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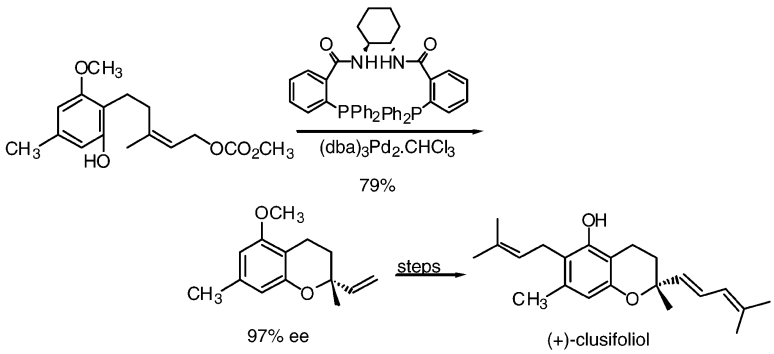

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Unusual Effects in the Pd-Catalyzed Asymmetric Allylic Alkylations: Synthesis of Chiral Chromans

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Chiral chromans are a class of important compounds possessing significant biological properties. For example, vitamin E[1] and its analogues trolox[2] and MDL-73404[3] are important lipophilic antioxidants. Daurichromenic acid and rhododaurichromanic acid A show potent anti-HIV activity.[4] Nebivolol is an antihypertensive agent.[5] Siccanin has potent antifugal activity.[6] Our interests in synthesizing these biologically important natural products prompt the development of a general and efficient methodology in constructing chiral chromans in a catalytic asymmetric fashion.

The synthesis of chiral chromans via Pd-catalyzed asymmetric allylic alkylation (AAA) of phenol **1** remains a challenge (eq 1, Figure 1). The groups of Achiwa[7] and Sinou[8] have screened a large variety of chiral ligands and reaction conditions. However, only modest ee's (<60%) of a limited scope of chiral chromans were obtained. Particularly noteworthy is that only 7% ee of chiral chroman was observed when ligand **3a** was applied by Sinou's group. In contrast to that observation, we reported one example wherein *trans*-allylic carbonate **1a** underwent a Pd-catalyzed intramolecular cyclization to form chiral chroman **2a** in 96% yield and 84% ee,[9] which led to the asymmetric synthesis of the core of vitamin E (entry 1, Table 2). In ascertaining the source of these difficulties, we uncovered unusual effects of alkene geometry and additives on ee that may have broad implications. We report herein these studies as well as our effort of applying this methodology to the first enantioselective total synthesis of (+)-clusifoliol (a constituent of a folk medicine used to treat malignant tumors[10,11]) which establishes its absolute configuration.

The substrates for the reaction can be readily prepared on the basis of the protocol described in the literature.[7−9] Our studies first focused on the influence of ligands and additives on the yield and ee of the reaction. As shown in Table 1, without additives, substrate **1b** gave 95% yield but only 14% ee favoring the formation of *S* chroman **2b** in the presence of 2% Pd_2dba_3 chloroform complex and 6% ligand **3a** (entry 1). The addition of 1 equiv of triethylamine slightly improved the ee and still favored the formation of *S* chroman (entry 2). *Counterintuitively, a dramatic increase of the ee was observed when 1 equiv of acetic acid was added (entries 3−7). Moreover, the absolute configuration of chroman* ***2b*** *was reversed to R.* After the optimization of substrate concentration and catalyst loading, *R*-chroman **2b** was obtained in 94% yield and 84% ee (entry 4, Table 1). Ligand **3a** is superior to **3b** or **3c** in terms of higher ee's, despite the similar yields for all ligands when acetic acid was added. Benzoic acid (entry 8) gave similar results. To determine whether the acidity was the source of the effect, phosphoric acid was employed (entry 9). While the yield remained excellent, the ee was similar to the absence of any additive. On the other hand, addition of an acetate salt gave results more similar to acetic acid (entry 10). These results strongly suggest a direct participatory role for carboxylate as a source of its beneficial role.[12] While this observation and the fast reaction (generally done within 1 h at room temperature) suggest that the enantiodiscriminating step presumably is the ionization event wherein enantiotopic faces of the allylic carbonate are differentiated, other results question such a conclusion.

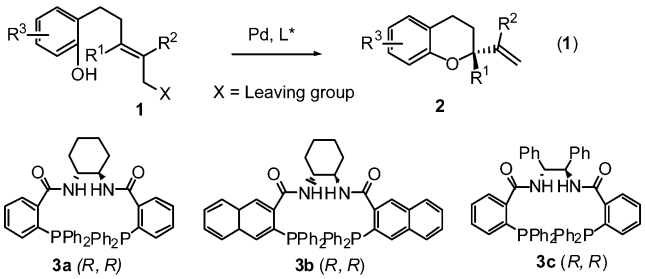
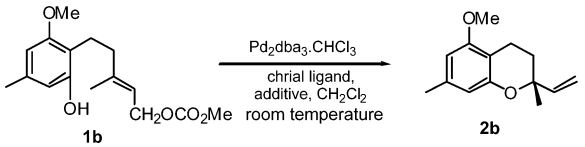


Figure 1. Catalyst for Pd-catalyzed AAA reaction of phenols.

Table 1. Studies of the Effects of Ligands and Additives



entry	Pd (%)	ligand (%)	additive (equiv)	[C] (M)	yield (%)	ee (%)[a]
1	4	**3a** (6)	none	0.2	95	−14
2	4	**3a** (6)	Et_3N (1)	0.2	96	−22
3	4	**3a** (6)	AcOH (1)	0.01	99	75
4	4	**3a** (6)	AcOH (1)	0.2	94	84
5	2	**3a** (3)	AcOH (1)	0.3	96	74
6	1	**3a** (1.5)	AcOH (1)	0.5	73	72
7	4	**3a** (6)	AcOH (1)	0.2	95	73
8	4	**3a** (6)	$PhCO_2H$(1)	0.2	98	75
9	4	**3a** (6)	H_3PO_4(0.5)	0.2	99	−5
10	4	**3a** (6)	*n*Bu_4NOAc(1)	0.2	99	66
11	4	**3a** (6)	*n*Bu_4NCl(1)[b]	0.2	40	63
12	4	**3a** (6)	*n*Bu_4NCl(0.3)	0.2	24	33
13	4	**3b** (6)	AcOH (1)	0.2	99	69
14	4	**3c** (6)	AcOH (1)	0.2	95	64

[a] Measured by chiral GC. [b] With HOAc.

The scope of this reaction has been explored with *E* allylic carbonates **1a**−**i** (Table 2). Under our conditions, substrate **1f** gave 99% yield and 84% ee of chroman **2f**, in contrast to the previously reported case with only 7% ee using the same ligand **3a**.[8]

Olefin geometry in the substrates has a profound impact on the enantioselectivity and the absolute configuration of the chiral chroman products. In all the cases shown in Table 2 and Table 3, the *E* allylic carbonates gave *R* chromans, whereas the *Z* allylic carbonates afforded *S* chromans. More interestingly, *Z* trisubsituted olefins **4a**−**b** (entries 1−2, Table 3) gave the highest ee's (95−97%) among all substrates we examined, significantly higher than their *E* counterparts **1b**, **1d** (entries 2, 4, Table 2). However, *E* disubstituted olefins **1e**−**g** gave substantially higher ee's than their *Z* counterparts.

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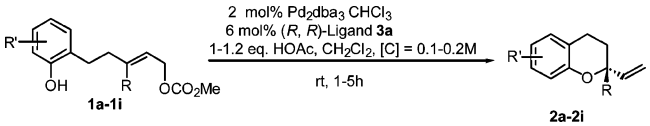
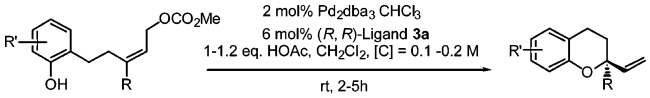
Table 2. Pd-catalyzed AAA Reaction of *E* Allylic Carbonate Phenols



entry	product (R, R′)	yield (%)	ee (%)[a]
1	Me, 3,5,6-trimethyl-4-benzyloxy (**2a**)	96	84
2	Me, 3-methoxy-5-methyl (**2b**)	94	84
3	Me,2,5-dimethoxy-3,4-dimethyl (**2c**)	99	80
4	Me, H (**2d**)	62	73
5	H, 4-fluoro (**2e**)	88	80
6	H, H (**2f**)	99	84
7	H, 4-methyl (**2g**)	97	87
8	H, 4-methoxy (**2h**)	82	89
9	H, 2-methoxy-4-methyl (**2i**)	82	82

[a] Measured by chiral HPLC except entries 2, 3 and 4 which are measured by chiral GC.

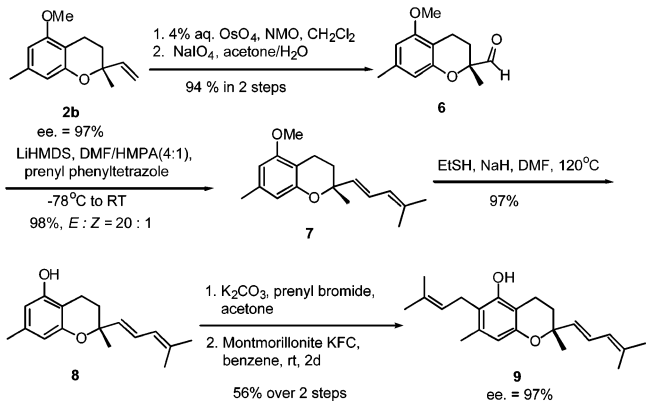
Table 3. Pd-catalyzed AAA Reaction of *Z* Allylic Carbonate Phenols



entry	product (R, R′)	yield (%)	ee (%)[a]
1	Me, H (**5a**)	68	95
2	Me, 3-methoxy-5-methyl (**5b**)	79	97
3	H, 4-methyl (**5c**)	72	48
4	H, H (**5d**)	67	34
5	H,4-fluoro (**5e**)	93	57

[a] Measured by chiral HPLC except entries 1 and 2 which are measured by chiral GC.

Scheme 1. Total Synthesis of (+)-clusifoliol



The asymmetric allylic alkylation (AAA) reaction has been applied to a total synthesis of (+)-clusifoliol **9** (Scheme 1). Chiral chroman **2b**, prepared in 97% ee from **4b** and (*S*,*S*)-ligand *ent*-**3a**, can be easily converted to aldehyde **6** via a dihydroxylation followed by an oxidative cleavage. The modified Julia olefination[13a] using phenyltetrazole prenyl sulfone gave a 20:1 mixture of *E*/*Z* isomers in 98% yield using LiHMDS as the base.[13b] Demethylation followed by prenylation[14] and a prenyl group rearrangement[15] proceeded smoothly to yield the desired (+)-clusifoliol **9**. The optical rotation, chiral HPLC eluting time, and all spectroscopic data of our synthetic sample matched those of the authentic sample.

The absolute configuration of the chiral center in (+)-clusifoliol was established on the basis of the phenylglycine methyl ester (PGME) derivative of the carboxylic acid corresponding to the method described by Kusumi and Yabuuchi,[16] which unambiguously allows the assignment of the *R* configuration for the chiral center in (+)-clusifoliol **9**.

In summary, we have demonstrated the application of Pd-catalyzed AAA reaction of phenol allylic carbonates to the synthesis of chiral chromans. We observed the remarkable influence on enantioselectivity by acetic acid as an additive and by the olefin geometry of the substrates. These effects can be understood in terms of an emerging mechanistic picture for this complex catalytic process (which will be reported in due course) and has ramifications for other AAAs.

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Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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