleum ether to afford chromen **62** (16 mg, 0.043 mmol, 74%) as a single isomer and a colorless oil.

$[\alpha]_D = +67.5$ (*c* 1.1, $CDCl_3$); IR (neat): 2964s, 2925s, 2856s, 1616s, 1572m, 1453m, 1404w, 1386m, 1325w, 1299w, 1232w, 12021, 1156s, 1109s, 1059s, 1008s, 945w, 924w, 827w, 777w, 709w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.67 (d, $J = 10.0$ Hz, 1H), 6.42 (s, 1H), 6.31 (d, $J = 1.0$ Hz, 1H), 5.48 (d, $J = 10.0$ Hz, 1H), 5.16 (s, 2H), 5.11 (t, $J = 7.0$ Hz, 1H), 5.08 (t, $J = 7.0$ Hz, 1H), 3.49 (s, 3H), 2.25 (s, 3H), 2.11 (m, 4H), 1.95 (dd, $J = 6.5$ Hz, 2H), 1.73 (ddd, $J = 6.0$, 10.5, 14.0 Hz, 1H), 1.67 (s, 3H), 1.66 (ddd, $J = 7.0$, 10.5, 13.5 Hz, 1H), 1.59 (s, 3H), 1.57 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7, 152.7, 139.5, 135.2, 131.3, 127.2, 124.3, 124.1, 117.2, 110.9, 108.7, 107.2, 94.7, 78.1, 56.1, 41.0, 39.7, 29.7, 26.6, 26.3, 25.7, 22.6, 21.9, 17.7, 15.9. HRMS: Calcd for $C_{24}H_{34}O_3$ [M^+]: 370.2508. Found: 370.2524.

Conclusion

In summary, the Pd-catalyzed intramolecular asymmetric allylic alkylation (AAA) of phenol allyl carbonates provides a facile access to chiral chromans. The acetic acid additive dramatically increased the yield and ee of this type of reaction. The influence of olefin geometry and substitution pattern on the ee, and the absolute configuration of the chiral chromans suggest a mechanism involving the cyclization of the more reactive π-allylpalladium diastereomer as the enantiodiscriminating step (Curtin−Hammett conditions). This methodology led to the first enantioselective total synthesis of clusifoliol, siccanin, and the enantioselective synthesis of intermediates leading to the enantioselective total synthesis of dodaurichromanic acid A and nebivolol.

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Supporting Information Available: Experimental procedures for the preparation of **15b**, **15c**, **15j−f 19−24**, **26**, **33**, **42−44**, **65−68**. This material is available free of charge via the Internet at http://pubs.acs.org.

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