EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300505

One-Pot Enantioselective Synthesis of 3-Nitro-2*H*-chromenes Catalyzed by a Simple 4-Hydroxyprolinamide with 4-Nitrophenol as Cocatalyst

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Keywords: Asymmetric catalysis / Oxygen heterocycles / Michael addition / Henry reaction / Domino reactions

The asymmetric domino oxa-Michael–Henry reaction of salicylaldehyde derivatives with *trans*-β-nitro olefins catalyzed by a readily available *trans*-4-hydroxy-L-prolinamide with 4-nitrophenol as an effective cocatalyst is presented. The corresponding 3-nitro-2*H*-chromenes were obtained in moderate to excellent yields (up to 99 %) and with up to 90 % *ee* under mild conditions. In addition, a preliminary study shows that this organocatalytic system is able to promote the domino aza-Michael–Henry reaction of 2-formylpyrrole derivatives with *trans*-β-nitro olefins to give chiral 2-nitro-3*H*-pyrrolizines.

Introduction

Chiral 2*H*-chromenes are important structural motifs frequently found in many natural products and synthetic molecules with unique biological and pharmacological activities. For example, Gaudichaudianic acid, a natural chromene isolated from *Piper gaudichaudianum*, has been described as a potent trypanocidal compound against the Y-strain of *Trypanosoma cruzi*,[1] and EM-800 shows antiestrogenic activity.[2] Moreover, this class of compounds could readily be used for the synthesis of valuable chiral chromans such as epigallocatechin gallate, a major constituent of green tea extract with potent anticancer activity,[3] and myristinin A, a DNA polymerase β inhibitor.[4] Consequently, much attention has been paid to the construction of chiral 2*H*-chromene scaffolds.[5] 3-Nitro-2*H*-chromenes are one of the most important subfamilies of 2*H*-chromenes, because of their biological activities[6] and their potential to be used as precursors in the synthesis of important targets.[3b,7] However, only a few strategies for the synthesis of 3-nitro-2*H*-chromenes in enantiomerically pure form have been explored to date, including: (i) tandem oxa-Michael–Henry reactions of salicylaldehyde derivatives with nitro olefins, catalyzed by chiral secondary amines;[8] (ii) organocatalytic kinetic resolution of racemic 3-nitro-2*H*-chromene derivatives;[9] (iii) intramolecular crossed Rauhut–Currier reactions of nitro olefins with tethered α,β-unsaturated esters, involving cooperative nucleophilic activation and hydrogen-bonding catalysis;[10] (iv) tandem oxa-Michael–aza-Henry-desulfonamidation of salicyl *N*-tosylimine with nitro olefins promoted by a bifunctional thiourea.[11] Unfortunately, these procedures suffer from poor to moderate enantioselectivities and/or low yields, and/or require commercially unavailable starting materials. Therefore, it is desirable to develop improved, efficient, catalytic methods for the synthesis of chiral 3-nitro-2*H*-chromenes.

Despite the fact that a range of substrates gave chiral 3-nitro-2*H*-chromenes with low *ee* values and in low yields, the condensation between salicylaldehyde derivatives and nitro olefins drew our attention, as it is a straightforward process that uses readily available starting materials.[8] Iminium-activated salicylaldehyde is a key intermediate in this process that was proposed and then confirmed by Xu's group.[8a] Over the past decade, chiral secondary amines, in particular, proline-based derivatives and MacMillan's imidazolidinones, have shown an extraordinary capacity to participate in asymmetric iminium activation with enals and enones.[12] On the other hand, the use of bifunctional organocatalysts to promote enantioselective transformations has recently emerged as a highly efficient tool for the construction of optically active molecules.[13] Synergistic activation by the functional groups on the catalyst can lead to control of the transition state structure, and so products can be formed with high enantioselectivities. We anticipated that a suitable bifunctional organocatalyst that could simultaneously activate both salicylaldehyde derivatives and nitro olefins could overcome the low *ee* values that were a limitation of this approach. In this paper, bifunctional organocatalysts **I** and **II**, based on the concepts of iminium catalysis and hydrogen-bonding activation using hydroxy group as hydrogen-bonding donor,[14] are reported to catalyze the asymmetric synthesis of 3-nitro-2*H*-chromenes by a domino oxa-Michael–Henry reaction. As shown in Scheme 1, hydrogen-bonding and electrostatic interactions were expected to help to connect the electrophile to the iminium-activated

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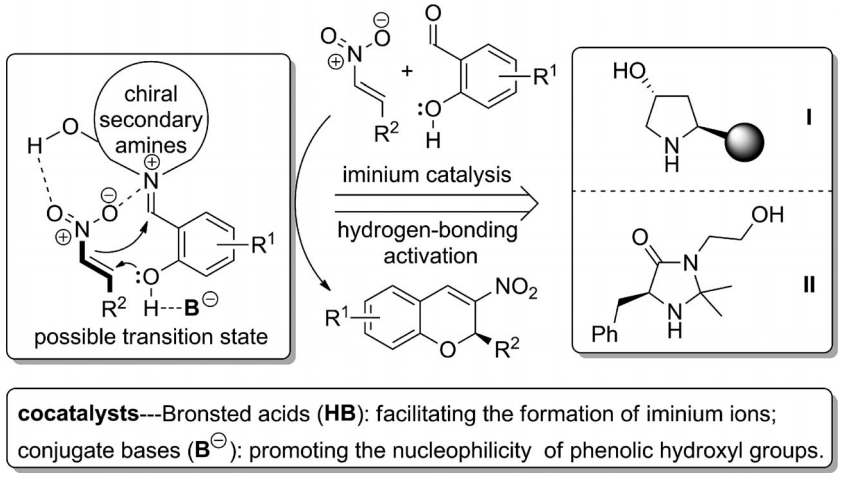
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300505.



Scheme 1. Strategy to simplify the catalytic system, and the possible transition state.

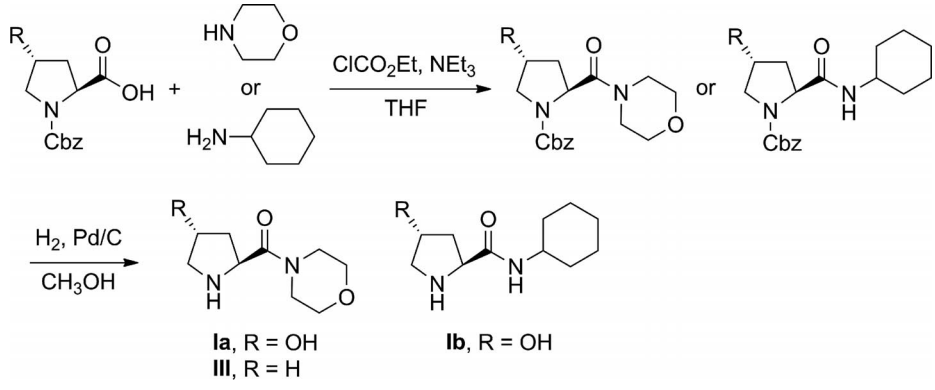
salicylaldehyde in the transition state. In addition, to facilitate the formation of iminium ions, an acid cocatalyst is generally needed in iminium catalysis.[12] We envisioned that the conjugate base of the acid cocatalyst might play an important role in promoting the nucleophilicity of iminium intermediate's phenolic hydroxy group by deprotonation or hydrogen-bonding interactions. As a result, improved yields could be achieved by using an appropriate acid cocatalyst.

Results and Discussion

Initially, organocatalysts **Ia** and **Ib** were synthesized from Cbz-protected *trans*-4-hydroxy-L-proline (Scheme 2). Treatment of Cbz-protected *trans*-4-hydroxy-L-proline with amines under standard coupling conditions (ethyl chloroformate and Et_3N in THF) provided the corresponding amides, which were then transformed into **Ia** and **Ib** by catalytic hydrogenation (Pd/C) in 29% and 57% overall yields, respectively. Starting from L-phenylalanine, imidazolidinone **II** was obtained according to the procedure described by Hansen.[15] To confirm whether the 4-hydroxy group in organocatalysts **I** plays an important role in activating *trans*-β-nitro olefins, as well as directing their approach, organocatalyst **III** was also prepared as shown in Scheme 2.

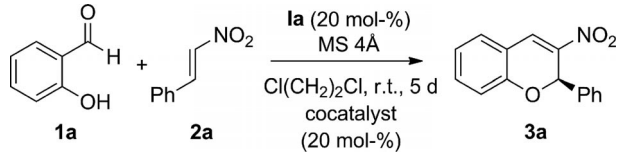
Having synthesized the desired organocatalysts, we first tested our hypothesis by treating salicylaldehyde (**1a**) with *trans*-β-nitrostyrene (**2a**) in the presence of organocatalyst **Ia**, together with benzoic acid as cocatalyst. Molecular sieves were added to remove the water generated in the reaction, and so push the equilibrium towards the formation of the iminium intermediate.[16] After five days of stirring in $Cl(CH_2)_2Cl$ at ambient temperature, 3-nitro-2-phenyl-2*H*-chromene (**3a**) was obtained in 28% yield and with 62% *ee* (Table 1, entry 1). The improved enantioselectivity but disappointing yield prompted us to search for an optimal cocatalyst by screening a range of acids (Table 1).

Similarly poor yields were observed with 4-toluenesulfonic acid, salicylic acid, or 4-nitrobenzoic acid as cocatalysts, regardless of the enantioselectivity (Table 1, entries 2–4). These results appeared to show that a less acidic cocatalyst gave the target compound in higher yield and with higher enantioselectivity. Thus, we turned to phenols including 2,4-dinitrophenol, 4-nitrophenol, and hydroquinone. To our delight, 4-nitrophenol gave a relatively high



Scheme 2. Synthesis of organocatalysts **Ia**, **Ib**, and **III**. Cbz = benzyloxycarbonyl.

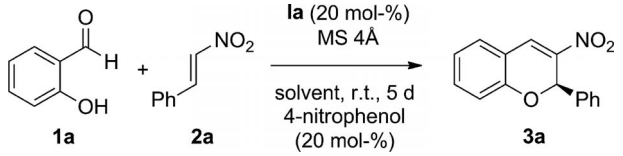
Table 1. Optimization of cocatalyst for the domino oxa-Michael–Henry reaction.[a]



Entry	Cocatalyst	Yield [%][b]	*ee* [%][c]
1	benzoic acid	28	62
2	4-toluenesulfonic acid	5	7
3	salicylic acid	10	56
4	4-nitrobenzoic acid	14	62
5	4-nitrophenol	63	72
6	2,4-dinitrophenol	4	54
7	hydroquinone	14	53
8	none	26	36

[a] All reactions were carried out with salicylaldehyde (**1a**; 0.1 mmol, 1.0 equiv.), *trans*-β-nitrostyrene (**2a**; 0.2 mmol, 2.0 equiv.), organocatalyst **Ia** (20 mol-%), cocatalyst (20 mol-%), and molecular sieves (4 Å; 100 mg) in $Cl(CH_2)_2Cl$ (0.5 mL) at room temperature for 5 d. [b] Determined by ^1H NMR spectroscopy using 4-nitrotoluene as internal standard. [c] Determined by chiral HPLC.

Table 2. Optimization of solvent for the domino oxa-Michael–Henry reaction.[a]



Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	$Cl(CH_2)_2Cl$	63	72
2	CH_2Cl_2	87	72
3	$CHCl_3$	93	80
4	toluene	62	62
5	CH_3OH	29	30
6	THF	7	44
7	DMSO	6	26
8	DMF	31	34
9	CH_3CN	42	45

[a] All reactions were carried out with salicylaldehyde (**1a**; 0.1 mmol, 1.0 equiv.), *trans*-β-nitrostyrene (**2a**; 0.2 mmol, 2.0 equiv.), organocatalyst **Ia** (20 mol-%), 4-nitrophenol (20 mol-%), and molecular sieves (4 Å; 100 mg) in solvent (0.5 mL) at room temperature for 5 d. [b] Determined by ^1H NMR spectroscopy using 4-nitrotoluene as internal standard. [c] Determined by chiral HPLC.

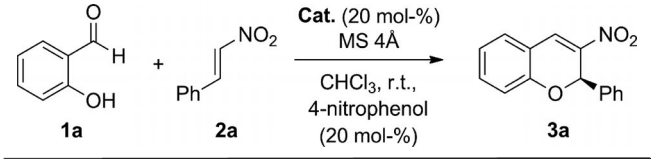
yield and good enantioselectivity (63% yield, 72% *ee*; Table 1, entry 5), whereas 2,4-dinitrophenol and hydroquinone were shown to be poor cocatalysts (Table 1, entries 6 and 7).

The domino oxa-Michael–Henry reaction was also investigated without any cocatalyst, and unsurprisingly, this gave the desired product in 26% yield and with 36% *ee* (Table 1, entry 8). It is well known that the stronger the acidity of the acid, the weaker the basicity of its conjugate base. The remarkable performance of 4-nitrophenol as cocatalyst could be rationalized by its having an acidity most appropriate for the formation of the iminium intermediate, and also its conjugate base being relatively strongly basic, which results in an enhancement of the nucleophilicity of the phenolic hydroxy group of the iminium intermediate.

Subsequently, we surveyed a number of solvents in an effort to further improve the yield and enantioselectivity (Table 2). In the presence of **Ia** and 4-nitrophenol, 2*H*-chromene product **3a** was obtained in high yields and high *ee* values in chlorinated solvents, of which $CHCl_3$ gave the best results (Table 2, entries 1–3). This is most likely to be due to the ability of the polar $CHCl_3$ to stabilize the charged iminium intermediate. As expected, the competition for hydrogen bonding made polar CH_3OH a poor medium for this process (Table 2, entry 5). Surprisingly little product was formed in both polar DMSO and less polar THF (Table 2, entries 6 and 7). We suppose that the electrostatic interactions between the charged iminium ion and the hydrogen-bond-acceptor solvents DMSO and THF, although helping to stabilize the iminium intermediate (unlike the polar, weak hydrogen-bond-donor solvent $CHCl_3$), hindered the facial approach of the *trans*-β-nitrostyrene to the iminium species, thereby resulting in poor yields and enantioselectivities.

We also screened different organocatalysts and reaction times for the domino oxa-Michael–Henry reaction. As shown in Table 3, **Ia** was the most effective organocatalyst in terms of yield and enantioselectivity. When structurally similar **Ib** was used as the catalyst, 2*H*-chromene **3a** was obtained in only 20% yield and with 40% *ee*. To our surprise, the use of MacMillan imidazolidinone **II** led to racemic product in 8% yield. The bulky chiral secondary amine might not easily form iminium ions with salicylaldehydes. With catalyst **III**, which doesn't bear a hydroxy group, a reduction in both the yield and the enantioselectivity was observed compared to **Ia**. This result clearly indicates that the hydroxy group in **Ia** plays an important role in activa-

Table 3. Optimization of organocatalyst and time for the domino oxa-Michael–Henry reaction.[a]



Entry	Catalyst	Time [d]	Yield [%][b]	*ee* [%][c]
1	**Ia**	5	93	80
2	**Ib**	5	20	40
3	**II**	5	8	0
4	**III**	5	55	62
5	**Ia**	4	85	80
6	**Ia**	6	91	80

[a] All reactions were carried out with salicylaldehyde (**1a**; 0.1 mmol, 1.0 equiv.), *trans*-β-nitrostyrene (**2a**; 0.2 mmol, 2.0 equiv.), organocatalyst (20 mol-%), 4-nitrophenol (20 mol-%), and molecular sieves (4 Å; 100 mg) in $CHCl_3$ (0.5 mL) at room temperature. [b] Determined by ^1H NMR spectroscopy using 4-nitrotoluene as internal standard. [c] Determined by chiral HPLC.

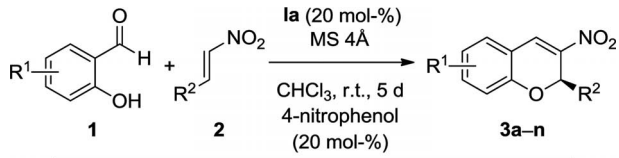
ting nitro olefins, as well as in directing their approach to the iminium intermediate through a hydrogen-bonding interaction. Next, the optimum reaction time for this process in the presence of **Ia**, 4-nitrophenol, and molecular sieves (4 Å) in $CHCl_3$ was confirmed to be 5 d.

Having established the optimal conditions, we investigated a range of salicylaldehyde derivatives and *trans*-β-nitro olefins to evaluate the scope of the domino process. The results are summarized in Table 4. It appears that the electronic properties and the positions of the substituents on the phenyl ring of the salicylaldehyde derivatives have a significant influence on the yield and enantioselectivity of the reaction (Table 4, entries 1–6). Relatively electron-rich salicylaldehyde derivatives showed higher reactivity, presumably due to the formation of more stable positive-charged iminium intermediates (Table 4, entries 1, 4, and 5). When salicylaldehyde derivatives with an electron-donating methoxy substituent at different positions were used in the reaction with *trans*-β-nitrostyrene (**2a**), 4-methoxysalicylaldehyde gave the best result (99% yield, 89% *ee*; Table 4, entry 3), whereas 3-methoxysalicylaldehyde and 5-methoxysalicylaldehyde led to **3b** and **3d**, respectively, with moderate enantioselectivities (Table 4, entries 2 and 4). Generally, *trans*-β-nitro olefins bearing electron-deficient or electron-rich aryl groups underwent the domino oxa-Michael–Henry reaction smoothly to give the corresponding 2*H*-chromenes in high yields and with good *ee* values (Table 4, entries 7–12). When a heteroaromatic β-furyl-substituted nitro olefin was used, a moderate yield of the product was observed (Table 4, entry 13). The aliphatic *trans*-β-nitro olefin derived from *n*-butyraldehyde also proved to be a viable substrate for this asymmetric transformation, resulting in the desired product (i.e., **3n**) in 78% yield and with 67% *ee* (Table 4, entry 14).

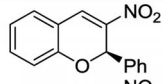
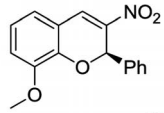
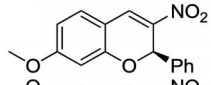
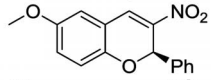
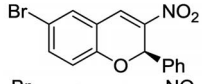
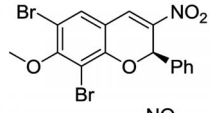
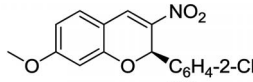
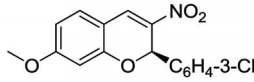
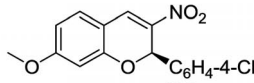
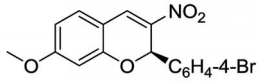
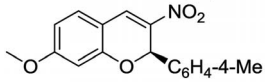
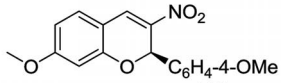
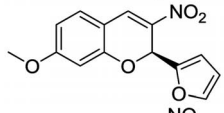
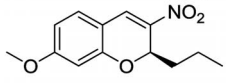
To account for the stereochemical outcome of the domino reaction, a plausible transition-state model has been proposed, and is shown in Figure 1. In this model, the amide side-chain sterically hinders one face of the iminium ion. Meanwhile, the 4-hydroxy group in catalyst **Ia**, together with the iminium ion, are believed to activate *trans*-β-nitro olefins and direct their approach from the opposite face through cooperative hydrogen-bonding and electrostatic interactions with the nitro group in substrate **2**. The performance of the organocatalysts, especially **Ia** and **III** (Table 3, entries 1 and 4), strongly support this proposed transition state. Moreover, this model can also be used to explain the moderate *ee* values of 2*H*-chromenes **3d**–**f** (Table 4, entries 4–6): the 5-substituents (-OMe, -Br) on the phenyl ring of the salicylaldehyde derivatives were close to the 4-hydroxy group in the iminium intermediates, which disturbed the formation of the hydrogen-bonding interaction with *trans*-β-nitro olefins **2**.

Next, our attention focused on finding further applications of this organocatalytic system. Inspired by the structural similarity between the salicylaldehyde derivatives and 2-formylpyrrole derivatives, we envisaged that an aza-Michael–Henry reaction between 2-formylpyrrole derivatives and *trans*-β-nitro olefins to give 2-nitro-3*H*-pyrrolizines could take place using the same organocatalytic system. To the best of our knowledge, the asymmetric synthesis of 2-nitro-3*H*-pyrrolizines has not been reported to date.

Table 4. Domino oxa-Michael–Henry reactions between salicylaldehyde derivatives **1** and *trans*-β-nitro olefins **2**.[a]



1 2 3a–n

Entry	Product		Yield [%][b]	*ee* [%][d]
1		**3a**	93[c]	80
2		**3b**	99	75
3		**3c**	99	89
4		**3d**	97	54
5		**3e**	68[c]	67
6		**3f**	37	65
7		**3g**	95	82
8		**3h**	98	84
9		**3i**	97	90
10		**3j**	99	88
11		**3k**	92	86
12		**3l**	99	86
13		**3m**	51	90
14		**3n**	78	67

[a] All reactions were carried out with salicylaldehyde derivatives (**1**; 0.1 mmol, 1.0 equiv.), *trans*-β-nitro olefins (**2**; 0.2 mmol, 2.0 equiv.), organocatalyst **Ia** (20 mol-%), 4-nitrophenol (20 mol-%), and molecular sieves (4 Å; 100 mg) in $CHCl_3$ (0.5 mL) at room temperature for 5 d. [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy using 4-nitrotoluene as internal standard. [d] Determined by chiral HPLC.

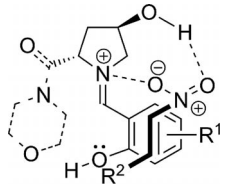
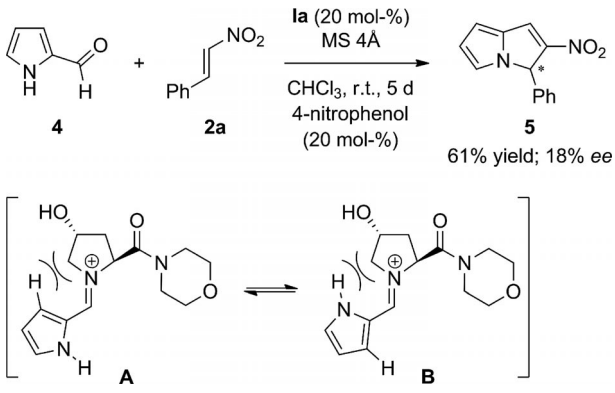


Figure 1. Proposed transition state in the asymmetric domino oxa-Michael–Henry reaction.

A preliminary study showed that 1*H*-pyrrole-2-carbaldehyde reacted with *trans*-β-nitrostyrene to give 2-nitro-3-phenyl-3*H*-pyrrolizine in 61% yield and with 18% *ee* (Scheme 3). An initial concern was that 2-nitro-3*H*-pyrrolizine **5** might undergo racemization under the reaction conditions. Racemization would lead to a reduction in *ee* as time went on.[17] Thus, a control experiment with a shortened reaction time (1 d) was performed to test for this possibility. Compound **5** was still formed with 18% *ee*, indicating that there was no racemization under the reaction conditions. Rather, a facile conformational switch between the two conformers (**A** and **B**), without a significant steric effect, accounts for the low *ee* of product **5**.



Scheme 3. Domino aza-Michael–Henry reaction of 1*H*-pyrrole-2-carbaldehyde with *trans*-β-nitrostyrene.

Conclusions

In summary, we have developed an efficient organocatalytic system, including a simple *trans*-4-hydroxyprolinamide catalyst and 4-nitrophenol as cocatalyst, for the synthesis of synthetically and biologically useful chiral 3-nitro-2*H*-chromenes. The domino oxa-Michael–Henry reaction between salicylaldehyde derivatives and *trans*-β-nitro olefins gave significantly better yields (up to 99%) and *ee* values (up to 90%) than those reported previously. The asymmetric synthesis of 2-nitro-3*H*-pyrrolizines has also been accomplished, albeit with poor enantioselectivity. Further investigations into applications of this organocatalytic system in domino aza-Michael–Henry reactions and other enantioselective domino reactions are ongoing in our laboratory.

Experimental Section

General Remarks: All reagents were used as purchased from commercial suppliers without further purification unless otherwise noted. Solvents were dried and purified according to standard procedures before use. Flash column chromatography was performed using 200–300 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer, and tetramethylsilane was used as a reference. ^{1}H NMR spectroscopic data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, br = broad), integration, coupling constants in Hertz (Hz). ^{13}C NMR spectroscopic data are reported in ppm. IR spectra were recorded with a Bruker Tensor 27 spectrometer and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were measured with a Bruker Daltonics micrOTOF-Q II instrument (ESI). Elemental analysis data were obtained with an Elementar Vario Micro cube instrument. Melting points were determined with a commercially available melting point apparatus. Optical rotations were measured with an Autopol II automatic polarimeter. Analytical chiral HPLC was performed using Daicel ChiralPak AS-H or Daicel Chiralcel OD columns.

Synthesis of Organocatalysts Ia and Ib

[(2*S*,4*R*)-4-Hydroxypyrrolidin-2-yl](morpholino)methanone (Ia): Ethyl chloroformate (3.61 g, 33.3 mmol) was added to a stirred solution of (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxyproline (8.73 g, 32.9 mmol) and triethylamine (3.35 g, 33.1 mmol) in anhydrous THF (50 mL) at 0 °C. After 30 min of stirring, morpholine (4.08 g, 46.8 mmol) was added, and the mixture was stirred further overnight. The resulting solid was removed by filtration and washed with EtOAc. The filtrate was concentrated under vacuum, and the residue was purified by silica gel flash column chromatography. The resulting product was dissolved in CH_3OH (10 mL), and Pd/C (20 wt-%) was added. The mixture was stirred at room temperature under an H_2 atmosphere (p = 1 atm) overnight. Then, the mixture was filtered through Celite, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to give title product **Ia** (1.91 g, 29% yield) as a white solid, m.p. 104–106 °C. $[\alpha]_D^{rt.}$ = –63.7 (c = 0.5 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.46 (s, 1 H), 4.18 (t, J = 7.6 Hz, 1 H), 3.65–3.70 (m, 6 H), 3.47–3.57 (m, 2 H), 3.36 (s, 2 H), 3.27 (dd, J = 11.2, J = 4.0 Hz, 1 H), 2.93 (d, J = 11.2 Hz, 1 H), 2.15 (dd, J = 12.8, J = 7.2 Hz, 1 H), 1.82–1.89 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 72.4, 66.8, 66.5, 56.4, 55.3, 45.5, 42.6, 40.0 ppm. HRMS (ESI): calcd. for $C_9H_{18}N_2O_3$ 201.1239 [M + H]$^+$; found 201.1230.

(2*S*,4*R*)-*N*-Cyclohexyl-4-hydroxypyrrolidine-2-carboxamide (Ib):[14e] White solid (57% yield), m.p. 160–162 °C; ref.[14e] 159–161.5 °C. $[\alpha]_D^{rt.}$ = –40.0 (c = 0.5 in CH_2Cl_2); ref.[14e] $[\alpha]_D^{28}$ = –40.5 (c = 0.2 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.0 Hz, 1 H), 4.42 (s, 1 H), 3.96 (t, J = 8.4 Hz, 1 H), 3.66–3.75 (m, 1 H), 3.02 (d, J = 12.4 Hz, 1 H), 2.78 (dd, J = 12.4, J = 3.2 Hz, 1 H), 2.64 (s, 2 H), 2.27 (dd, J = 14.0, J = 8.4 Hz, 1 H), 1.82–1.95 (m, 3 H), 1.69 (s, 2 H), 1.60–1.62 (m, 1 H), 1.32–1.42 (m, 2 H), 1.11–1.23 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 73.0, 59.7, 55.3, 47.4, 40.1, 33.1, 33.0, 25.5, 24.8 ppm. HRMS (ESI): calcd. for $C_{11}H_{22}N_2O_2$ 213.1603 [M + H]$^+$; found 213.1595.

General Procedure for the Asymmetric Domino Oxa-Michael–Henry Reaction: *trans*-β-Nitro olefin **2** (0.2 mmol, 2.0 equiv.) was added to a stirred mixture of molecular sieves (4 Å; 0.1 g), catalyst **Ia** (20 mol-%), 4-nitrophenol (20 mol-%), and salicylic aldehyde **1** (0.1 mmol, 1.0 equiv.) in chloroform (0.5 mL) at room temperature.

After stirring for 5 d, the solvent was removed in vacuo, and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 500:1–3000:1) on silica gel to give the corresponding 3-nitro-2*H*-chromene (i.e., **3**).

(*R*)-3-Nitro-2-phenyl-2*H*-chromene (3a):[8a,9a] Yellow solid (93% yield, 80% *ee*), m.p. 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.32–7.41 (m, 7 H), 7.02 (t, J = 7.6 Hz, 1 H), 6.89 (d, J = 8.4 Hz, 1 H), 6.61 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 141.2, 136.9, 134.3, 130.4, 129.5, 129.2, 128.9, 127.0, 122.5, 118.0, 117.3, 74.3 ppm. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 90:10; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 8.8 min, t_R (minor) = 15.0 min.

(*R*)-8-Methoxy-3-nitro-2-phenyl-2*H*-chromene (3b):[8a] Yellow solid (99% yield, 75% *ee*), m.p. 125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.39–7.41 (m, 2 H), 7.30–7.32 (m, 3 H), 6.95 (s, 3 H), 6.67 (s, 1 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 142.8, 141.4, 136.7, 129.4, 129.3, 128.8, 126.9, 122.5, 122.1, 118.8, 116.8, 74.2, 56.3 ppm. The enantiomeric excess was determined by HPLC with a Chiralpak OD column (hexane/2-propanol, 99:1; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 15.7 min, t_R (minor) = 37.6 min.

(*R*)-7-Methoxy-3-nitro-2-phenyl-2*H*-chromene (3c):[8a,9a] Yellow solid (99% yield, 89% *ee*), m.p. 147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.34–7.41 (m, 5 H), 7.26 (d, J = 8.4 Hz, 1 H), 6.57–6.59 (m, 2 H), 6.42 (d, J = 1.6 Hz, 1 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 155.6, 138.4, 137.1, 131.7, 129.8, 129.4, 128.9, 127.1, 111.1, 109.8, 102.2, 74.5, 55.7 ppm. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 85:15; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 15.4 min, t_R (minor) = 25.9 min.

(*R*)-6-Methoxy-3-nitro-2-phenyl-2*H*-chromene (3d):[8a] Yellow solid (97% yield, 54% *ee*), m.p. 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.31–7.36 (m, 5 H), 6.89 (dd, J = 8.8, J = 2.8 Hz, 1 H), 6.82 (d, J = 2.8 Hz, 1 H), 6.80 (d, J = 8.8 Hz, 1 H), 6.54 (s, 1 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 147.5, 141.8, 136.6, 129.4, 128.8, 127.0, 120.7, 118.5, 118.1, 113.7, 74.0, 55.8 ppm. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 85:15; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 12.0 min, t_R (minor) = 27.7 min.

(*R*)-6-Bromo-3-nitro-2-phenyl-2*H*-chromene (3e):[8c] Yellow solid (68% yield, 67% *ee*), m.p. 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.47 (d, J = 2.0 Hz, 1 H), 7.41 (dd, J = 8.8, J = 2.0 Hz, 1 H), 7.36 (s, 5 H), 6.78 (d, J = 8.8 Hz, 1 H), 6.60 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 142.0, 136.7, 136.2, 132.4, 129.8, 129.0, 127.8, 127.0, 119.8, 119.1, 114.5, 74.4 ppm. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 90:10; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 9.5 min, t_R (minor) = 16.5 min.

(*R*)-6,8-Dibromo-7-methoxy-3-nitro-2-phenyl-2*H*-chromene (3f): Yellow solid (37% yield, 65% *ee*), m.p. 146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.51 (s, 1 H), 7.36–7.41 (m, 5 H), 6.76 (s, 1 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 151.2, 141.5, 135.8, 132.3, 129.7, 128.9, 127.4, 126.8, 116.5, 110.6, 108.5, 74.7, 60.9 ppm. IR (KBr): $\tilde{\nu}$ = 1649, 1589, 1510, 1334, 1297, 1273 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{11}Br_2NO_4Na$ 463.8932 [M + Na]$^+$; found 463.8929. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 90:10; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 11.0 min, t_R (minor) = 16.0 min.

(*R*)-2-(2-Chlorophenyl)-7-methoxy-3-nitro-2*H*-chromene (3g): Yellow solid (95% yield, 82% *ee*), m.p. 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.50 (d, J = 7.6 Hz, 1 H), 7.26–7.32 (m, 2 H), 7.22 (dd, J = 7.6, J = 1.6 Hz, 1 H), 7.16 (t, J = 7.2 Hz, 1 H), 7.08 (s, 1 H), 6.59 (dd, J = 8.4, J = 2.4 Hz, 1 H), 6.38 (d, J = 1.6 Hz, 1 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 155.2, 137.2, 134.2, 133.5, 131.7, 130.8, 130.8, 130.6, 128.0, 127.1, 110.8, 110.1, 102.2, 71.1, 55.7 ppm. IR (KBr): $\tilde{\nu}$ = 1649, 1607, 1558, 1509, 1498, 1336, 1304, 1271, 1244 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{12}ClNO_4Na$ 340.0353 [M + Na]$^+$; found 340.0343. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 99:1; flow rate = 0.9 mL/min; λ = 380 nm): t_R (minor) = 48.7 min, t_R (major) = 53.0 min.

(*R*)-2-(3-Chlorophenyl)-7-methoxy-3-nitro-2*H*-chromene (3h): Yellow solid (98% yield, 84% *ee*), m.p. 139–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.37 (s, 1 H), 7.30–7.35 (m, 1 H), 7.26–7.28 (m, 3 H), 6.60 (dd, J = 8.8, J = 2.4 Hz, 1 H), 6.56 (s, 1 H), 6.43 (d, J = 1.6 Hz, 1 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 155.3, 139.0, 137.6, 134.8, 131.9, 130.2, 130.2, 129.6, 127.3, 125.2, 110.9, 110.1, 102.3, 73.8, 55.7 ppm. IR (KBr): $\tilde{\nu}$ = 1645, 1611, 1556, 1491, 1332, 1314, 1279, 1243 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{12}ClNO_4Na$ 340.0353 [M + Na]$^+$; found 340.0347. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 85:15; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 15.7 min, t_R (minor) = 25.8 min.

(*R*)-2-(4-Chlorophenyl)-7-methoxy-3-nitro-2*H*-chromene (3i):[8a,9a] Yellow solid (97% yield, 90% *ee*), m.p. 96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.30–7.35 (m, 4 H), 7.26 (d, J = 8.4 Hz, 1 H), 6.60 (dd, J = 8.8, J = 2.4 Hz, 1 H), 6.55 (s, 1 H), 6.42 (d, J = 1.6 Hz, 1 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 155.4, 138.0, 135.6, 135.4, 131.8, 129.9, 129.1, 128.4, 111.0, 110.0, 102.3, 73.8, 55.7 ppm. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 85:15; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 14.7 min, t_R (minor) = 25.4 min.

(*R*)-2-(4-Bromophenyl)-7-methoxy-3-nitro-2*H*-chromene (3j):[8a,9a] Yellow solid (99% yield, 88% *ee*), m.p. 94–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.47 (d, J = 8.4 Hz, 2 H), 7.25–7.28 (m, 3 H), 6.59 (dd, J = 8.4, J = 2.4 Hz, 1 H), 6.54 (s, 1 H), 6.41 (d, J = 2.0 Hz, 1 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 155.4, 137.9, 136.1, 132.0, 131.8, 130.0, 128.7, 123.6, 111.0, 110.0, 102.3, 73.8, 55.7 ppm. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 85:15; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 15.5 min, t_R (minor) = 26.4 min.

(*R*)-7-Methoxy-3-nitro-2-*p*-tolyl-2*H*-chromene (3k):[9a] Yellow solid (92% yield, 86% *ee*), m.p. 123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1 H), 7.24–7.29 (m, 3 H), 7.14 (d, J = 7.6 Hz, 2 H), 6.57 (dd, J = 8.4, J = 2.4 Hz, 1 H), 6.55 (s, 1 H), 6.40 (d, J = 1.6 Hz, 1 H), 3.80 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 155.6, 139.4, 138.5, 134.1, 131.6, 129.6, 129.5, 127.0, 111.2, 109.7, 102.2, 74.4, 55.6, 21.2 ppm. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 85:15; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 12.0 min, t_R (minor) = 19.3 min.

(*R*)-7-Methoxy-2-(4-methoxyphenyl)-3-nitro-2*H*-chromene (3l):[8a,9a] Yellow solid (99% yield, 86% *ee*), m.p. 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 2 H), 6.57 (d, J = 8.4 Hz, 1 H), 6.53 (s, 1 H), 6.39 (s, 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 160.4, 155.6,

138.5, 131.6, 129.6, 129.2, 128.6, 114.2, 111.2, 109.7, 102.2, 74.2, 55.6, 55.3 ppm. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 85:15; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 26.1 min, t_R (minor) = 40.3 min.

(*S*)-2-(Furan-2-yl)-7-methoxy-3-nitro-2*H*-chromene (3m): Yellow solid (51% yield, 90% *ee*), m.p. 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.40 (s, 1 H), 7.28 (d, J = 8.4 Hz, 1 H), 6.64 (s, 1 H), 6.61 (dd, J = 8.4, J = 2.4 Hz, 1 H), 6.46 (d, J = 1.6 Hz, 1 H), 6.34 (d, J = 3.2 Hz, 1 H), 6.31 (s, 1 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 155.4, 149.7, 143.9, 136.1, 131.8, 130.5, 111.2, 110.6, 110.1, 110.0, 102.3, 67.4, 55.7 ppm. IR (KBr): $\tilde{\nu}$ = 1639, 1609, 1557, 1493, 1325, 1275, 1247 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{11}NO_5Na$ 296.0535 [M + Na]$^+$; found 296.0529. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 85:15; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 15.9 min, t_R (minor) = 27.8 min.

(*R*)-7-Methoxy-3-nitro-2-propyl-2*H*-chromene (3n): Yellow oil (78% yield, 67% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 7.18 (d, J = 8.8 Hz, 1 H), 6.57 (dd, J = 8.4, J = 2.4 Hz, 1 H), 6.47 (d, J = 1.6 Hz, 1 H), 5.54 (dd, J = 9.2, J = 2.4 Hz, 1 H), 3.84 (s, 3 H), 1.78–1.89 (m, 1 H), 1.43–1.66 (m, 3 H), 0.95 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 155.5, 140.0, 131.6, 128.8, 111.6, 109.4, 102.4, 73.2, 55.6, 34.5, 18.1, 13.5 ppm. IR (KBr): $\tilde{\nu}$ = 2962, 1643, 1617, 1558, 1505, 1330, 1305, 1274, 1246 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{15}NO_4Na$ 272.0899 [M + Na]$^+$; found 272.0893. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-propanol, 90:10; flow rate = 1.0 mL/min; λ = 380 nm): t_R (major) = 7.5 min, t_R (minor) = 12.0 min.

Procedure for the Asymmetric Domino Aza-Michael–Henry Reaction: *trans*-β-Nitrostyrene **2a** (0.4 mmol, 2.0 equiv.) was added to a stirred mixture of molecular sieves (4 Å; 0.2 g), catalyst **Ia** (20 mol-%), 4-nitrophenol (20 mol-%), and 1*H*-pyrrole-2-carbaldehyde **4** (0.2 mmol, 1.0 equiv.) in chloroform (1.0 mL) at room temperature. After stirring for 5 d, the solvent was removed in vacuo, and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 1000:1) on silica gel to give the corresponding 2-nitro-3-phenyl-3*H*-pyrrolizine (i.e., **5**). Yellow solid (61% yield, 18% *ee*), m.p. 99–100 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27 (s, 1 H), 7.35–7.42 (m, 3 H), 7.17 (dd, J = 7.6, J = 2.0 Hz, 2 H), 7.12 (s, 1 H), 6.67 (d, J = 4.0 Hz, 1 H), 6.45 (t, J = 4.0 Hz, 1 H), 6.37 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 149.6, 137.6, 133.8, 130.2, 129.5, 129.3, 127.9, 122.3, 116.4, 110.6, 63.9 ppm. IR (KBr): $\tilde{\nu}$ = 1548, 1534, 1465, 1364, 1306, 1266, 1238 cm^{-1}. $C_{13}H_{10}N_2O_2$ (226.23): calcd. C 69.02, H 4.46, N 12.38; found C 68.81, H 4.56, N 12.38. The enantiomeric excess was determined by HPLC with a Chiralpak OD column (hexane/2-propanol, 99:1; flow rate = 1.0 mL/min; λ = 380 nm): t_R (minor) = 16.3 min, t_R (major) = 33.6 min.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra of **Ia**, **Ib**, **3a**–**3n**, and **5**, and the HPLC spectra of **3a**–**3n** and **5**.

Acknowledgments

The authors are grateful to Prof. Wan and his group for their support in our research.

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Received: April 8, 2013
Published Online: July 8, 2013

