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Enantioselective organocatalytic domino Michael–acetalization–Henry reactions of 2-hydroxynitrostyrene and aldehyde for the synthesis of tetrahydro-6*H*-benzo[*c*]chromenones†

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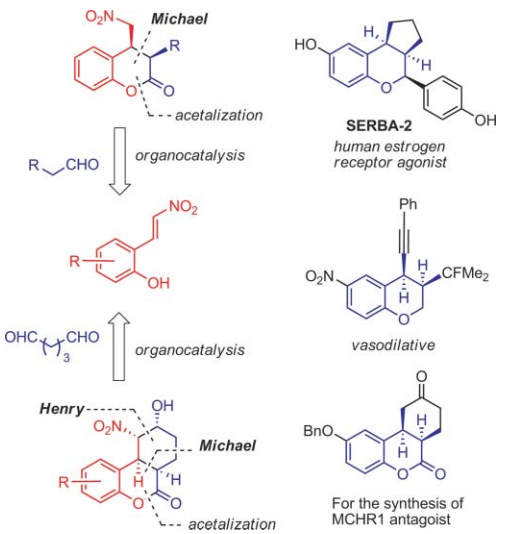
Asymmetric domino Michael–acetalization reactions of 2-hydroxynitrostyrene and aldehydes "on water" followed by oxidation providing the *cis*-3,4-disubstituted dihydrocoumarins with excellent enantioselectivities (up to >99% *ee*). The variant with glutaraldehyde underwent a highly stereoselective domino Michael–acetalization–Henry reaction to afford the tetrahydro-6*H*-benzo[*c*]chromen-6-ones after the subsequent oxidation.

The splendid recent progress in organocatalysis *via* cascade, tandem, domino,[1] or sequential reaction sequence has led to the development of new methodologies for the efficient enantioselective production of diverse arrays of compounds. Among annulation methodologies, the [4 + 2] annulation represents a powerful synthetic tool because two rings, two covalent bonds, and up to four contiguous stereocenters may be generated in a one-pot reaction. Recent advances in organocatalytic [4 + 2] annulations have further enriched this territory, including the Michael–Henry,[2] Michael/acetalization,[3] Mannich/*N*-cyclization,[4] double-Michael,[5] aldol-acetalization,[6] Rauhut–Currier reaction,[7] Michael-aldol,[8] and the hetero Diels–Alder reactions.[9]

Molecules containing coumarin or dihydrocoumarin skeletons are prevalent in nature, and their derivatives have been shown to exhibit a wide spectrum of pharmacological properties, including antineoplastic activity,[10] antiherpetic activity,[11] as well as the inhibition of protein kinases,[12] aldose reductase,[13] and HIV-1 reverse transcriptase.[14] As a result, extensive synthetic studies of this skeleton have been reported, including the synthesis of 3,4-disubstituted dihydrocoumarins,[15] 3,4-dihydro-4-alkyl-2*H*-chromen-2-ol,[16] and tetrahydro-6*H*-benzo[*c*]chromen-6-ones.[17] However, most of these syntheses have provided the dihydrocoumarin derivatives with *trans*- (*anti*-) disubstituents.

Taking into account the above background in the context of asymmetric synthesis, especially for organocatalytic reactions,[18] we envisioned an approach to *cis*-3,4-disubstituted dihydrocoumarins that could be accomplished by a domino Michael–acetalization reaction[19] of 2-hydroxynitrostyrene[20] and aldehydes, followed by oxidation (Scheme 1). Herein, we describe the first example of enantioselective organocatalytic domino Michael–acetalization–Henry reactions of 2-hydroxynitrostyrene and aldehyde "on water." This methodology permits production of *cis*-3,4-dialkyl-3,4-dihydrocoumarins and tetrahydro-6*H*-benzo[*c*]chromenones in excellent yields with up to 99% *ee*.



Scheme 1 Retrosynthetic analysis of *cis*-3,4-dialkyl-3,4-dihydrocoumarins and examples of biologically active derivatives.

Initially, we chose 2-((*E*)-2-nitrovinyl)phenol **1a** and butyraldehyde **2a** for the proposed Michael–acetalization reaction[21] in the presence of the Jørgensen–Hayashi catalyst **I**. Dihydrocoumarin **3a** was obtained, as we expected, after 144 h reaction in $CHCl_3$ at 30 °C and subsequent oxidation by PCC in CH_2Cl_2, with 77% and 82% yields, respectively (Table 1, entry 1). Various solvents were screened for the Michael–acetalization reaction, and the best results were obtained in regular ethanol (95%), Table 1, entries 1–6. In the worst case, the reaction did not occur in DMF (Table 1, entry 5). Because regular ethanol contains a certain amount of water, a series of reactions in the presence of varying amounts of water content was studied. The reaction took much longer in absolute ethanol, but the addition of more water in the ethanol system

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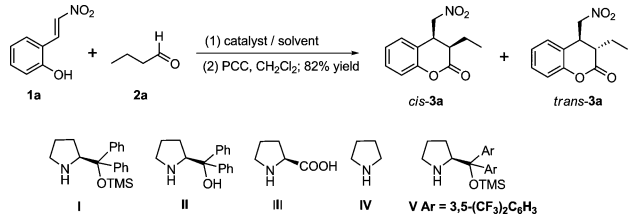
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compound, crystallographic data, and HPLC analysis. CCDC reference numbers 794373 for (–)-**3a**, 794374 for (–)-**3b** and 794375 for (–)-**3m**·H_2O. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00834f

Table 1 Screening of the catalyst, solvent, and reaction conditions for the domino reaction[a]



Entry	Solvent	Cat	Additive (20 mol%)	*t*/h	Yield (%)[f]	*cis* : *trans* (%)[g]	*ee* (%)[h]
1	$CHCl_3$	**I**	AcOH	144	77	72 : 28	>99
2	THF	**I**	PhCOOH	92	20	nd	nd
3	CH_2Cl_2	**I**	PhCOOH	42	81	82 : 18	nd
4	ACN	**I**	PhCOOH	96	43	nd	nd
5	DMF	**I**	PhCOOH	96	nr	na	na
6	EtOH[b]	**I**	PhCOOH	15	87	85 : 15	>99
7	EtOH[c]	**I**	PhCOOH	92	84	73 : 27	>99
8	EtOH–H_2O[d]	**I**	PhCOOH	48	83	74 : 26	nd
9	H_2O–EtOH[e]	**I**	PhCOOH	72	70	77 : 23	nd
10	H_2O	**I**	PhCOOH	92	69	78 : 22	>99
11[i]	H_2O[j]	**I**	AcOH	1	89	84 : 16	>99
12[i]	H_2O[j]	**I**	AcOH	52[k]	92	91 : 9	>99
13	EtOH[b]	**I**	PNBA	24	78	80 : 20	nd
14[i]	EtOH[b]	**I**	PhCOOH	48[k]	93	92 : 8	>99
15	EtOH[b]	**II**	PhCOOH	72	78	80 : 20	nd
16	H_2O	**II**	PhCOOH	144	70	79 : 21	nd
17	EtOH[b]	**III**	TEA	8	70	75 : 25	9
18	EtOH[b]	**IV**	AcOH	8	63	77 : 23	~0
19	EtOH[b]	**V**	PhCOOH	32	88	80 : 20	nd

[a] Unless otherwise noted, the reactions were performed in the presence of 20 mol% catalyst in 0.10 M **1a** with a ratio of 1 : 3 of **1a** : **2a** at 30 °C. [b] 95% EtOH was used. [c] Absolute EtOH was used. [d] EtOH–H_2O (5 : 1), [e] H_2O–EtOH (5 : 1). [f] Isolated yield for the Michael–acetalization step. [g] Determined by ^{1}H NMR after oxidation. [h] Determined by chiral column (Chiralpak IA). [i] A ratio of 1 : 6 of **1a** : **2a**. [j] 0.3 mmol **1a** in 0.5 mL H_2O. [k] Reaction at 15 °C. nr = no reaction, na = not applicable, nd = not determined.

also did not improve the reaction rate and yields (Table 1, entries 6–9). The optimal results were obtained in 95% ethanol (Table 1, entry 6). Encouraged by the recent success of other organocatalysis reactions in aqueous media (in water, on water or by water),[22] this reaction was studied extensively in water alone, and the best result was obtained under conditions of 0.3 mmol **1a**, a ratio of 1 : 6 **1a** : **2a**, conducted in 0.5 mL water with HOAc. To our delight, the reaction was facilitated and completed in *ca.* 1 h with an 89% yield of **3a** and excellent enantioselectivity (Table 1, entry 11). Apparently, substitution of benzoic acid with acetic acid in pure water was necessary to facilitate the reaction and promote the yield, probably due to the different solubilities of these two acids in water (Table 1, entries 10–11). Despite the numerous reports of the aldol reaction in water, only limited success has been achieved for the efficient Michael addition until quite recently.[23] The high yield and high enantioselectivity, as well as the regioselectivity, which favored the *cis*-adduct of the Michael–acetalization on water is noteworthy. Moreover, when the reaction was performed at low temperatures (15 °C), a better dr of the product, up to 91 : 9, was observed although with a longer time for achieving completion (Table 1, entry 12). Replacement of benzoic acid with *p*-nitrobenzoic acid in 95% EtOH did not improve the yields (Table 1, entry 13). On the other hand, reactions conducted with other catalysts, *e.g.*, **II–V**, gave lower yields (Table 1, entries 15–19).

The structure and relative stereochemistry of the reaction adduct were revealed by single crystal X-ray analysis of the (–)-*cis*-**3a** (Fig. 1).

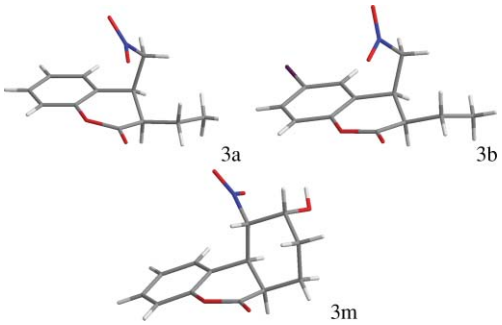
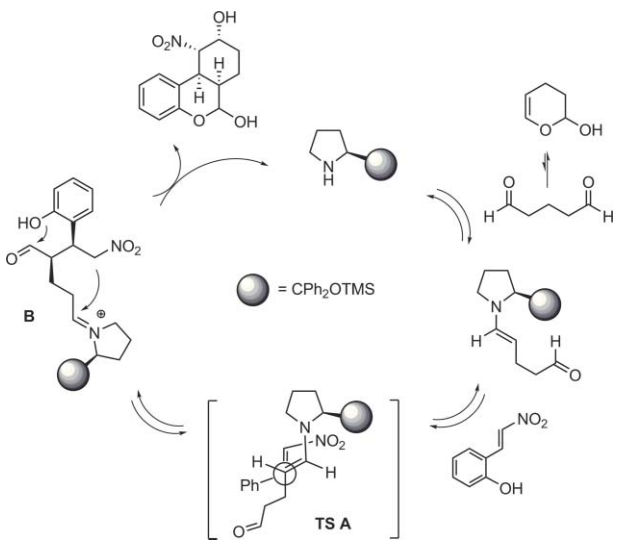


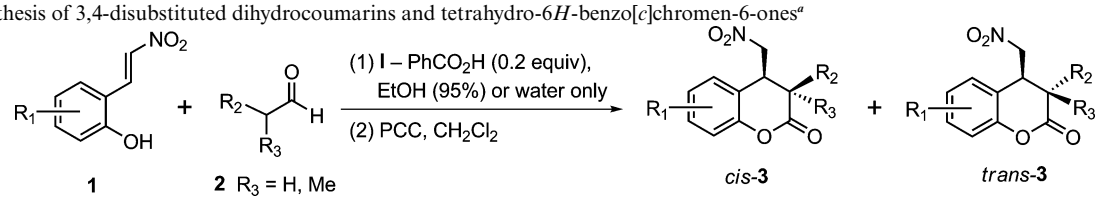
Fig. 1 Stereo plots of the X-ray crystal structures of (–)-**3a**, (–)-**3b** and (–)-**3m**: C, gray; N, blue; O, red; Br, purple.

Having established the optimal reaction conditions (Table 1, entries 6, 11, 12 and 14), we next examined the scope and limitations of the above system with various 2-hydroxynitrostyrenes and aldehydes. The reaction appears quite general with respect to the substrates tested, providing the desired adducts with excellent *ee* and good dr in good yields (Table 2). Reactions at lower temperature gave a better dr and favored the *cis*-adduct (*e.g.*, 92 : 8 in 95% EtOH—reaction at 15 °C *versus* 85 : 15 at 30 °C, Table 2, entry 1). Reaction with α-*tert*-butyldimethylsilyloxyacetaldehyde gave a less selective dr than the regular aldehydes, but the *trans*-adduct was obtained with much better *ee* than the regular alkyl aldehyde (Table 2, entry 9 and entry 5). Apparently, the OTBS group had a very different electronegativity and bulkiness than the regular alkyl substituents, which introduced discrepancies in the stereoselectivity of reactions with other alkyl substituents. The underlying reasons for these variations, however, are not yet clear. The reactions with isobutyraldehyde took a longer time to reach completion and led to products possessing an α-quaternary carbon (Table 2, entries 10–12). Reaction of the isobutyraldehyde and 4-methoxynitrostyrene gave much slower rates than usual,



Scheme 2 Proposed mechanism for the organocatalytic tandem Michael–acetalization–Henry reactions.

Table 2 Synthesis of 3,4-disubstituted dihydrocoumarins and tetrahydro-6*H*-benzo[*c*]chromen-6-ones[a]



1 **2** R_3 = H, Me *cis*-**3** *trans*-**3**

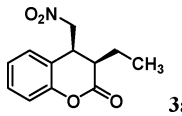
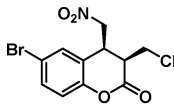
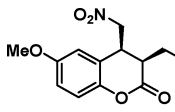
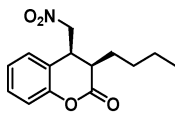
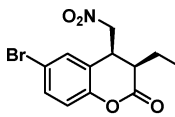
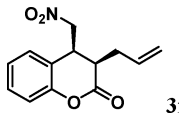
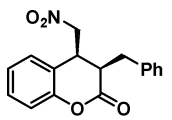
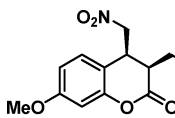
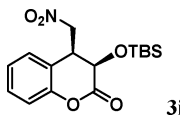
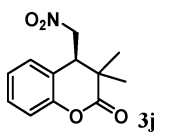
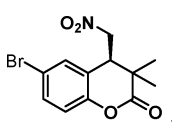
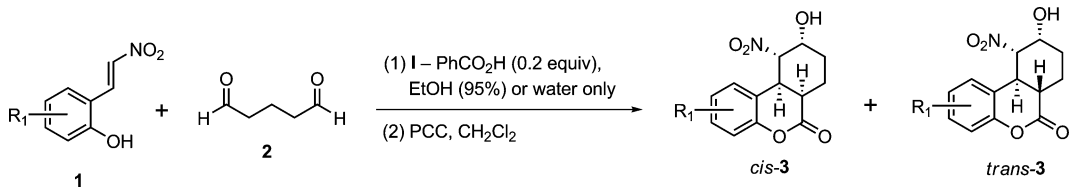
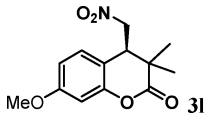
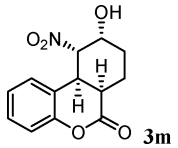
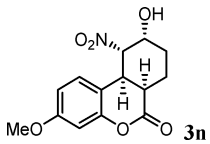
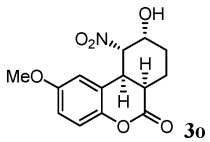
Entry	Product	Time/h[b]	*cis* : *trans* (%)[c]	Time/h[d]	*cis* : *trans* (%)[e]	Yield (%)[f]	*ee* (%)[g,h]
1	 **3a**	15 (48)	85 : 15 (92 : 8)	1 (52)	84 : 16 (91 : 9)	87/82	>99
2	 **3b**	13 (36)	82 : 18 (90 : 10)	1 —	81 : 19 —	81/72	>99[i]
3	 **3c**	32 (48)	85 : 15 (90 : 10)	2 —	84 : 16 —	79/75	>99[i]
4	 **3d**	24 (42)	86 : 14 (92 : 8)	1 —	83 : 17 —	77/76	>99[i]
5	 **3e**	16 (42)	70 : 30 (88 : 12)	1 —	83 : 17 —	75/77	>99[i](87)[g]
6	 **3f**	20 (42)	86 : 14 (93 : 7)	1 —	86 : 14 —	86/85	>99
7	 **3g**	24 (46)	83 : 17 (90 : 10)	3	80 : 20	83/86	>99
8	 **3h**	24 (38)	86 : 14 (92 : 8)	1	88 : 12	89/77	>99[i]
9	 **3i**	15 (32)	59 : 42 (66 : 33)	8	51 : 49	87/79	87(96)[i,g]
10	 **3j**	90	na	60	na	77/81	92[i]
11	 **3k**	82	na	52	na	89/72	90

Table 2 *(Contd.)*



Entry	Product	Time/h[b]	*cis* : *trans* (%)[c]	Time/h[d]	*cis* : *trans* (%)[e]	Yield (%)[f]	*ee* (%)[g,h]
12	 **3l**	120	na	82	na	88/75	80
13	 **3m**	42	88 : 12	24	81 : 19	50/76	>99
14	 **3n**	45	86 : 14	24	88 : 12	63/77	>99
15	 **3o**	46	87 : 13	30	80 : 20	65/81	>99

[a] The reactions were performed in 0.10 M **1** with a ratio of 1 : 6 of **1**:**2** in 95% EtOH at 15 °C, or "on water," in a ratio of 1 : 3 of **1** : **2** in 95% EtOH at 30 °C, a ratio of 1 : 2 of **1** : **2** for the reaction toward **3m**, **3n**, and **3o**. [b] The reaction time for the Michael–acetalization step in 95% EtOH at 30 °C, reaction at 15 °C in parentheses. [c] Determined by ^{1}H NMR after oxidation, dr ratio for the Michael–acetalization reactions in 95% EtOH at 30 °C, dr ratio for the reaction at 15 °C in parentheses. [d] The reaction time for the Michael–acetalization step on water at 30 °C, reaction at 15 °C in parentheses. [e] Determined by ^{1}H NMR after oxidation, dr ratio for the reactions on water at 30 °C, dr ratio for the reaction at 15 °C in parentheses. [f] Isolated yield (Michael–acetalization in 95% EtOH at 30 °C/oxidation), Michael–acetalization under other conditions gave similar yields. [g] The *ee* of the major oxidation product (*i.e.*, *cis*-**3**) of the Michael–acetalization at 30 °C in 95% EtOH; the minor products (*i.e.*, *trans*-**3**) are indicated in parentheses. The *ee* values of the reactions "on water" gave the same (or very similar) *ee* values as the reactions in 95% EtOH. [h] Unless otherwise noted, determined by chiral column (Chiralpak IA). [i] Determined by chiral column (Chiralcel OD-H). [j] Determined by chiral column (Chiralpak IB). na = not applicable.

and a 120 h reaction time was necessary to achieve completion (Table 2, entry 12). Interestingly, the reaction with glutaraldehyde provided the tetrahydro-6*H*-benzo[*c*]chromenones with excellent dr and *ee* (Table 2, entry 13–15); moreover, as compared to the monoaldehyde, a lower quantity of the aldehydes (two equivalents) was sufficient for the process, probably due to the fact that the self-acetalization equilibrium of glutaraldehyde hampered the self-aldol side reaction in the process. On the other hand, to our delight, the reactions performed "on water" were successful in all cases and dramatically facilitated without the presence of organic solvents in the Michael–acetalization reaction media. The remarkable rate enhancement of the reaction "on water," with similar yields, dr, and *ee* selectivity in 95% EtOH, is particularly attractive. The structure as well as the absolute configuration of the products were assigned unambiguously based on the X-ray analysis of (–)-**3b** and (–)-**3m** (Fig. 1). Thus, the origin of the stereoselectivity in this nitro-Michael reaction by catalyst **I** was similar to that observed in other examples of organocatalytic conjugate addition of aldehydes to nitroalkenes.[24]

A plausible mechanism, which may account for the highly stereoselective nature of this process, is shown in Scheme 2. Upon reaction with the organocatalyst, glutaraldehyde formed the enamine–aldehyde, which reacted with nitrostyrene *via* the transition state (TS) **A** to produce the *cis* intermediate **B**. The iminium **B** was then subject to the intramolecular Henry reaction and acetalization to produce the chromanol. The observed high stereoselectivity of the Henry reaction is noteworthy.

In conclusion, we have discovered an unprecedented asymmetric domino Michael–acetalization reaction and Michael–acetalization–Henry reaction for the synthesis of *cis*-3,4-disubstituted dihydrocoumarins and tetrahydro-6*H*-benzo[*c*]-chromen-6-ones with excellent enantioselectivities (up to >99% *ee*). Remarkably, this methodology proceeds facilely "on water" and provides a simple, environmentally benign, efficient, and direct protocol for the stereoselective construction of functionalized dihydrocoumarins. The presence of four contiguous chiral centers with high enantioselectivity in a three-bond-forming cascade Michael–acetalization–Henry reaction is especially noteworthy.

The structures and absolute configurations of the products were confirmed by X-ray analysis of three representative adducts. Further work is underway to gain additional insight into this annulation as well as the exploration of its synthetic applications.

Acknowledgements

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