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Stereoselective synthesis of chromane derivatives via a domino reaction catalyzed by modularly designed organocatalysts

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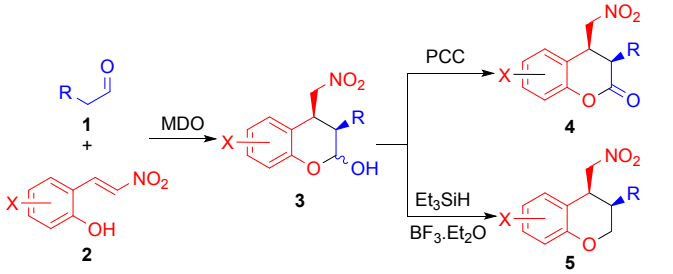
A highly enantio- and diastereoselective method for the synthesis of functionalized chroman-2-ones and chromanes was achieved by using an organocatalytic domino Michael/hemiacetalization reaction of aliphatic aldehydes and (*E*)-2-(2-nitrovinyl)phenols followed by a PCC oxidation and dehydroxylation, respectively. Using the modularly designed organocatalysts (MDOs) self-assembled from cinchona alkaloid derivatives and amino acids in the reaction media, the title products were obtained in good to high yields (up to 97%) and diastereoselectivities (up to 99:1 dr) and excellent enantioselectivities (up to 99% ee).

Introduction

Michael addition to nitroalkenes is a powerful tool in organic synthesis that enables the synthesis of complex organic molecules bearing the synthetically useful nitro group. Not surprisingly, organocatalytic nitro-Michael reactions have been extensive investigated in the past decades.[1]

Chroman-2-one and chromane are important classes of benzopyran derivatives. [1] The dihydrocoumarin and chromane scaffolds are found in many natural products and synthetic molecules that frequently exhibits unique biological and pharmacological activities,[2] such as antineoplastic activity,[3] antiherpetic activity,[4] and the inhibitive activities against protein kinases,[5] aldose reductase,[6] and HIV-1 reverse transcriptase.[7] Owing to the importance of the chromane scaffold, its stereoselective synthesis has attracted considerable attention.[8] Indeed, several organocatalytic methods have been developed to access this core structure in an asymmetric manner.[9-13] For examples, Ramachary,[9] Enders,[10] Gong,[11] and Hong[12] have independently developed organocatalytic domino[14] Michael/hemiacetalization reactions followed by an oxidation reaction for the efficient synthesis of chroman-2-one derivatives in a highly stereoselective manner.

Our group is interested in developing novel catalytic methods[15] using the modularly designed organocatalysts (MDOs),[16,17] which are self-assembled in the reaction media from cinchona alkaloid derivatives and amino acids. Herein, we wish to report that, using MDOs as the catalysts, the reaction between aliphatic aldehydes and (*E*)-2-(2-nitrovinyl)phenols gives the expected domino Michael/hemiacetalization products, which may be converted to functionalized chroman-2-ones and chromanes by PCC oxidation and dehydroxylation, respectively (Scheme 1). The desired chroman-2-ones and chromanes were both obtained in good yields and high stereoselectivities.



Scheme 1 Synthesis of chroman-2-ones and chromanes using MDOs as the catalysts

Results and discussion

Hydrocinnamaldehyde (**1a**) and (*E*)-2-(2-nitrovinyl)phenol (**2a**) was adopted as the model substrates. Several cinchona alkaloid derivatives and amino acids (Figure 1) were adopted as the precatalyst modules. These two modules have complementary basic and acidic functional groups that can help them self-assemble in situ in the reaction media. The most interesting results of the catalyst screening are collected in Table 1. As the results in Table 1 show, when quinidine thiourea **6a** and L-proline (**7a**) were adopted as the stereocontrolling module and the reaction-center module, respectively, the reaction of **1a** and **2a** gave product **4a** (after oxidation with PCC) in a high yield (94%) and excellent diastereoselectivity (96:4 dr) and ee value (99%, entry 1). Control experiments conducted with either **6a** or **7a** alone as the catalyst did not yield any product under otherwise identical conditions (entries 2 and 3). These results confirm that the observed catalytic activity is indeed due to the in-situ generated MDO.

Similar results were obtained when the MDO self-assembled from cinchonine thiourea **6b** and **7a** was applied, except that the obtained product yield (80%) and diastereoselectivity (87:13 dr) were slightly lower (entry 4). Much lower product ee

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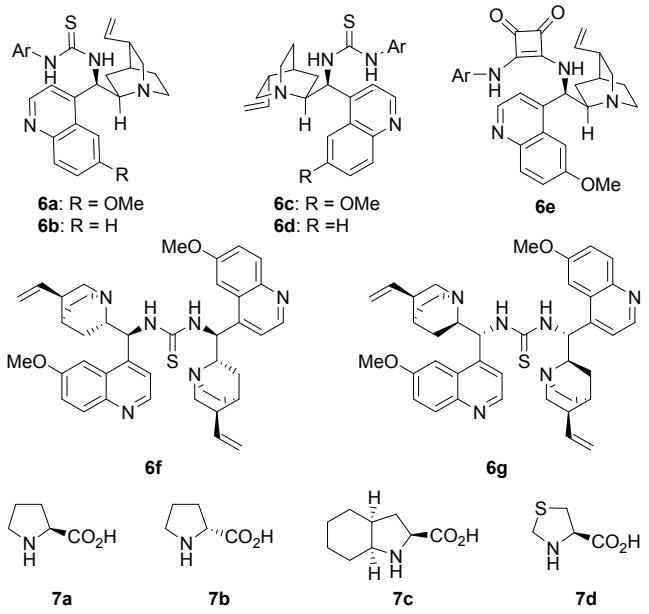


Figure 1 Structure of the precatalyst modules [Ar = 3,5-$(CF_3)_2C_6H_3$-].

value (78% ee) was obtained when the MDO **6c**/**7a** was employed as the catalyst (entry 5). The MDO **6d**/**7a** yielded very similar stereoselectivities as **6c**/**7a** did, but the product yield (97%) was much better (entry 6). Similar results were also obtained for the MDOs **6e**/**7a** and **6f**/**7a** (entries 7-8). In contrast, a poor product ee value (32% ee) was obtained when the MDO **6g**/**7a** was applied (entry 9). These screening identified the stereocontrolling module **6a** is the best one for this reaction in terms both the product yield and stereoselectivities (entry 1). Using **6a** as the stereocontrolling module, we next screened several amino acids as the reaction-center module. The pseudo-diastereomeric MDO formed from **6a** and D-proline (**7b**) led to the formation of the enantiomer of **4a** in a high yield, but only moderate stereoselectivities (84:16 dr, 75% ee) (entry 10). Very good results were also obtained from the MDO **6a**/**7c** (entry 11), which was only slightly inferior to that of **6a**/**7a** (entry 1). However, almost no product could be isolated from the reaction catalyzed by the MDO self-assembled from **6a** and L-thioproline (**7d**) (entry 12). Thus, the above screening identified MDO **6a**/**7a** (entry 1) as the best catalyst for this domino Michael/hemiacetalization reaction. Next the solvent was screened for this best MDO. Common organic solvents, such as xylenes (entry 13), benzene (entry 14), and CH_2Cl_2 (entry 15) all yielded inferior diastereoselectivities. Slightly inferior results in terms of both yield and stereoselectivities were also obtained from the environmentally benign solvent cyclopentyl methyl ether (entry 16). On the other hand, much poorer product ee value was obtained (14% ee) in MeOH (entry 17). THF (entry 18), 1,4-dioxane (entry 19), and CH_3CN (entry 20) also turned out to be poor solvents for this reaction since either only trace amount product or no product could be obtained from these solvents. When the catalyst loading was reduced to 5 mol%, the yield and stereoselectivities obtained for **4a** were only slightly lower (entry 21).

Table 1 Catalyst screening and optimization of the reaction conditions[a]

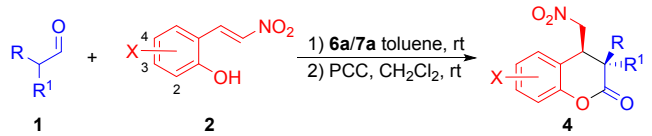
1a 2a 4a

Entry	Modules		Solvent	Yield[b] (%)	dr[c]	ee[d] (%)
1	**6a**	**7a**	Toluene	94	96:4	99
2	**6a**	---	Toluene	---	---	---
3	---	**7a**	Toluene	---	---	---
4	**6b**	**7a**	Toluene	80	87:13	98
5	**6c**	**7a**	Toluene	80	81:19	78
6	**6d**	**7a**	Toluene	97	83:17	78
7	**6e**	**7a**	Toluene	90	85:15	87
8	**6f**	**7a**	Toluene	87	84:16	84
9	**6g**	**7a**	Toluene	80	80:20	32
10	**6a**	**7b**	Toluene	97	84:16	75[e]
11	**6a**	**7c**	Toluene	94	88:12	98
12	**6a**	**7d**	Toluene	<5	---	---
13	**6a**	**7a**	Xylenes[f]	99	88:12	99
14	**6a**	**7a**	Benzene	99	80:20	99
15	**6a**	**7a**	CH_2Cl_2	87	82:18	96
16	**6a**	**7a**	CPME[g]	70	95:5	91
17	**6a**	**7a**	MeOH	94	84:16	14
18	**6a**	**7a**	THF	<5	---	---
19	**6a**	**7a**	1,4-Dioxane	---	---	---
20	**6a**	**7a**	CH_3CN	---	---	---
21[h]	**6a**	**7a**	Toluene	89	93:7	98

[a]Unless otherwise specified, all reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), and the precatalyst modules (0.010 mmol each, 10 mol%) in dry toluene (1.0 mL) at room temperature for 16 h. Once the reaction was complete, the initial products were purified by flash column chromatography and then oxidized with PCC (3.0 equiv.) in CH_2Cl_2 at rt for 24 h. [b]Yield of the isolated product after flash column chromatography (overall yield after two steps of reactions). [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by HPLC analysis on a ChiralPak AD-H column. [e]The opposite enantiomer was obtained as the major product. [f]A mixture of all dimethylbenzene isomers. [g]Cyclopentyl methyl ether. [h]The loading of the precatalyst modules **6a** and **7a** was 5 mol% each.

Once the reaction conditions were optimized, the scope of this reaction was studied and the results are collected in Table 2. As the results in Table 2 show, besides hydrocinnamaldehyde (**1a**, entry 1), other linear aldehydes, such as propanal (entry 2), butanal (entry 3), pentanal (entry 4), heptanal (entry 5), also react with (*E*)-2-(2-nitrovinyl)phenol (**2a**) to give the desired chroman-2-ones **4b**-**e** after oxidation in high yields (83-97%), good to excellent diastereoselectivities (81:19 to 98:2 dr), and excellent ee values (97-99% ee). In general, higher diastereoselectivities were obtained with longer chain aldehyde substrates. With the branched 3-methylbutanal high diastereoselectivity of 99:1 dr and enantioselectivity of 93% ee were obtained for the corresponding chroman-2-one **4f** (entry 6). Similarly, 2-methylpropanal also yielded the expected **4g** after oxidation in 96% ee, although in a lower yield (69%, entry 7). Using pentanal as the aldehyde component, various

Table 2 Substrate scope of the domino Michael/hemiacetalization reactions[a]



1 2 4

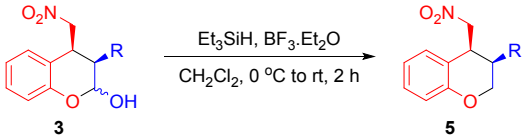
Entry	R	R¹	X	4/Yield[b] (%)	dr[c]	ee[d] (%)
1	Bn	H	H	**4a**/94	96:4	99
2	Me	H	H	**4b**/86	89:11	99
3	Et	H	H	**4c**/97	81:19	96
4	*n*-Pr	H	H	**4d** /83	98:2	96
5	*n*-Pent	H	H	**4e**/90	95:5	97
6	*i*-Pr	H	H	**4f**/91	99:1	93
7[e]	Me	Me	H	**4g**/69	----	96
8[f]	*n*-Pr	H	4-Cl	**4h**/74	84:16	98
9[f]	*n*-Pr	H	4-Br	**4i**/73	85:15	98
10[f]	*n*-Pr	H	4-NO_2	**4j**/68	80:20	87
11	*n*-Pr	H	4-Me	**4k**/68	89:11	96
12[f]	*n*-Pr	H	4-OMe	**4l**/72	80:20	96
13[f]	*n*-Pr	H	2-Me	**4m**/65	95:5	98
14	*n*-Pr	H	3-Me	**4n**/87	89:11	99
15[f]	*i*-Pr	H	4-Cl	**4o**/74	98:2	98
16[f]	*i*-Pr	H	4-Br	**4p**/73	87:13	89
17[g]	Bn	H	H	**4a**/90	94:6	98

[a]Unless otherwise specified, all reactions were carried out with **1** (0.12 mmol), **2** (0.10 mmol), and the precatalyst modules **6a** and **7a** (0.010 mmol each, 10 mol%) in dry toluene (1.0 mL) at room temperature for 16 h. Once the reaction was complete, the initial products were purified by flash column chromatography and then oxidized with PCC (3.0 equiv.) in CH_2Cl_2 at rt for 24 h. [b]Yield of the isolated product after flash column chromatography (overall yield after two steps of reactions). [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by HPLC analysis on ChiralPak AD-H, OD-H, or IC columns. The absolute stereochemistry was assigned by comparing the measured optical rotation of compound **4d** with that reported in the literature (Ref. 12). [e]The reaction time was 72 h. [f]The reaction time was 24 h. [g]Reaction performed in 0.50 mmol scale.

substituted (*E*)-2-(2-nitrovinyl)phenols were then screened. It was found that these substituted (*E*)-2-(2-nitrovinyl)phenols usually led to slightly lower yields (65-87%) and diastereoselectivities (80:20 to 95:5 dr) of the corresponding chroman-2-ones (**4h**-**n**, entries 8-14) as compared to those obtained from the unsubstituted (*E*)-2-(2-nitrovinyl)phenol (entry 4). However, the product ee values remained high (entries 8-14). On the other hand, the electronic nature and the position of the substituent on the phenyl ring of (*E*)-2-(2-nitrovinyl)phenol had no significant effects on the diastereoselectivities or the product ee values (entries 8-14), except that a slightly lower ee value was obtained for the chroman-2-one product of the 4-nitro-substituted phenol (entry 10). Using the branched 3-methylbutanal as the aldehyde component yielded comparable results with those of pentanal (entries 15-16 vs. 8-9).

To demonstrate the synthetic utility of this method, the same reaction was also carried out at 0.5-mmol scale of **1a** and **2a**. As the results in Table 2 show, product **4a** was obtained in comparable yield, diastereoselectivity, and ee value as those of the small-scale reaction (entry 17 vs. entry 1).

Table 3 Converting the primary hemiacetal products **3** to chromanes **5** via dehydroxylation[a]

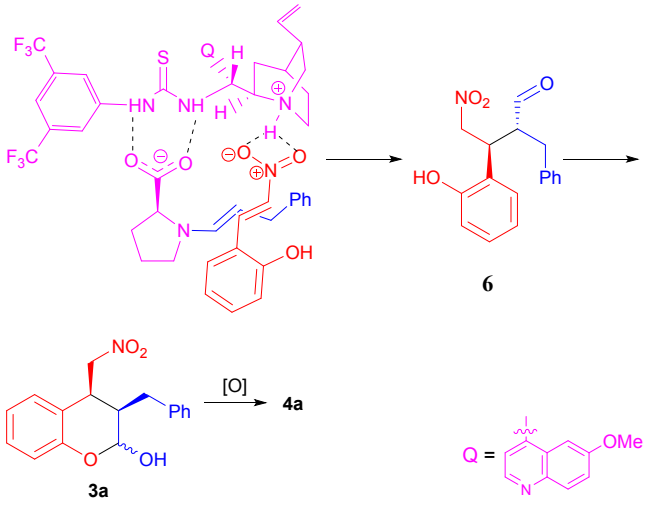


3 5

Entry	R	**5**/Yield[b] (%)	dr[c]	ee[d] (%)
1	Et	**5a**/90	88:12	98
2	*n*-Pr	**5b**/94	85:15	98
3	*i*-Pr	**5c**/72	95:5	92

[a]Unless otherwise specified, all reactions were carried out with **3** (0.10 mmol), triethylsilane (0.30 mmol), and boron trifluoride diethyl etherate (0.30 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C to room temperature for 2 h. [b]Yield of the isolated product after flash column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by HPLC analysis on ChiralPak OD-H or IB columns. The absolute stereochemistry was assigned by comparing the measured optical rotation of compound **5a** with that reported in the literature (Ref. 12).

To obtain the 3,4-substituted chromanes **5**, the primary domino Michael/hemiacetalization products **3** were dehydroxylated by treating with triethylsilane and boron trifluoride diethyl etherate in dichloromethane (Table 3). As shown in Table 3, the dehydroxylation reaction provided the desired products **5a-c** in good to excellent yields (72–94%) with preservation of the diastereoselectivities (85:15 to 95:5 dr:) and enantioselectivities of the domino reaction (92 to 98% ee).



Scheme 2 Proposed transition state that accounts for the formation of the major stereoisomer.

The absolute stereochemistry of the major enantiomeric products of compounds **4** and **5** was determined as shown in the Tables by comparing the measured optical rotation of compounds **4d** and **5a** with those reported in the literature.[12] Based on the product stereochemistry and a recent computational study our MDO catalytic system,[18] a plausible

transition state is proposed to account for the formation of the major stereoisomer of the domino Michael/hemiacetalization reaction (Scheme 2). As shown in Scheme 2, the *Si-Si* attack of the preferred *syn*-(*E*)-enamine[18] of hydrocinnamaldehyde onto the (*E*)-2-(2-nitrovinyl)phenol (**2a**) yields the Michael addition intermediate **6** with the expected stereochemistry of the two stereogenic centers, which, after an intramolecular hemiacetalization reaction, gives product **3a**. Product **3a** yields the expected **4a** upon oxidation.

Experimental

Representative procedure for the synthesis of chroman-2-ones via the domino Michael/hemiacetalization followed by an oxidation reaction: To a vial were added sequentially the precatalyst modules **6a** (5.9 mg, 0.010 mmol, 10.0 mol %) and **7a** (1.1 mg, 0.010 mmol, 10.0 mol %) and dry toluene (1.0 mL). The resulting mixture was stirred at room temperature for 15 min. Compound **1a** (16.0 mg, 0.12 mmol, 1.2 equiv.) was then added and the mixture was further stirred for 5 min. before the addition of compound **2a** (16.5 mg, 0.1 mmol, 1.0 equiv.). The resulting solution was stirred at room temperature for 16 h until the reaction was complete (monitored by TLC). Then the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography to give the chroman-2-ol **3a** as a colorless oil (29.9 mg). A solution of the chroman-2-ol **3a** (29.9 mg, 0.10 mmol) in CH_2Cl_2 (3.0 mL) and PCC (64.5 mg, 0.30 mmol, 3.0 equiv.) was stirred at room temperature for 24 h until the completion of reaction (monitored by TLC). The suspension was filtered through a short pad of silica gel and washed with ethyl acetate. Removing the solvents under reduced pressure afforded the crude product **4a**, which was then purified by flash chromatography (30:70 EtOAc/hexane as the eluent) to afford product **4a** (28.0 mg, 94%) as a colorless oil.

General procedure of the dehydroxylation reaction:[10,12] To a solution of chroman-2-ol **3** (0.10 mmol, 1.0 equiv.) in CH_2Cl_2 (3.0 mL) at 0 °C were added triethylsilane (34.9 mg, 0.30 mmol, 3.0 equiv.) and boron trifluoride etherate (42.6 mg, 0.30 mmol, 3.0 equiv.) with stirring. The ice bath was removed after 15 min and the mixture was further stirred for 2 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ solution (3 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the corresponding chromane **5**.

Conclusions

In summary, we have developed a highly stereoselective synthesis of *cis*-3,4-disubstituted chroman-2-ones and chromanes using a domino Michael/hemiacetalization- reaction of aliphatic aldehydes and (*E*)-2-(2-nitrovinyl)phenols catalyzed by modularly designed organocatalysts (MDOs) followed by a PCC oxidation or dehydroxylation. The corresponding chroman-2-ones and chromanes were obtained in good to excellent yields and diastereomeric ratios and high ee values.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Table of Content Entry

Stereoselective synthesis of chromane derivatives via a domino reaction catalyzed by modularly designed organocatalysts

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A highly enantio- and diastereoselective synthesis of functionalized chroman-2-ones and chromanes was achieved.