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Synthesis of Functionalized Chromans by P^{n}Bu$_3$-Catalyzed Reactions of Salicylaldimines and Salicylaldehydes with Allenic Ester

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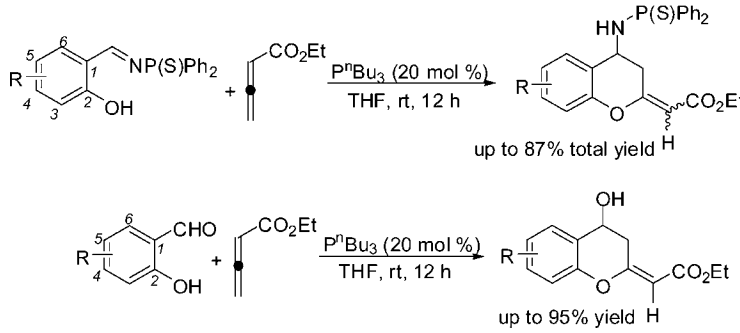
ABSTRACT



P^{n}Bu$_3$-catalyzed cyclization reactions of salicylaldimines and salicylaldehydes with ethyl 2,3-butadienoate gave the corresponding functionalized chromans in moderate to good yields in THF under mild conditions. The new reaction provides a new method for the synthesis of biologically active chroman products.

2*H*-1-Chromenes or chromans are important classes of oxygenated heterocycles that have attracted much synthetic interest because of the biological activity of naturally occurring representatives.[1,2] The synthesis of 2*H*-1-chromenes or chromans via the cyclization of suitably elaborated phenyl ethers commonly suffers from a lack of regioselectivity control at the key cyclization step. Recently, the reactions of salicyclic aldehydes with various conjugated olefins, such as acrylate derivatives and α,β-unsaturated ketones, to give different substituted chromenes or chromans have been reported.[3] Moreover, the reactions of salicylaldehydes or salicylaldimines with allenic ketones or esters[4−6] have also been disclosed thus far. For example, Huang and co-workers recently have found phosphine-catalyzed interesting domino reactions of salicyl *N*-thiophosphinyl imines with electron-deficient allenes, affording *cis*-2,3-dihydrobenzofurans or chroman derivatives in good yields under mild conditions (Scheme 1).[7]

During our ongoing investigation on the phosphine- or nitrogen-containing Lewis base-catalyzed domino cyclization of salicylaldehydes or salicylaldimines with electron-deficient

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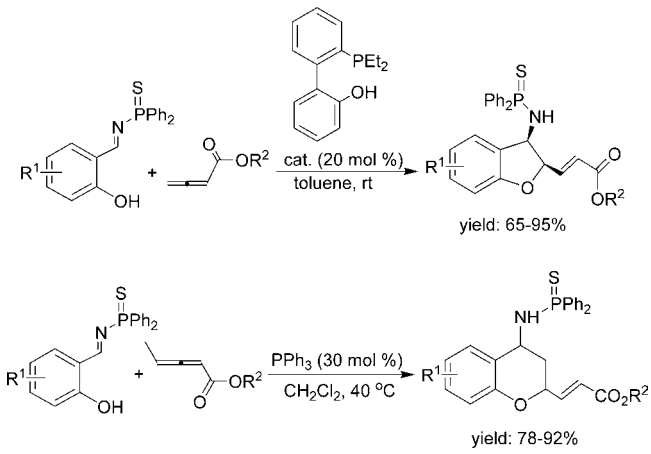
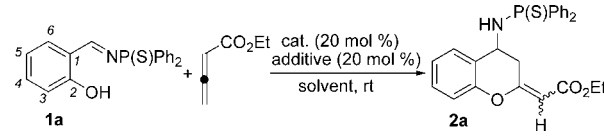
Scheme 1. Phosphine-Catalyzed Domino Reaction of Salicyl *N*-Thiophosphinyl Imines with Electron-Deficient Allenes



olefins as well as allenic ketones or esters, we found that the nucleophilicity and electronic property of the employed phosphine- or nitrogen-containing Lewis base can significantly affect the reaction outcomes. Herein, we wish to report the cyclization reactions of salicylaldimines and salicylaldehydes with allenic ester catalyzed by P^nBu_3 to give the corresponding functionalized chromans in moderate to good yields under mild conditions.

Initially, we examined the reactions of salicylaldimine **1a** (0.1 mmol, 1.0 equiv) with ethyl 2,3-butadienoate (0.2 mmol, 2.0 equiv) catalyzed by various phosphine Lewis bases (20 mol %) in tetrahydrofuran (THF) (1.5 mL) at 20 °C (room temperature) in the presence of phenol (20 mol %) as an additive. The results are summarized in Table 1. Using P^nBu_3,

Table 1. Screening of Catalysts and Solvents for the Reaction



entry[a]	catalyst	additive	solvent	time (h)	yields (%)[b] **2a** (*E*:*Z*)
1	P^nBu_3	phenol	THF	12	57 (3:1)
2[c]	PMe_3	phenol	THF	12	52 (4:1)
3	$PPhMe_2$	phenol	THF	12	46 (5:1)
4	PPh_2Me	phenol	THF	12	18
5[d]	P^nBu_3	phenol	THF	12	45 (2:1)
6	P^nBu_3	phenol	THF	2.5	56 (3:1)
7	P^nBu_3	4-nitrophenol	THF	12	50 (2:1)
8	P^nBu_3	1,3,5-trihydroxybenzene	THF	12	55 (5:1)
9	P^nBu_3	4-*tert*-butylphenol	THF	12	58 (4:1)
10	P^nBu_3	2-naphthol	THF	12	44 (4:1)
11	P^nBu_3	4-*tert*-butylphenol	toluene	12	11
12	P^nBu_3	4-*tert*-butylphenol	Et_2O	12	14
13	P^nBu_3	4-*tert*-butylphenol	CH_2Cl_2	48	NR
14	P^nBu_3	4-*tert*-butylphenol	MeCN	48	NR
15	P^nBu_3	4-*tert*-butylphenol	DMSO	12	complex
16[e]	P^nBu_3	none	THF	12	79 (2:1)
17[f]	P^nBu_3	none	THF	12	86 (3:1)
18[f]	P^nBu_3	4-*tert*-butylphenol	THF	12	67 (2:1)
19[g]	P^nBu_3	none	THF	12	87 (3:1)

[a] The reaction was carried out on a 0.1 mmol scale in solvents (1.5 mL), and the ratio of **1**/allene is 1:2. [b] Isolated yields. [c] PMe_3 is a 1.0 mol/L solvent in THF. [d] At 60 °C. [e] 2.5 mL of THF was used. [f] 5.0 mL of THF was used. [g] 7.5 mL of THF was used.

PMe_3, $PPhMe_2$, and PPh_2Me as the Lewis base promoters, it was found that the corresponding chroman derivative **2a** was formed in 18−57% yields as *E*- and *Z*-isomeric mixtures after 12 h, and P^nBu_3 is the best catalyst in this reaction (Table 1,

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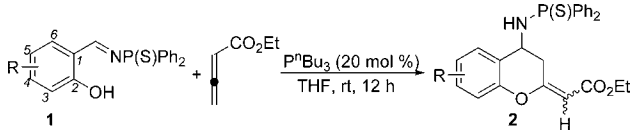
(7) (a) Meng, X.; Huang, Y.; Chen, R. *Org. Lett.* **2009**, *11*, 137–140. (b) Meng, X.; Huang, Y.; Zhao, H.; Xie, P.; Ma, J.; Chen, R. *Org. Lett.* **2009**, *11*, 991–994.

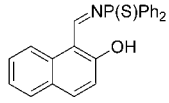
(8) The crystal data of *E*-**4c** have been deposited in CCDC with number 792029. Empirical Formula: $C_{13}H_{13}BrO_4$; Formula Weight: 313.14; Crystal Color, Habit: colorless; Crystal Dimensions: 0.402 × 0.357 × 0.313 mm; Crystal System: Triclinic; Lattice Type: Primitive; Lattice Parameters: a = 6.9575(10) Å, b = 8.3542(12) Å, c = 11.9845(17) Å, α = 74.696(3)°, β = 75.421(2)°, γ = 74.571(3)°, V = 635.22(16) Å^3; Space group: P-1; Z = 2; D_{calc} = 1.637 g/cm^3; F_{000} = 316; Diffractometer: Rigaku AFC7R; Residuals: R; R_w: 0.0582, 0.1410.

entries 1−4). Raising the reaction temperature did not facilitate the formation of **2a**, and the reaction could in fact complete within 2.5 h if using P^nBu_3 as the catalyst under otherwise identical conditions (Table 1, entries 5 and 6). Other phenolic compounds such as 4-nitrophenol, 1,3,5-trihydroxyphenol, 4-*tert*-butylphenol, and 2-naphthol also facilitated the formation of **2a** under the standard conditions, affording **2a** in 44−58% yields (Table 1, entries 7−10). The solvent effects have also been examined in the presence of P^nBu_3 (20 mol %) and 4-*tert*-butylphenol (20 mol %) (Table 1, entries 11−15). We found that THF is the solvent of choice for this reaction, and other solvents such as toluene, Et_2O, CH_2Cl_2, MeCN, and DMSO did not favor the formation of **2a**. During our further examination of the reaction conditions, we found that when the reaction was carried out in diluted THF solution **2a** could be obtained in higher yields even in the absence of phenolic additives (Table 1, entries 16−19). The best reaction conditions were found that when 0.1 mmol (1.0 equiv) of **1a** and 0.2 mmol (2.0 equiv) of ethyl 2,3-butadienoate were employed and the reaction was carried out at 20 °C (room temperature) in THF (7.5 mL), affording the product **2a** in 87% yield as *E*- and *Z*-isomeric mixtures (3:1) within 12 h (Table 1, entry 19).

Next, we examined the substrate scope of this reaction using a variety of salicylaldimines **1** with ethyl 2,3-butadienoate under these optimized conditions. The results are shown in Table 2. The corresponding cyclization products

Table 2. Scope of the Reaction in the Presence of P^nBu_3



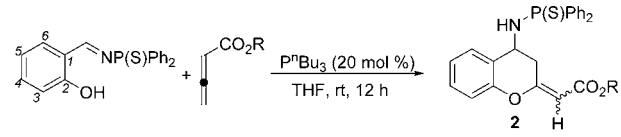
entry[a]	R	yield (%)[b]	yield (%)[b]
1	3-Me	E-**2b**, 61	Z-**2b**, 20
2	4-MeO	E-**2c**, 40	Z-**2c**, 13
3	5-Br	E-**2d**, 27	Z-**2d**, 10
4	5-Cl	E-**2e**, 28	Z-**2e**, 11
5		E-**2f**, 33	Z-**2f**, 28

[a] The reaction was carried out on a 0.3 mmol scale in THF (22.5 mL), and the ratio of **1**/allene is 1:2. [b] Isolated yields.

2 were obtained in moderate to good yields as *E*- and *Z*-isomers at room temperature (Table 2, entries 1−5). These two isomers can be easily separated via silica gel chromatography (Supporting Information). For the starting materials **1** having an electron-withdrawing group on the aromatic ring, the corresponding adducts **2d** and **2e** were obtained in lower yields, which is presumably due to the electronic effects.

To improve the stereoselectivity of the product, isopropyl or *tert*-butyl 2,3-butadienoates were employed in this reaction under these optimized conditions. However, the yields of the corresponding products **2g** and **2h** declined remarkably along with similar *E*/*Z* ratios (Scheme 2).

Scheme 2. Using Isopropyl or *tert*-Butyl 2,3-Butadienoates in the Reaction



2g, R = ^{i}Pr, 65% yield, *E*/*Z* = 4/1
2h, R = ^{t}Bu, 56% yield, *E*/*Z* = 4/1

Their structures were determined by ^1H and ^{13}C NMR spectroscopic data and MS and HRMS analyses. The major isomers of **2** have been identified as *E*-configuration on the basis of their ^1H NMR spectroscopic data with its analogue *E*-**4c**, which has been unambiguously determined as *E*-configuration by X-ray diffraction. The ORTEP drawing of *E*-**4c** is shown in Figure 1, and its CIF data are presented in the Supporting Information.[1]

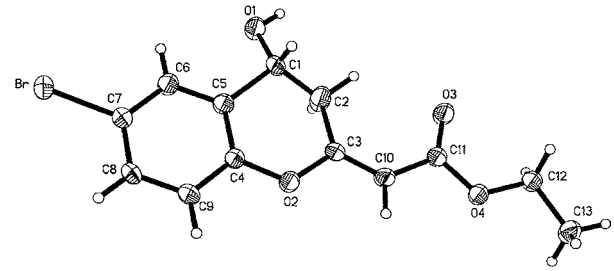
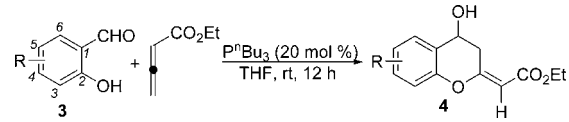


Figure 1. X-ray crystal structure of *E*-**4c**.

The reactions of salicylic aldehydes **3** with ethyl 2,3-butadienoate were also examined under the standard conditions. The results are summarized in Table 3. The corre-

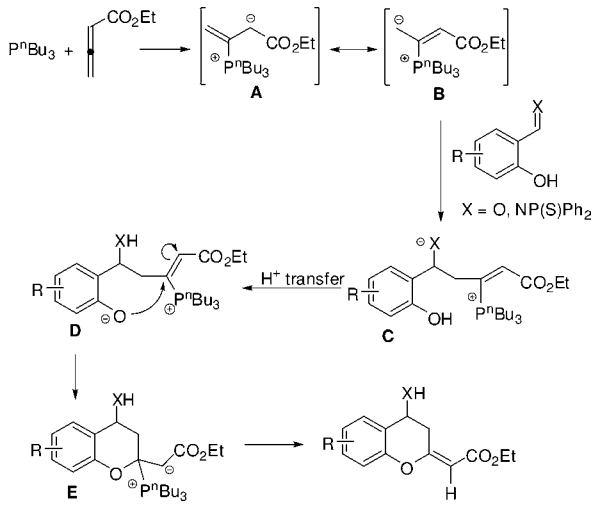
Table 3. Scope of the Reaction Using Salicylic Aldehydes as the Substrates



entry[a]	R	yield (%)[b]
1	H	**4a**, 84
2	3-Me	**4b**, 85
3	5-Br	**4c**, 45
4	5-Cl	**4d**, 55
5	3,5-Br_2	**4e**, 15
6	3-MeO	**4f**, 95
7	4-MeO	**4g**, 23
8	5-MeO	**4h**, 73

[a] The reaction was carried out on a 0.3 mmol scale in THF (22.5 mL), and the ratio of the **3**/allene is 1:2. [b] Isolated yields.

Scheme 3. Plausible Mechanism for the Formation of Functionalized Chromans



sponding adducts **4** were formed in moderate to good yields as *E*-configuration exclusively on the basis of spectroscopic data (Table 3, entries 1−8). In some cases, such as the salicylic aldehydes **3e** and **3g**, the corresponding products **4e** and **4g** were obtained in lower yields, presumably due to the electronic properties of these substituents on the aromatic rings (Table 3, entries 5 and 7).

The mechanism of this unprecedented reaction has not been unequivocally established, but a plausible explanation is proposed in Scheme 3.[4−7] Initially the Lewis base promoter P^{n}Bu$_3$ acts as a nucleophilic trigger, producing the zwitterionic intermediate **A** or another resonance-stabilized zwitterionic intermediate **B**, which undergoes the nucleophilic attack with salicylaldimine **1** or salicylaldehyde **3** to give the corresponding intermediate **C**. Subsequent proton transferring produces intermediate **D**. The cyclization of the resulting intermediate **D** affords the intermediate **E**, which is followed by elimination of P^{n}Bu$_3$ to produce chroman derivative **2** or **4** and regenerates P^{n}Bu$_3$ promoter.

In this paper, we have presented a fairly efficient, P^{n}Bu$_3$-catalyzed reaction of salicylaldimines and salicylaldehydes with allenic ester, which provides an easy access to the synthesis of the corresponding functionalized chroman derivatives under mild reaction conditions in moderate to good yields as well as good geometric selectivities for salicylaldehydes. The diluted reaction condition is crucial to produce **2** or **4** in higher yield, presumably due to that it can avoid the further alteration of the reaction product in the presence of P^{n}Bu$_3$ and ethyl 2,3-butadienoate. Efforts are in progress to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

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Supporting Information Available: ^{13}C and ^{1}H NMR spectroscopic and analytic data for compounds **2** and **4** and the ORTEP drawing of *E*-**4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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