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Organocatalytic Asymmetric Tandem Michael Addition−Hemiacetalization: A Route to Chiral Dihydrocoumarins, Chromanes, and 4*H*-Chromenes

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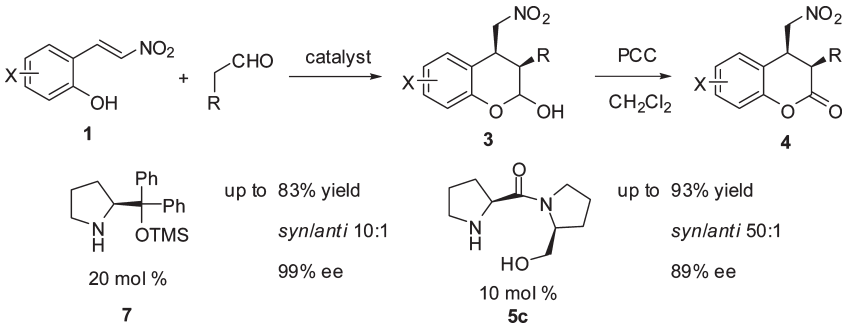

Asymmetric tandem Michael addition−hemiacetalization between aliphatic aldehydes and (*E*)-2-(2-nitrovinyl)phenols was investigated for constructing benzopyran backbones. Interestingly, the diastereo- and enantioselectivities changed markedly when the reaction was mediated by different types of secondary amine catalysts. The diphenylprolinol silyl ether **7** promoted the reaction with excellent enantioselectivities (up to 99% ee) but with moderate diastereoselectivities (2.8:1 to 10:1). Prolylprolinols are another type of efficient catalyst. Among them, L,L-prolylprolinol **5c** is identified as the optimal species, showing high catalytic activity, good enantioselectivities (up to 89% ee), and excellent diasereoselectivities (up to 50:1 dr). Various aliphatic aldehydes and substituted (*E*)-2-(2-nitrovinyl)phenols were proven to be well tolerated in this tandem reaction. In addition, the chroman-2-ols **3** yielded in the above reactions could be conveniently transformed to synthetically and biologically significant chiral dihydrocoumarin, chroman, and 4*H*-chromene derivatives.

Introduction

Dihydrocoumarins, chromans, and chromenes are important classes of benzopyran derivatives found in many natural products and synthetic molecules exhibiting unique biological and pharmacological activities.[1] For instances, splitomicin and its analogues are known to be Sir2 inhibitors,[2] vitamin E and trolox are well-known antioxidants,[3,4] and δ-*trans*-tocotrienoloic acid has antibacterial activity.[5] Rhododaurichromanic acid A shows potent anti-HIV activity,[6] and siccanin possesses strong antifungal activity.[7] Owing to the importance of the benzopyran framework, its construction has attracted considerable attention, and various synthetic

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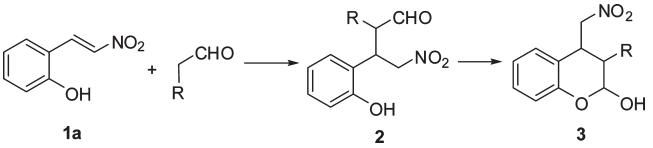
methods have been established,[8] such as cyclization of diols,[9g] Friedel−Crafts reactions,[9b,c] cycloadditions,[9a,i,k,n] ring-closing metathesis (RCM),[9f,l,p] and domino reactions.[10] Chiral benzopyran represents a privileged structural motif that is ubiquitous in a range of natural products and drug candidates with broad biological implications. Thus, it is crucial to develop asymmetric strategies to construct optically active dihydrocoumarins, chromans, and chromenes.[8a]

On the other hand, recent years have witnessed a tremendous growth in the number of organocatalyzed highly stereoselective chemical transformations.[11] On the basis of the iminium−enamine strategy, organocatalytic cascade reactions have become a powerful tool in the enantioselective synthesis of chiral drugs and natural molecules.[12] Organocatalysts are metal-free, usually nontoxic, readily available, and often very robust. Therefore, the organocatalytic synthesis of benzopyran derivates has also become an attractive research topic.[9] Salicylic aldehyde and its derived electron-deficient olefins are important starting materials for constructing oxygen-containing heterocycles in cascade reactions,[13] where the phenolic hydroxyl group often participates in the process through either oxa-Michael addition or carbonyl addition. Recently, several successful examples have been reported,

SCHEME 1. Constructing Chroman-2-ols by Tandem Michael Addition/Hemiacetalization of Aldehydes to 2-(2-Nitrovinyl)phenols



and most of them are initiated by oxa-Michael addition and then cyclized through enamine attack.[10b,c,k,j,h]

Michael addition is a highly efficient and atom-economic reaction for constructing carbon−carbon bonds in organic synthesis, providing useful synthetic blocks.[14] The secondary amine-catalyzed asymmetric Michael addition of aliphatic aldehydes to electron-deficient alkenes provides direct entries to chiral γ-functionalized aldehydes. Very recently, we have developed the novel bifunctional amine catalyst **5c**, which promotes the asymmetric Michael addition of aliphatic aldehydes to nitroalkenes with high efficiency by preventing the acetal formation between catalyst and aldehyde.[15] On the basis of this observation, we envisaged that the chroman-2-ols **3**, versatile intermediates to dihydrocoumarin, chroman, or 4*H*-chromene derivatives, would be generated by Michael addition and subsequent intramolecular hemiacetalization when 2-(2-nitrovinyl)-phenol **1** served as the substrate (Scheme 1).

Nevertheless, 2-(2-nitrovinyl)phenols have seldom been applied directly as Michael acceptors in previous publications,[16] probably owing to the decrease in reactivity and the complication of stereoselectivity caused by the hydroxyl group. Fortunately, we found that the tandem Michael addition−hemiacetalization between aliphatic aldehydes and (*E*)-2-(2-nitrovinyl)phenols occurred smoothly in the presence of catalysts **5c** or **7**, providing high yields of chroman-2-ols **3** with satisfactory enantioselectivity and diastereoselctivity. The details are described below.

Results and Discussion

The reaction between butyraldehyde and (*E*)-2-(2-nitrovinyl)-phenol **1a** was first performed using prolylprolinol **5c** as the catalyst, and the expected hemiacetal chroman-2-ol **3b** was afforded in high yield. In order to avoid the interference of the chiral center generated by hemiacetalization, the diastereo- and enantioselectivities of the reaction were determined respectively by ^{1}H NMR[17] and by chiral HPLC after **3b** was oxidized to 3,4-dihydrocoumarin **4b** by pyridinium chlorochromate (PCC).[18] On the basis of the established

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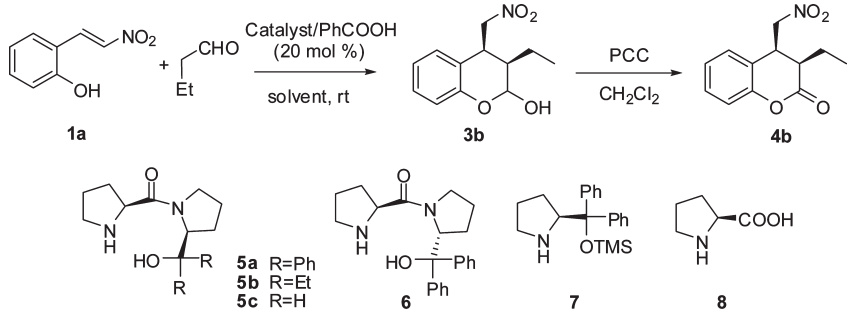
(17) The ^{1}H NMR data of minor diastereomers are given in the Supporting Information.

(18) Attempts to determine the ee value of **3b** directly proved unsuccessful; therefore, product **3a** was oxidized to the corresponding lactone derivative **4b**. PCC is a mild oxidant widely used in oxidation of hemiacetals to lactones and usually does not affect the adjacent chiral centers under the reaction conditions. For examples, see: (a) Yao, W.; Pan, L.; Wu, Y.; Ma., C. *Org. Lett.* **2010**, *12*, 2422–2425. (b) Wang, J.; Yu, F.; Zhang, X.; Ma., D. *Org. Lett.* **2008**, *10*, 2561–2564. (c) Demchenko, A. V.; Wolfert, M. A.; Santhanam, B.; Moore, J. N.; Boons, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 6103–6112.

TABLE 1. Optimization of Catalytic Tandem Reaction of Butyraldehyde with (*E*)-2-(2-Nitrovinyl)phenol[a]



entry	catalyst	solvent	*t* (h)	yield[b] (%)	dr[c]	ee[d,e] (%)
1	**5a**	CH_2Cl_2	24	82	18:1	50
2	**5b**	CH_2Cl_2	48	75	17:1	46
3	**5c**	CH_2Cl_2	18	89	22:1	56
4	**6**	CH_2Cl_2	36	78	22:1	21
5	**7**	CH_2Cl_2	50	78	3.5:1	99
6[f]	**8**	THF	40	68	1.7:1	−18
7	**7**	$CHCl_3$	48	79	3.5:1	99.5
8	**7**	$PhCH_3$	60	75	2.3:1	98
9	**7**	Et_2O	72	68	4.4:1	98
10	**7**	MeOH	72	< 20	n.d.[g]	n.d.
11	**7**	CH_3CN	72	< 20	n.d.	n.d.
12	**7**	DMF	72	< 20	n.d.	n.d.

[a]Reactions performed with butyraldehyde (0.6 mmol), (*E*)-2-(2-nitrovinyl)phenol (0.2 mmol), 20 mol % of catalyst, and 20 mol % of benzoic acid in 1 mL of the indicated solvent at room temperature. [b]Isolated yield of **4b**. [c]Syn:anti determined by ^{1}H NMR of crude **4b**. [d]Determined by chiral HPLC analysis of **4b**. [e]ee value of the major diastereomer. [f]TEA as additive. [g]Not determined.

analysis method, the catalytic efficiency of several chiral secondary amines was estimated utilizing the above reaction as the model reaction. All the results are given in Table 1. In the presence of 20 mol % of L,L-prolylprolinols **5a**−**c** and 20 mol % of benzoic acid, the above reaction proceeded smoothly and was accomplished within 18−48 h. After oxidation by PCC, the dihydrocoumarin **4b** was isolated in good yields with high diastereomeric ratios up to 22:1 and moderate ee values (Table 1, entries 1−3). L,D-Prolylprolinol **6** also showed good catalytic activity and diastereoselectivity but poor enantioselectivity (Table 1, entry 4). As an excellent catalyst for the direct addition of aldehydes to nitroalkenes reported by Hayashi et al.,[19c] diphenylprolinol silyl ether **7** was also tried. In contrast, the employment of **7** as catalyst and benzoic acid as additive led to the formation of **4b** with excellent ee (99%), whereas the diastereomeric ratio decreased markedly (3.5:1) and an extended time was required in this situation (Table 1, entry 5). Unmodified L-proline **8** together with TEA as the additive could also catalyze this reaction, but rather poor stereoselectivity and reversed enantioselectivity were observed (Table 1, entry 6). From the above results, we noticed that the introduction of an *o*-hydroxyl group into 2-nitrostyrene indeed depressed the substrate reactivity and the reaction stereoselectivity to some extent, for the corresponding reaction of 2-nitrostyrene catalyzed by either **5c** or **7** provided both excellent yields and stereoselectivities.[15,19c]

(19) For examples of excellent catalysts on Michael addition of aldehydes to nitroalkenes, see: (a) Belot, S.; Massaro, A.; Tenti, A.; Mordini, A.; Alexakis, A. *Org. Lett.* **2008**, *10*, 4557–4560. (b) Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984–5987. (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215. (d) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369–1371.

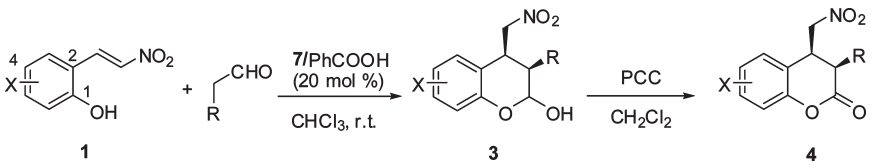
TABLE 2. Effect of the Additives on 7-Catalyzed Reactions[a]

entry	additive	*t* (h)	yield[b] (%)	dr[c]	ee[d,e] (%)
1	none	96	31	6.6:1	98/66
2	PhCOOH	48	79	3.5:1	99/78
3	2-NO_2-PhCOOH	64	79	3.3:1	99/62
4	4-NO_2-PhCOOH	48	75	3.5:1	99/71
5	3,5-diNO_2-PhCOOH	60	72	2.8:1	99/76
6	3-F-PhCOOH	60	72	3.4:1	99/71
7	4-F-PhCOOH	48	68	3.7:1	99/70
8	4-Cl-PhCOOH	54	79	3.5:1	99/64
9	4-MeO-PhCOOH	80	52	3.5:1	98/64
10	2-Br-PhCOOH	54	75	3.4:1	99/72
11	2-I-PhCOOH	48	75	3.5:1	99/74
12	4-HO-PhCOOH	96	48	4.5:1	99/58
13	2-NH_2-PhCOOH	80	48	3.8:1	97/51
14	isophthalic acid	96	42	5.0:1	98/61
15	TEA	96	trace	n.d.[f]	n.d.
16	imidazole	96	trace	n.d.	n.d.
17	pyridine	96	trace	n.d.	n.d.

[a]Reactions performed with butyraldehyde (0.6 mmol), (*E*)-2-(2-nitrovinyl)phenol (0.20 mmol), 20 mol % of **7**, and 20 mol % of additive in 1 mL of chloroform at room temperature. [b]Isolated yield of **4b**. [c]Syn:anti determined by ^{1}H NMR of crude **4b**. [d]Determined by chiral HPLC analysis. [e]ee values of syn/anti diastereomers. [f]Not determined.

We have made some efforts to improve the diastereoselectivity of the **7**-catalyzed reaction by optimizing the reaction conditions. A range of typical solvents were first screened. Among these solvents used, chloroform was the most appropriate one, in which a good yield of **4b** was obtained with an ee value up to 99.5% (Table 1, entry 7). Toluene, usually a good solvent for **7**-catalyzed reactions, herein led to relatively low stereoselectivity (Table 1, entry 8). The dr value was slightly raised in ether (4.4:1), but a much longer time was required and the enantioselectivity somewhat decreased (Table 1, entry 9). Polar solvents such as methanol, acetonitrile, and dimethyl sulfoxide were not suitable for this reaction, owing to the low

TABLE 3. Scope of the 7-Catalyzed Tandem Michael Addition−Hemiacetalization[a]



1 3 4

entry	R, X	t (h)	yield[b] (%)	dr[c]	ee[d,e] (%)
1	Me, H	40	83 (**4a**)	2.8:1	99/67
2	Et, H	48	79 (**4b**)	3.5:1	99/78
3	*n*-Pr, H	50	78 (**4c**)	3:1	99/79
4	*i*-Pr, H	80	80 (**4d**)	3.3:1	99/96
5	*n*-Bu, H	64	78 (**4e**)	3:1	99/83
6	*n*-pent, H	64	78 (**4f**)	3.5:1	99/nd[f]
7	Bn, H	60	80 (**4g**)	4:1	99/nd
8	Et, 6-Me	180	56 (**4h**)	10:1	98/nd
9	Et, 4-Me	96	68 (**4i**)	4:1	98/61
10	Et, 4-*t*-Bu	100	70 (**4j**)	5.1:1	99/nd
11	Et, 4-Cl	60	74 (**4k**)	3:1	99/78
12	Et, 4,6-diBr	72	70 (**4l**)	3:1	98/79
13	Et, 4-OMe	72	68 (**4m**)	3.4:1	99/56

[a]Reactions performed with the corresponding aldehyde (0.6 mmol), substituted (*E*)-2-(2-nitrovinyl)phenol (0.20 mmol), and 20 mol % of **7**/PhCOOH in 1 mL of chloroform at room temperature. [b]Isolated yield of **4**. [c]Syn:anti determined by ^{1}H NMR of crude **4**. [d]Determined by HPLC analysis. [e]ee value of syn/anti diastereomers. [f]Not determined.

conversions of 2-(2-nitrovinyl)phenol **1** (less than 20%) after 72 h (Table 1, entries 10−12).

The effect of additives was also taken into consideration. Some typical acids and bases were surveyed in chloroform, and the data are given in Table 2. Apparently, the reaction proceeded very slowly in the absence of acid or base additives and offered poor yield after 96 h (Table 2, entry 1). Acid additives accelerated this process significantly without any erosion of enantioselectivity, but all other substituted benzoic acids tested failed to offer diastereoselectivities superior to that of benzoic acid on the premise of satisfactory yields (Table 2, entries 2−14). On the other hand, addition of some typical amines as base additives almost hindered the formation of the target product. Therefore, benzoic acid was chosen for substrate expansion.

Under the above optimized conditions, the scope of the tandem Michael addition−hemiacetalization was investigated in the presence of 20 mol % of **7**/PhCOOH at room temperature. As illustrated in Table 3, good yields and excellent ee values were achieved for a variety of aldehydes. The steric hindrance of the R group for aliphatic aldehydes lowered the reaction rate to some degree. For examples, the reaction of propanal was completed within 40 h (Table 3, entry 1), while that of isovaleraldehyde took nearly 80 h to achieve a similar conversion (Table 3, entry 4). Moreover, with the hindrance of the R group, the ee values of the major diastereomers were almost kept unchanged, whereas those of the minor isomers increased from 67 to 96% ee (Table 3, entries 1−5). At the same time, the dr values were slightly improved; however, they still remained within the scope from 2.8:1 to 4:1.

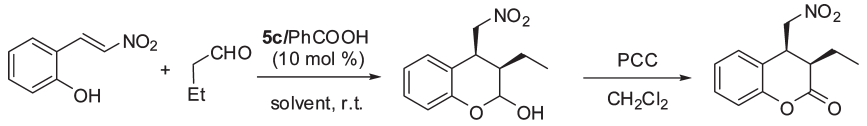
The reaction of several different (*E*)-2-(2-nitrovinyl)-phenols with butyraldehyde was also investigated under the same conditions.[20] Both the electron-withdrawing and electron-donating substituents were tolerated well in this reaction, although the reactions of these substituted 2-(2-nitrovinyl)-phenols proceeded more slowly. The corresponding dihydrocoumarins **4h**−**m** were furnished after subsequent oxidation with excellent enantioselectivities and moderate diastereoselectivities (Table 3, entries 8−13). Notably, the diastereomeric ratio determined for the case of 6-methyl-2-(2-nitrovinyl)-phenol was higher (10:1) than others (Table 3, entry 8); this reaction probably benefited from both the slow conversion and the hindrance of the 6-methyl group.

Although the utilization of diphenylprolinol trimethylsilyl ether **7** as the catalyst provided dihydrocoumarins with excellent enantioselectivities, there were still some disadvantages such as unsatisfactory diastereoselectivity, high catalyst loading (20 mol %), and long reaction period after the above optimization and the substrate scope expansion. We noticed that, except for the enantioselectivity, both the diastereoselectivity and the yield were superior when prolylprolinol **5c** was used as the catalyst instead (Table 1, entry 3). Additionally, the **5c**-catalyzed reaction proceeded much more quickly under the same conditions, indicative of its high catalytic activity. Thus, prolylprolinol **5c** was deemed to be a more potent catalyst for this Michael addition−hemiacetalization cascade if the enantioselectivity could be enhanced. As a result, a careful optimization for the **5c**-catalyzed tandem reaction between butyraldehyde and (*E*)-2-(2-nitrovinyl)phenol **1a** was next executed.

The influence of solvents was preferentially studied as usual by the model reaction in the presence of 10 mol % of **5c**/PhCOOH at room temperature. In chloroform or dichloromethane, the reaction proceeded smoothly and was complete within 40 h with similar yields and stereoselectivities (Table 4, entries 1 and 2). The use of ether solvents gave higher diastereo- or enantioselectivities but made the reaction much slower (Table 4, entries 3 and 4). To our delight, not only the reaction rate but also the diastereo- and enantioselectivities were improved when the reaction was conducted in toluene (Table 4, entry 5). Alcoholic solvents

(20) The (*E*)-2-(2-nitrovinyl)phenols were synthesized from the corresponding substituted salicylaldehydes in the AcOH/AcNH$_4$ system, according to the literature: Zhang, B.-L.; Wang, F.-D.; Yue, J.-M. *Synlett* **2006**, *4*, 567–570.

TABLE 4. Influence of Solvents on the 5c-Catalyzed Reaction[a]



1a **3b** **4b**

entry	solvent	*t* (h)	yield[b] (%)	dr[c]	ee[d,e] (%)
1	CH_2Cl_2	40	89	20:1	56
2	$CHCl_3$	40	89	30:1	53
3	Et_2O	64	87	28:1	82
4	*t*-BuOMe	90	87	40:1	65
5	$PhCH_3$	22	91	36:1	75
6	*i*-PrOH	90	85	8:1	38
7	MeOH	96	trace	nd[f]	nd
8	MeCN	96	trace	nd	nd
9	THF	96	21	24:1	75
10	DMF	96	trace	nd	nd

[a]Reactions performed with butyraldehyde (0.6 mmol), (*E*)-2-(2-nitrovinyl)phenol (0.20 mmol), and 10 mol % of **5c**/PhCOOH in 1 mL of the indicated solvent at room temperature. [b]Isolated yield of **4b**. [c]Syn:anti determined by ^{1}H NMR of crude **4b**. [d]Determined by chiral HPLC analysis. [e]ee value of the syn diastereomer. [f]Not determined.

TABLE 5. Effects of Additives on the 5c-Catalyzed Reaction[a]

entry	additive	*t* (h)	yield[b] (%)	dr[c]	ee[d,e] (%)
1	none	33	87	21:1	73
2	PhCOOH	22	91	36:1	75
3	2-NO_2-PhCOOH	22	89	27:1	74
4	4-NO_2-PhCOOH	12	91	34:1	77
5	3,5-diNO_2-PhCOOH	16	91	28:1	75
6	3-F-PhCOOH	16	91	31:1	78
7	4-F-PhCOOH	16	91	26:1	73
8	4-Cl-PhCOOH	22	86	28:1	71
9	4-MeO-PhCOOH	33	85	24:1	76
10	4-HO-PhCOOH	36	< 50	nd[f]	nd
11	2-NH_2-PhCOOH	33	85	24:1	74
12	2-Br-PhCOOH	12	93	30:1	56
13	2-I-PhCOOH	12	91	31:1	71
14	isophthalic acid	36	< 30	nd	nd
15	TEA	36	< 30	nd	nd
16	imidazole	36	67	20:1	55
17	pyridine	36	65	25:1	57
18[g]	3-F-PhCOOH	36	91	44:1	87

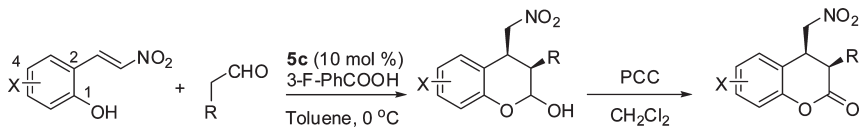
[a]Unless otherwise stated, reactions were performed with butyraldehyde (0.6 mmol), (*E*)-2-(2-nitrovinyl)phenol (0.20 mmol), 10 mol % of **5c**, and 10 mol % of the indicated additive in 1 mL of toluene at room temperature. [b]Isolated yield of **4b**. [c]Determined by ^{1}H NMR of crude **4b**. [d]Determined by chiral HPLC analysis. [e]ee value of the syn diastereomer. [f]Not determined. [g]Reaction conducted at 0 °C.

were not advisible choices, since the reaction became sluggish with poor stereoselectivity in isopropyl alcohol and almost did not take place in methanol (Table 4, entries 6 and 7). Other polar solvents did not benefit the **5c**-catalyzed reaction as well, for the 2-(2-nitrovinyl)phenol could not be fully consumed even after 96 h in acetonitrile, THF, and DMF (Table 4, entries 8−10). Therefore, toluene was finally chosen for the next investigations in view of both the reaction rate and the stereoselectivity.

As shown in Table 5, the additives also played a significant role in this situation. The same acids and bases given in Table 2 were examined in toluene. Unlike the **7**-catalyzed case, the reaction mediated by **5c** was complete after 33 h with satisfactory results when no additive was employed, indicative of its higher catalytic activity (Table 5, entry 1). Stronger acids seemed to benefit the **5c**-catalyzed reaction, because benzoic acids with electron-withdrawing substituents accelerated the reaction remarkably. For instance, 2-(2-nitrovinyl)phenol was consumed within 12 h when 4-nitro-, 2-bromo-, and 2-iodobenzoic acids were employed (Table 5, entries 4, 12, and 13), and the best enantioselectivity was obtained with 3-fluorobenzoic acid after 16 h (Table 5, entry 6). Electron-donating groups in substituted benzoic acids showed little effect (Table 5, entries 9 and 11), while compounds with two acidic groups such as 4-hydroxybenzoic acid and isophthalic acid were even detrimental to this reaction (Table 5, entries 10 and 14). Negative effects were also observed when amine additives were employed (Table 5, entries 15−17). With 3-fluorobenzoic acid as an additive, the dr and ee values of this reaction could be further elevated to 44:1 and 87%, respectively, when the temperature was lowered to 0 °C (Table 5, entry 18).

With the optimal reaction conditions in hand, we next examined a variety of aliphatic aldehydes and substituted (*E*)-2-(2-nitrovinyl)phenols to establish the general utility of the catalytic transformation. The Michael addition−hemiacetalization cascade was conducted in the presence of **5c**/3-F-PhCOOH (10 mol %) in toluene at 0 °C. To our delight, excellent diastereoselectivities and good enantio selectivities were obtained in most cases. The less bulky propanal exhibited high reactivity, and its reaction was completed in 12 h; however, it provided relatively inferior stereoselectivity (Table 6, entry 1). Other normal aliphatic aldehydes also underwent smooth transformations, yielding the dihydrocoumarins **4b**−**f** after two steps in good yields with similarly excellent diastereoselectivities and good enantioselevtivities (Table 6, entries 2−6). The reaction of bulkier isovaleralaldehyde required an extended period to achieve completion. Notably, the anti isomer was hardly observed when the crude adduct **4d** was tested by ^{1}H NMR (Table 6, entry 4). 3-Phenylpropanal was also successfully applied in this case, providing the dihydrocoumarin **4g** in excellent yield with 20:1 dr and 87% ee value (Table 6, entry 7). Furthermore, the products **4b**−**f** can be obtained in nearly enantiopure form after simple recrystallization in isopropyl alcohol. The reactions of butyraldehyde with other substituted (*E*)-2-(2-nitrovinyl)phenols were also carried out under the same conditions. Para-substituted 2-(2-nitrovinyl)phenols were tolerated well and their reactions were accomplished

TABLE 6. Scope of the 5c-Catalyzed Tandem Michael Addition−Hemiacetalization[a]



entry	R, X	t (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	Me, H	12	92 (**4a**)	38:1	81
2	Et, H	32	91 (**4b**)	44:1	87 (99[e])
3	*n*-Pr, H	36	89 (**4c**)	46:1	85 (99[e])
4	*i*-Pr, H	48	87 (**4d**)	> 50:1	85 (99[e])
5	*n*-Bu, H	44	91 (**4e**)	42:1	87 (99[e])
6	*n*-pent, H	48	88 (**4f**)	41:1	87 (97[e])
7	Bn, H	48	93 (**4g**)	20:1	87
8	Et, 6-Me	120	79 (**4h**)	34:1	74
9	Et, 4-Me	48	88 (**4i**)	44:1	84
10	Et, 4-*t*-Bu	48	90 (**4j**)	50:1	86
11	Et, 4-Cl	60	86 (**4k**)	35:1	81
12	Et, 4,6-diBr	80	88 (**4l**)	20:1	89
13	Et, 4-OMe	64	84 (**4m**)	25:1	81

[a]Reactions were performed with the corresponding aldehyde (0.6 mmol), substituted 2-(2-nitrovinyl)phenol (0.20 mmol), 10 mol % of **5c**, and 10 mol % of 3-fluorobenzoic acid in 1 mL toluene at 0 °C. [b]Isolated yield of **4**. [c]Syn:anti determined by ^{1}H NMR of the crude product **4**. [d]Determined by chiral HPLC analysis. [e]Values in parentheses in this column are ee values after simple recrystallization.

within 48−64 h in good yields with excellent diastereoselectivities and good enantioselectivities (Table 6, entries 9−11 and 13), but the 2-(2-nitrovinyl)phenols with ortho substituents experienced apparently slower transformations (Table 6, entries 8 and 12).

The potential reversibility of the reactions was next investigated under these conditions. When the chroman-2-ol **3b** resulting from the **5c**/3-F-PhCOOH catalyzed reaction was treated with (±)-**7**/PhCOOH for 32 h, it was clear that no detectable 2-(2-nitrovinyl)phenol was regenerated under the reaction conditions and the dr and ee values for **3b** remained unchanged.[21] Thus, we recognized that the formation of a hemiacetal structure would stabilize the adduct **3** and cause this tandem reaction to be hardly reversible under the reaction conditions. In addition, a slight increase in the ee value for **3b** was observed during the **5c**/3-F-PhCOOH catalyzed reaction of butyraldehyde with (*E*)-2-(2-nitrovinyl)phenol **1a** with reaction progress, but after the reaction was complete, the ee value remained constant.[22]

The major diastereomer of dihydrocoumarin **4b** was easily separated from the minor species by column chromatography, and its absolute configuration was determined to be 3*R*,4*S* by single-crystal X-ray diffraction.[23] The absolute configuration is consistent with that of the adduct between butyraldehyde and nitrostyrene.[19b,c]

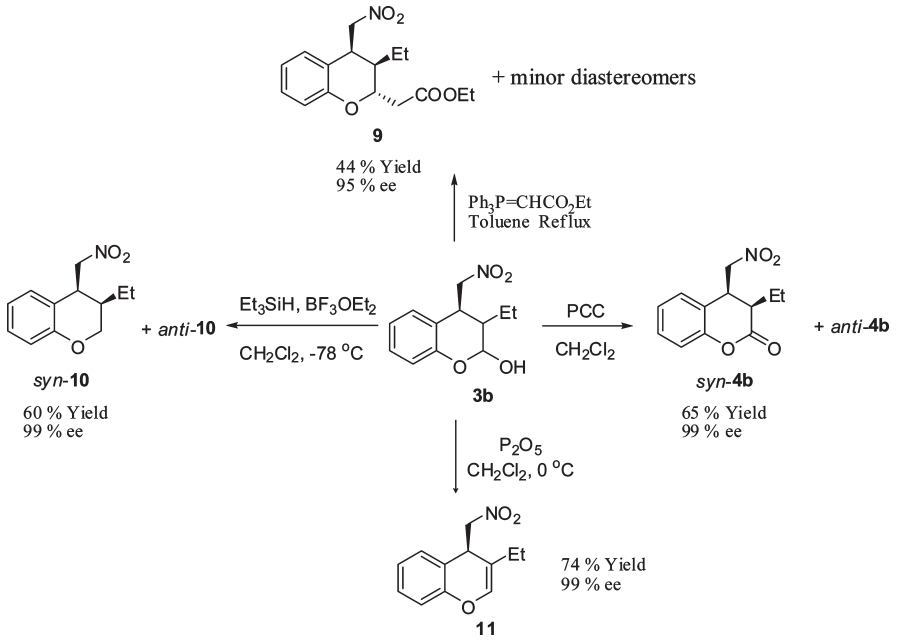
The choman-2-ols **3** obtained from the above reactions are useful intermediates which can be conveniently transformed into dihydrocoumarins, chromans, and 4*H*-chomenes. As we know, 3,4-dihydrocoumarins are widely distributed in nature and are present as important active ingredients in many traditional Chinese herbal medicines.[1b,c] Their synthesis has attracted great interest in recent years.[24] Our work has provided a mild and efficient approach to optically active 3,4-dihydrocoumarins **4b** via Michael addition, hemiacetalization, and subsequent oxidation. In the following derivation studies, the hemiacetal **3b**, resulting from the **7**-catalyzed reaction, was used as the starting material. As illustrated in Scheme 2, a highly substituted chroman could be produced by a Wittig reaction and subsequent intramolecular oxa-Michael addition. The major isomer **9** was separated in 44% yield with 95% ee. Treatment of **3b** with Et_3SiH and $BF_3\cdot Et_2O$ at −78 °C afforded the 3*R*,4*S*-disubstituted chroman **10** as the major product, which was isolated by flash chromatography in 60% yield in nearly enantiopure form. Additionally, dehydration of the hemiacetal **3b** mediated by P_2O_5 in dichloromethane at 0 °C furnished the chiral 4*H*-chromene **11** as almost a pure enantiomer, which is a core structural feature of an array of fascinating natural products with intriguing biological activities.[1a]

Conclusion

In summary, we have developed a tandem Michael addition−hemiacetalization between aliphatic aldehydes and (*E*)-2-(2-nitrovinyl)phenols for constructing chiral choman-2-ols, which are versatile intermediates to synthetically and biologically significant chiral benzopyran derivates. Prolylprolinol **5c** and diphenylprolinol trimethylsilyl ether **7** are two prominent catalysts with different merits for this tandem reaction. The former shows high catalytic efficiency, excellent diastereoselectivity, and good enantioselectivity, while the latter provides excellent enantioselectivity and moderate diastereoselectivity. In addition, successful derivations to chiral 3,4-dihydrocoumarin, chromans, and chromene

(21) The ee values were determined after oxidation of **3b** to **4b**.
(22) The details are given in the Supporting Information.
(23) The ORTEP plot for the X-ray crystal structure of **4b** is presented in the Supporting Information.
(24) For recent publications on synthesis of 3,4-dihydrocoumarins, see: (a) Prakash, G. K. S.; Paknia, F.; Vaghoo, H.; Rasul, G.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2010**, *75*, 2219–2226. (b) Gu, Y.; Xue, K. *Tetrahedron Lett.* **2010**, *51*, 192–196. (c) Han, X.; Lu, X. *Org. Lett.* **2010**, *12*, 108–111. (d) Duan, S.; Jana, R.; Tunge, J. A. *J. Org. Chem.* **2009**, *74*, 4612–4614. (e) Lv, H.; You, L.; Ye, S. *Adv. Synth. Catal.* **2009**, *351*, 2822–2826. (f) Zeitler, K.; Rose, C. A. *J. Org. Chem.* **2009**, *74*, 1759–1762. (g) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105–108. (h) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10*, 4951–4953. (i) Shaabani, A.; Soleimani, E.; Rezayan, A. H.; Sarvary, A.; Khavasi, H. R. *Org. Lett.* **2008**, *10*, 2581–2584. (j) Piao, C.-R.; Zhao, Y.-L.; Han, X.-D.; Liu, Q. *J. Org. Chem.* **2008**, *73*, 2264–2269.

SCHEME 2. Various Transformations of Chroman-2-ol 3b



have been performed, corroborating this methodology as an efficient approach to chiral benzopyran derivatives. The differences in reactivity and stereoselectivity between 2-(2-nitrovinyl)phenol and nitrostyrene evidently suggest the involvement of the former's hydroxyl group in the transition state, and a theoretical study of the transition state is ongoing in our laboratory.

Experimental Section

General Information. Solvents were purified by standard procedures and distilled before use. Reagents and starting materials obtained from commercial suppliers were used without further purification unless otherwise stated. All the aldehydes were distilled freshly prior to use. NMR spectra were recorded on a 400 MHz spectrometer. ^{1}H NMR chemical shifts were reported in ppm with tetramethylsilane (TMS) as the internal standard. Data for ^{1}H are reported as follows: chemical shift (in ppm) and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Splitting patterns that could not be clearly distinguished are designated as multiplets (m). Data for ^{13}C NMR are reported in ppm. High-resolution mass spectral analyses (HRMS) were measured using ESI ionization. High-performance liquid chromatography (HPLC) analysis was performed on chiral columns. Optical rotations were measured in the solvent indicated. Flash chromatography was performed on 200−300 mesh silica gel.

General Procedure of the Organocatalytic Michael Addition−Hemiacetalization Cascade between Aldehydes and 2-(2-Nitrovinyl)-phenols. To a solution of 2-(2-nitrovinyl)phenol (0.2 mmol, 1.0 equiv) in 1 mL of the indicated solvent were added the catalyst and additive; after stirring was carried out at the indicated temperature for 20 min, freshly distilled aldehyde (0.6 mmol, 3.0 equiv) was then added to the mixture. The resulting solution was stirred at the indicated temperature until completion of the reaction. After the reaction was quenched by 1 M aqueous HCl (1 mL), the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in 4 mL of dichloromethane and 150 mg of PCC was added, and the mixture was stirred at room temperature for 12 h. The suspension was filtered through a short pad of silica gel and washed with diethyl ether. Removing the solvents under vacuum afforded the crude product **4**, which was then purified by flash chromatography with ethyl acetate and petroleum ether as eluent. The diastereomeric ratio of the crude product **4** was determined by ^{1}H NMR. To avoid the interference of the minor diastereomer, the ee value and the optical rotation of the major diastereomer were determined by HPLC and polarimeter, respectively, after separation from the minor species by flash chromatography in most cases. The ee value of the minor diasereomer was measured by direct HPLC analysis of the mixed diastereomers.

3-Ethyl-4-(nitromethyl)chroman-2-ol (3b). The chroman-2-ol **3b** was obtained as a mixture of two inseparable diastereomers. Major diasteromer: ^{1}H NMR (400 MHz, DMSO) δ 7.39−7.25 (m, 1H), 7.23−7.11 (m, 1H), 6.90−6.71 (m, 2H), 5.44 (dd, J = 3.6, 2.4 Hz, 1H), 4.98 (dd, J = 12.8, 4.0 Hz, 1H), 4.69 (dd, J = 12.8, 9.6 Hz, 1H), 3.66−3.52 (m, 1H), 2.13−2.00 (m, 1H), 1.62−1.42 (m, 1H), 1.37−1.25 (m, 1H), 1.00 (t, J = 7.6 Hz, 3H). Minor diastereomer: ^{1}H NMR (400 MHz, DMSO) δ 7.39−7.25 (m, 1H), 7.23−7.11 (m, 1H), 7.02−6.95 (m, 1H), 6.90−6.71 (m, 1H), 5.39 (t, J = 3.6 Hz, 1H), 5.11 (dd, J = 13.2, 8.0 Hz, 1H), 4.86 (dd, J = 13.2, 6.8 Hz, 1H), 3.86−3.94 (m, 1H), 2.12−2.03 (m, 1H), 1.62−1.42 (m, 1H), 1.25−1.11 (m, 1H), 0.93 (t, J = 7.6 Hz, 1H). Major + minor diastereomers: ^{13}C NMR (100 MHz, DMSO) δ 152.4, 151.5, 129.3, 128.8, 127.1, 122.9, 122.0, 120.9, 120.8, 117.4, 117.0, 93.2, 93.1, 79.2, 76.8, 40.6, 40.5, 34.8, 33.2, 20.7, 18.9, 11.9, 11.7.

(3*R*,4*S*)-3-Ethyl-4-(nitromethyl)chroman-2-one (4b). $[\alpha]_D^{25}$ = −86.41° (c = 1.0, $CHCl_3$). Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.32 (m, 1H), 7.20−7.07 (m, 3H), 4.60 (dd, J = 12.4, 4.8 Hz, 1H), 4.31 (dd, J = 12.4, 10.4 Hz, 1H), 3.90 (dt, J = 10.4, 5.2 Hz, 1H), 2.84 (td, J = 7.2, 5.2 Hz, 1H), 2.17−2.04 (m, 1H), 1.62−1.50 (m, 1H), 1.15 (t, J = 3.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 150.9, 130.2, 128.1, 125.0, 122.7, 117.4, 75.4, 43.4, 37.4, 20.0, 11.9; HRMS (ESI, m/z) calcd for $C_{12}H_{13}NNaO_4$ ($M + Na^+$) 258.073 68, found 258.073 14.

Ethyl 2-((2*S*,3*R*,4*S*)-3-Ethyl-4-(nitromethyl)chroman-2-yl)acetate (9). To a toluene (5 mL) solution of **3b** (obtained via the catalysis of **7**; a mixture of four diastereomers, 119 mg, 0.5 mmol) was

added the Wittig reagent (261 mg, 0.75 mol, 1.5 equiv) at room temperature. The reaction mixture was heated to reflux for 8 h. After the mixture was cooled to room temperature, the solvent was removed under vacuum, and the residue was purified by flash chromatography (AcOEt/ petroleum ether 1:20 to 1:10) to afford **9** (72 mg, 44%). According to the configuration of **4b**, the absolute configuration of **9** was determined to be 2*S*,3*R*,4*S* by NOE analysis. $[\alpha]_D^{25} = -110.33°$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.13 (m, 1H), 7.03−6.94 (m, 1H), 6.91−6.80 (m, 2H), 4.71−4.53 (m, 2H), 4.52−3.92 (m, 1H), 4.30−4.15 (m, 2H), 3.89−3.76 (m, 1H), 2.78−2.58 (m, 2H), 2.03−1.88 (m, 1H), 1.64−1.43 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 152.8, 129.2, 127.9, 121.2, 120.9, 117.4, 76.9, 73.2, 60.9, 40.0, 39.3, 34.9, 20.1, 14.2, 11.2. HRMS (ESI, m/z): calcd for $C_{16}H_{21}NNaO_5$ ($M + Na^+$) 330.131 19, found 330.13172.

(3*R*,4*S*)-3-Ethyl-4-(nitromethyl)chroman (10). To a CH_2Cl_2 solution (3 mL) of **3b** (obtained via the catalysis of **7**; a mixture of four diastereomers, 119 mg, 0.5 mmol) and triethylsilane (239 μL, 1.5 mmol) was added trifluoroborane diethyl etherate (127 μL, 1.0 mmol) at −78 °C. After it was stirred at −78 °C for 1 h, the reaction mixture was slowly raised to room temperature. After the completion of the reaction indicated by TLC, the resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The organic phase was combined and dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt/petroleum ether 1:100 to 1:30) to afford the main diastereomer **10** (66 mg, 60% yield,). $[\alpha]_D^{25} = -82.92°$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.15 (m, 1H), 7.08−6.97 (m, 1H), 6.92−6.82 (m, 2H), 4.64 (dd, J = 12.0, 6.4 Hz, 1H), 4.52 (dd, J = 12.0, 7.6 Hz, 1H), 4.25 (ddd, J = 11.2, 3.6, 0.8 Hz, 1H), 3.92 (dd, J = 11.2, 10.0 Hz, 1H), 3.83 (dd, J = 12.0, 6.8 Hz, 1H), 2.24−2.08 (m, 1H), 1.59−1.28 (m, 2H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 129.2, 128.7, 120.8, 120.7, 117.1, 77.6, 66.2, 36.9, 36.3, 20.1, 11.6. HRMS (ESI, m/z): calcd for $C_{12}H_{15}NNaO_3$ ($M + Na^+$) 244.094 41, found 244.094 43.

(*S*)-3-Ethyl-4-(nitromethyl)-4*H*-chromene (11). To a CH_2Cl_2 solution (3 mL) of **3b** (obtained via the catalysis of **7**; a mixture of four diastereomers, 119 mg, 0.5 mmol) was added P_2O_5 (213 mg, 1.5 mmol, 3 equiv) at 0 °C. After it was stirred at the same temperature for 40 min, the mixture was filtered through a short pad of silica gel, washed with CH_2Cl_2, concentrated under vacuum, and purified by flash chromatography (AcOEt/ petroleum ether 1:100 to 1:30) to afford the optically pure **11** (81 mg, 74% yield). $[\alpha]_D^{25} = 32.70°$ (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.19 (m, 1H), 7.15−7.01 (m, 2H), 7.00−6.92 (m, 1H), 6.56 (t, J = 1.2 Hz, 1H), 4.51 (dd, J = 12.0, 4.8 Hz, 1H), 4.39 (dd, J = 12.0, 8.0 Hz, 1H), 4.20 (dd, J = 8.0, 4.8 Hz, 1H), 2.29−2.00 (m, 2H), 1.13 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 138.6, 128.8, 128.2, 123.9, 119.5, 116.6, 113.4, 80.0, 37.0, 23.3, 12.1. HRMS (ESI, m/z): calcd for $C_{12}H_{14}NO_3$ ($M + H^+$) 220.096 82, found 220.096 90.

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Supporting Information Available: Text, figures, and a CIF file giving characterization data for all new compounds as well as X-ray structural data, NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.