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Asymmetric Synthesis of *cis*-3,4-Disubstituted Chromans and Dihydrocoumarins *via* an Organocatalytic Michael Addition/ Hemiacetalization Reaction

Dieter Enders,[a,*] Chuan Wang,[a] Xuena Yang,[a] and Gerhard Raabe[a]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax: (+49)-241-809-2127; e-mail: enders@rwth-aachen.de

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Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday.

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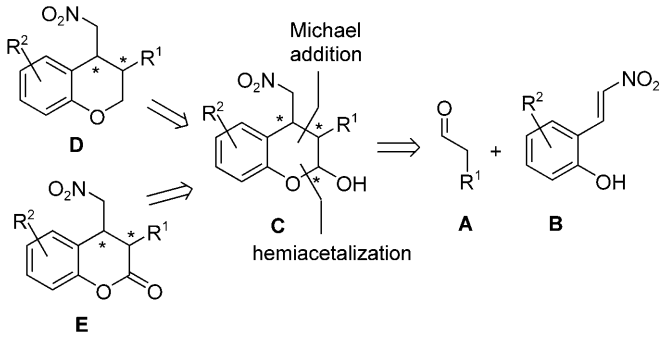
Abstract: The organocatalytic domino Michael/hemiacetalization reaction between various aldehydes and *ortho*-nitrovinylphenols has been developed. Under the catalysis of diphenyl prolinol trimethylsilyl ether, *cis*-3,4-disubstituted chromanols are obtained in high to excellent yields (81–98%) and stereoselectivities (*dr*: 86:14 to >99:1, *ee* 96 to >99%). The corresponding disubstituted chromans are available by dehydroxylation of the domino products in good to excellent yields (58–95%). Furthermore, oxidation of the domino products with pyridinium chlorochromate provided 3,4-dihydrocoumarins in good yields (65–83%) without any epimerization.

Keywords: chromans; 3,4-dihydrocoumarins; hemiacetalization; Michael addition; organocatalysis

After first reports by List et al., Barbas et al. and our group, organocatalyzed Michael additions to nitroalkenes were developed with breathtaking speed in the last decade.[1–3] Much effort has been devoted to the development of new organocatalysts to improve the efficiency and the stereoselectivity of this Michael addition.[4] Furthermore, considerable attention has been given to the expansion of the substrate spectrum of both the donor and the acceptor structures with known catalysts.[5] Moreover, domino or tandem reactions involving Michael additions to nitroalkenes, which provide direct access to structurally complex cyclic compounds bearing the synthetically useful nitro group, have also been intensively investigated in the last years.[6,7]

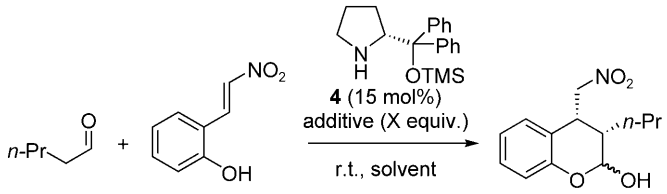
The chroman core is the central structural skeleton present in various biologically active compounds and thus many reports on the asymmetric synthesis of this moiety have been published.[8,9] The dihydrocoumarin structure is also present as a subunit in diverse compounds exhibiting biological activities.[10] Therefore, numerous methods have been developed to approach this moiety in an asymmetric manner.[11] To access these two structural motifs we envisaged an organocatalytic Michael/hemiacetalization reaction[12,13] using aldehydes (**A**) and (*E*)-2-(2-nitrovinyl)phenols (**B**) as substrates (Scheme 1). This cascade is initiated by an enamine-mediated Michael addition, followed by an intramolecular hemiacetalization. In this process 3,4-disubstituted chroman-2-ols (**C**) are provided as the domino product, which can be converted into 3,4-disubstituted chromans (**D**) by removal of the OH group or into 3,4-dihydrocoumarins (**E**) by oxidation of the lactol moiety.

In the first instance we performed the reaction of (*E*)-2-(2-nitrovinyl)phenol (**2a**) and 3 equivalents of



Scheme 1. Asymmetric synthesis of substituted chromans (**C**, **D**) and dihydrocoumarins (**E**) *via* an organocatalytic Michael/hemiacetalization reaction – retrosynthetic analysis.

Table 1. Additive and solvent screening for the organocatalytic Michael/hemiacetalization reaction.[a]



1a **2a** **3a**

Entry	Solvent	Additive	X [equiv.]	*t* [h]	Yield [%][b]	*dr*[c] *cis*:*trans*	*ee* [%][d] *cis, trans*
1	toluene	–	–	96	32	60:40	99, 83
2	toluene	$PhCO_2H$	0.2	96	66	62:38	99, 88
3	toluene	$4\text{-}NO_2C_6H_4CO_2H$	0.2	96	54	61:39	98, 85
4	toluene	CF_3CO_2H	0.2	96	30	59:41	98, 88
5	toluene	CH_3CO_2H	0.2	96	74	66:34	99, 87
6	toluene	NEt_3	1.0	96	0	–	–
7	toluene	CH_3CO_2H	1.0	72	96	76:24	99, 74
8	CH_2Cl_2	CH_3CO_2H	1.0	72	80	81:19	99, 69
9	MeOH	CH_3CO_2H	1.0	72	72	52:48	97, 71
10	MeCN	CH_3CO_2H	1.0	72	56	76:24	99, 64
11	H_2O	CH_3CO_2H	1.0	12	98	79:21	>99, 63
12	H_2O	CH_3CO_2H	5.0	12	98	86:14	99, 45
13	**H_2O**	**CH_3CO_2H**	**25.0**	**12**	**98**	**92:8**	**>99, 10**
14	H_2O	CH_3CO_2H	50.0	24	traces	–	–
15	CH_3CO_2H	–	–	24	traces	–	–
16[e]	H_2O	CH_3CO_2H	25.0	24	98	92:8	>99, 19

[a] Unless otherwise specified, reactions were performed on a 1.0-mmol scale of (*E*)-2-(2-nitrovinyl)phenol (**2a**) using 3.0 equivalents of pentanal (**1a**), 15 mol% catalyst **4** and X equivalents of additive at room temperature in 4.0 mL of solvent.

[b] Yield of the isolated product after flash chromatography.

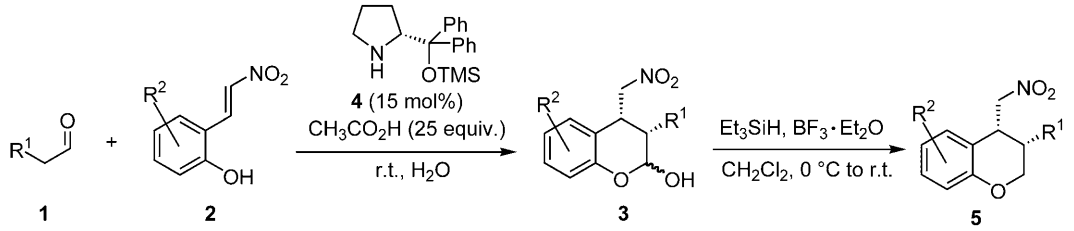
[c] Determined by ^{1}H NMR spectroscopy on the corresponding dehydroxylated derivatives.

[d] Determined by HPLC or GC analysis on a chiral stationary phase on the corresponding dehydroxylated derivatives.

[e] Carried out at 4 °C.

pentanal (**1a**) in toluene at room temperature. The catalyst diphenylprolinol TMS-ether **4**[14,15] (15 mol%) was used because it shows good catalytic activity and excellent asymmetric induction in enamine-mediated Michael additions to nitrostyrens.[4e,5c] The reaction afforded the chromanol **3a** after 96 h in a low yield (32%) and diastereomeric ratio (*cis*:*trans* = 60:40). However, an excellent enantiomeric excess was achieved for the major enantiomer (*ee* 99%) (Table 1, entry 1). To improve both the yield and the diastereoselectivity of this reaction, various acidic and basic additives were tested with toluene as solvent. In the cases of acidic co-catalysts similar or improved yields and diastereoselectivities were obtained and the best result was achieved when acetic acid was used as additive (Table 1, entries 2–5). No product was formed in the case of triethylamine (Table 1, entry 6). When the amount of acetic acid was increased from 0.2 to 1.0 equiv. the reaction was complete after 72 h to give **3a** in an excellent yield (96%), enantioselectivity (*ee* 99%) and moderate diastereomeric ratio (*cis*:*trans* = 76:24) (Table 1, entry 7). Based on these results, a brief solvent screening was undertaken. Excellent enantiomeric excesses were obtained in all solvents used (Table 1, entries 8–11). The best outcome with respect to yield and stereoselectivities was achieved when the reaction was conducted in water (Table 1, entry 11). The obtained results indicated that both the efficiency and the diastereoselectivity of this reaction could be improved by increasing the quantity of the acetic acid. Taking this into account we performed the reaction in water with 5.0, 25.0 and 50.0 equivalents of acetic acid, respectively (Table 1, entries 12–14). In the case of 25.0 equivalents of acetic acid the reaction was complete after 12 h furnishing the product in excellent yield (98%), very good diastereomeric ratio (*cis*:*trans* = 92:8) and perfect enantioselectivity (*ee* >99%) (Table 1, entry 13). Surprisingly, when the amount of added acetic acid was increased to 50.0 equivalents only a very low conversion of (*E*)-2-(2-nitrovinyl)phenol (**2a**) was observed (Table 1, entry 14). A similar result was obtained when the reaction was carried out with acetic acid as solvent (Table 1, entry 15). Finally, the reaction was per-

Table 2. Organocatalytic Michael/hemiacetalization reactions between aldehydes **1** and (*E*)-2-(2-nitrovinyl)phenols (**2**)[a] to form the hemiacetals **3** and dehydroxylation to the chromans **5**.[b]



3/5	R^1	R^2	*t* [h]	Yield [%][c]	Yield [%][d]	*dr*[e] *cis:trans*	*ee* [%][f]
a	*n*-Pr (**1a**)	H (**2a**)	12	98	80	92:8	>99
b[g]	Et (**1b**)	H (**2a**)	12	98	81	95:5	–98
c[g]	*n*-Bu (**1c**)	H (**2a**)	12	98	95	92:8	–99
d	allyl (**1d**)	H (**2a**)	12	98	80	92:8	98
e	Bn (**1e**)	H (**2a**)	24	95	68	86:14	98
f	*i*-Pr (**1f**)	H (**2a**)	24	98	85	>99:1	>99
g	*i*-Pr (**1f**)	2-MeO (**2b**)	72	85	58	>99:1	>99
h[g]	*i*-Pr (**1f**)	4-Br (**2c**)	24	98	58	>99:1	–96
i[g]	*i*-Pr (**1f**)	4-Cl (**2d**)	24	95	60	>99:1	–99
j	*i*-Pr (**1f**)	5-Me (**2e**)	24	81	92	>99:1	>99
k	*i*-Pr (**1f**)	3-MeO (**2f**)	72	86	78	>99:1	>99

[a] Unless otherwise specified, reactions were performed on a 1.0 mmol scale of (*E*)-2-(2-nitrovinyl)phenols **2** using 3.0 equivalents of aldehydes (**1**), 15 mol% catalyst **4** and 25.0 equivalents of CH_3CO_2H at room temperature in 4.0 mL of H_2O.

[b] Reactions were performed on a 0.75-mmol scale of 3,4-disubstituted chroman-2-ols **3** using 3.0 equivalents of triethylsilane and 3.0 equivalents of boron trifluoride etherate in 3.0 mL of CH_2Cl_2.

[c] Yield of the isolated product **3** after flash chromatography.

[d] Yield of the isolated product **5** after flash chromatography.

[e] Determined by ^1H NMR spectroscopy on the isolated product **5**.

[f] Determined by HPLC or GC analysis on a chiral stationary phase on the isolated product **5**.

[g] (*S*)-**4** was used as the catalyst.

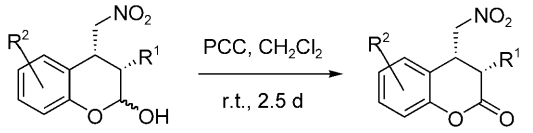
formed at 4 °C, giving no better results than at room temperature (Table 1, entry 16).

Based on the optimized conditions, we investigated the scope of the reaction by variation of the structure of both the aldehydes **1** and the nitrovinylphenols **2** (Table 2). In the cases of the linear aldehydes pentanal (**1a**), butanal (**1b**), hexanal (**1c**) and 4-pentenal (**1d**) with (*E*)-2-(2-nitrovinyl)phenol (**2**), the reactions were complete after 12 h furnishing the products **3a–d** in excellent yields (98%), high diastereoselectivities (*dr*: 95:5–92:8) and excellent enantiomeric excesses (*ee* 98 to >99%). 3-Phenylpropanal (**1e**) reacted well, too, providing the cascade product **3e** in an outstanding yield (95%) and enantiostereoselectivity (*ee* 98%), but relatively low diastereomeric ratio (*dr*: 86:14). When 3-methylbutanal (**1f**) was used as the donor, the product was obtained in a virtually diastereo- and enantiomerically pure form (*dr*: >99:1, *ee* >99%) with excellent yield (98%). Next, we reacted 3-methylbutanal (**1f**) with several substituted (*E*)-2-(2-nitrovinyl)phenols **2b–f**. Generally, the electronic features and the position of the substituent on the aromatic ring had no significant influence on the level of the asymmetric induction of this reaction, while excellent results (*dr*: >99:1, *ee* 96 to >99%) were obtained in all cases. The reactions employing (*E*)-5-methyl-2-(2-nitrovinyl)phenol (**2e**) and the halogen-substituted nitrovinylphenols **2c, d** were complete within 24 h, affording the corresponding chromanols **3h–j** in good to excellent yields (81–98%). In the cases of the methoxy-substituted nitrovinylphenols **2b**, **f** a longer reaction time (72 h) was needed to provide the product in good yields (85–86%).

In order to obtain the 3,4-substituted chromans **5** the domino products **3** were dehydroxylated by treatment with triethylsilane and boron trifluoride etherate using dichloromethane as solvent. The reaction provided the desired products **5** in good to excellent yields (58–95%), diastereomeric ratios (*dr*: 86:14 to >99:1) and excellent enantiomeric excesses (*ee* 96 to >99%) (Table 2).

Some chromanols **3a**, **f**, **j**, **k** were oxidized with pyridinium chlorochromate (PCC) at room temperature in dichloromethane furnishing the *cis*-disubstituted 3,4-dihydrocoumarins **5a**, **f**, **j**, **k** in good to high yields (65–83%) and in a virtually diastereo- and enantiomerically pure form (*dr*: >99:1, *ee* >99%) (Table 3). In all the cases no racemization was observed. Nota-

Table 3. Asymmetric synthesis of *cis*-3,4-disubstituted dihydrocoumarins **6**.[a]



3 **6**

6	R^1	R^2	Yield [%][b]	*dr*[c]	*ee* [%][d]
a	*n*-Pr	H	74	>99:1	>99
f	*i*-Pr	H	83	>99:1	>99
i	*i*-Pr	4-Cl	78	>99:1	>99
j	*i*-Pr	5-Me	65	>99:1	>99
k	*i*-Pr	3-MeO	82	>99:1	>99

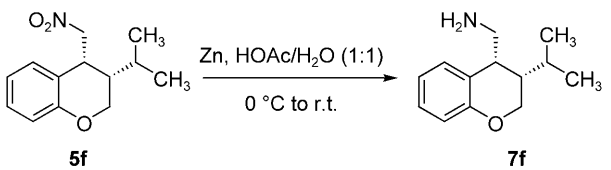
[a] Unless otherwise specified, reactions were performed on a 0.75 mmol scale of 3,4-disubstituted chroman-2-ols **3** using 2.0 equiv of PCC in 2.3 mL CH_2Cl_2 at rt.
[b] Yield of the isolated product after flash chromatography.
[c] Determined by ^{1}H NMR-spectroscopy on the isolated product.
[d] Determined by HPLC or GC analysis on a chiral stationary phase on the isolated product.

bly, when the chromanol **3a** was employed as the substrate, the corresponding dihydrocoumarin **6a** was obtained in a better diastereomeric ratio (*dr*: >99:1) in comparison to its precursor **3a**. This can be explained by the removal of the minor *trans*-isomer of **6a** during the chromatographic purification.

Furthermore, a *cis*-3,4-disubstituted chroman **5f** was readily converted into the corresponding amine **7f** in excellent yield (90%) by treatment with zinc powder in H_2O/HOAc as a 1:1 mixture (Scheme 2).

The relative and absolute configurations of the title compounds were unambiguously determined to be 3*S*,4*R* in the case of **5i** by X-ray structure analysis (Figure 1).

In summary, we have developed an organocatalytic Michael/hemiacetalization reaction in water between various aldehydes and *ortho*-nitrovinylphenols under diphenylprolinol TMS ether catalysis providing the *cis*-3,4-disubstituted chroman-2-ols in good to excellent yields (81–98%) and stereoselectivities (*dr*: 86:14 to >99:1, *ee* 96 to >99%). The domino products have



5f **7f**

90%
dr: >99:1, *ee* >99%

Scheme 2. Synthesis of the amine **7f** by reduction of the chroman **5f**.

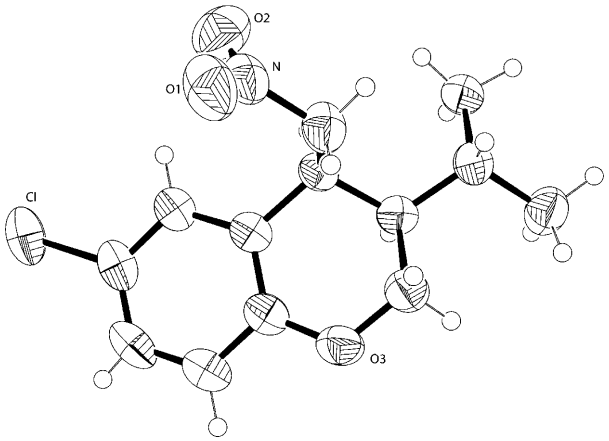


Figure 1. X-ray crystal structure of **5i**.[16]

been successfully converted to the corresponding *cis*-3,4-disubstituted chromans by means of a dehydroxylation reaching good to excellent yields and stereoselectivities. Furthermore, *cis*-3,4-disubstituted dihydrocoumarins are available by pyridinium chlorochromate oxidation of the domino products.

Experimental Section

General Procedure of the Organocatalytic Domino Reaction

To a solution of diphenylprolinol TMS ether (**4**) (0.15 mmol, 15 mol%), acetic acid (25.0 mmol, 25.0 equiv.) and (*E*)-2-(2-nitrovinyl)phenols **2** (1.0 mmol, 1.0 equiv.) in water (4.0 mL) was added aldehyde **1** (3.0 mmol, 3.0 equiv.) at room temperature. After stirring for the time given in Table 2, the reaction mixture was extracted with ethyl acetate or dichloromethane. The combined organic phases were washed with saturated aqueous $NaHCO_3$ and NaCl solution successively, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (pentane:ether mixture) affording the corresponding chroman-2-ols **3** as a syrup or solid.

General Procedure for the Dehydroxylation

To a solution of chroman-2-ols **3** (0.75 mmol, 1.0 equiv.) in dichoromethane (3.0 mL) was added triethylsilane (2.25 mmol, 3.0 equiv.) and boron trifluoride etherate (2.25 mmol, 3.0 equiv.) at 0 °C successively. After 15 min the ice bath was removed and the mixture was stirred at room temperature for the time given in the Supporting Information. Then the reaction was quenched with saturated aqueous $NaHCO_3$ solution and the mixture was extracted with dichloromethane. The combined organic phases were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (pentane:ether mixture) affording the corresponding chromans **5** as a syrup or a solid.

General Procedure for the Oxidation

To a solution of the chroman-2-ols **3** (0.75 mmol, 1.0 equiv.) in dichloromethane (2.25 mL) were added silica gel (1.0 mass equiv.) and pyridinium chlorochromate (2.0 mmol, 2.0 equiv.) at room temperature successively. After stirring for 2.5 d, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (pentane:ether or pentane:dichloromethane mixture) affording the corresponding 3,4-dihydrocoumarins **5** as a syrup or solid.

Acknowledgements

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