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**Year:** 2018

**Version:** Accepted version (Final draft)

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**Please cite the original version:**

Kumar, M., Chauhan, P., Bailey, S. J., Jafari, E., von Essen, C., Rissanen, K., & Enders, D. (2018). Organocatalytic Oxa-Michael/Michael/Michael/Aldol Condensation Quadruple Domino Sequence : Asymmetric Synthesis of Tricyclic Chromanes. *Organic Letters*, 20(4), 1232-1235. <https://doi.org/10.1021/acs.orglett.8b00175>

# Organocatalytic Oxa-Michael/Michael/Michael/Aldol Condensation Quadruple Domino Sequence: Asymmetric Synthesis of Tricyclic Chromanes

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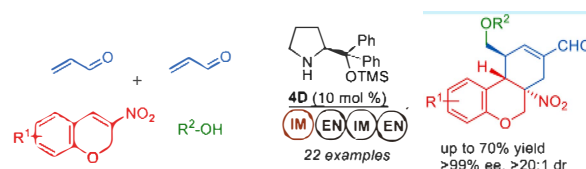
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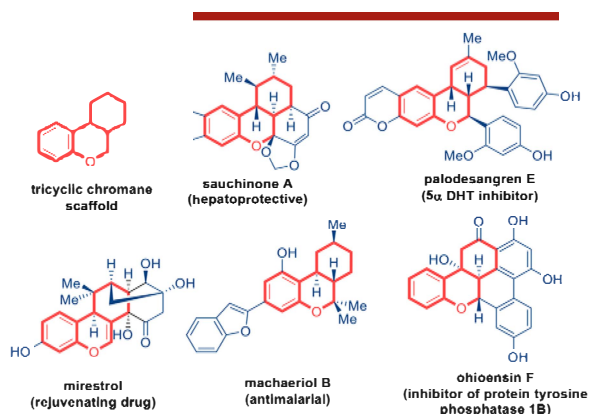
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## Supporting Information

**ABSTRACT:** An efficient and highly stereoselective one-pot, four-component synthesis of functionalized tricyclic chromanes has been achieved through an organocatalyzed quadruple domino reaction. The reaction sequence involves an oxa-Michael/Michael/Michael/aldol condensation between alcohols, 2 equiv of acrolein, and nitrochromenes to generate the pharmaceutically important tricyclic chromanes bearing three contiguous stereogenic centers including a chiral tetrasubstituted carbon center in good domino yields (30–70%) and excellent diastereo- and enantioselectivities (>20:1 dr and >99% ee).



Natural products are considered as one of the most important sources for the drug development process.<sup>1</sup> Therefore, chemists working in the fields of organic synthesis, medicinal chemistry and chemical biology have focused their efforts on the generation of natural product inspired compound collections and libraries. Characteristic for many of the privileged natural product classes are their complex structures, which needs the development of efficient catalytic asymmetric synthesis methods.<sup>2</sup> One such natural product class are the tricyclic chromanes, a privileged structural framework found in many natural products and pharmaceutical compounds exhibiting a broad range of biological properties (Figure 1).<sup>3</sup>



**Figure 1.** Selected bioactive natural products bearing a tricyclic chromane scaffold.

For example, sauchinone A, a highly oxygenated tetracyclic compound isolated from *Saururus chinensis*, displayed hepatoprotective activities,<sup>3a</sup> whereas palodesangren E, obtained from the bark of *Brosimum rubescens*, shows potent inhibition of the binding of 5 $\alpha$ -dihydrotestosterone (DHT) with the androgen receptor.<sup>3b</sup> Mirestrol, an estrogenic agent used as a rejuvenating drug, is isolated from the tuber of *Pueraria mirifica*.<sup>3c</sup> Machaeriol B, isolated from *Machaerium multiflorum*, exhibits antimalarial property,<sup>3d</sup> whereas ohioensin F acts as an inhibitor of protein tyrosine phosphatase 1B.<sup>3e</sup>

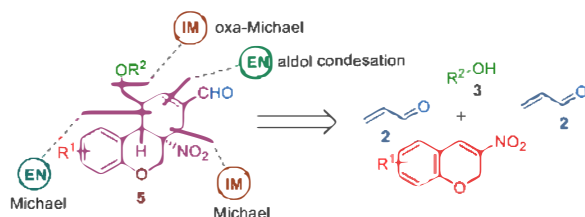
In light of the importance of tricyclic chromane scaffolds and their diverse biological properties, several elegant strategies have been developed for the synthesis of this family of heterocycles and their derivatives.<sup>4</sup> In 2009, Hong and co-workers described an appealing strategy for the enantioselective synthesis of tricyclic chromanes via a quadruple domino sequence using a secondary amine–acetic acid salt as an organocatalyst.<sup>5</sup> Later, this research group reported the total synthesis of (+)-conicol, a chromane natural product employing the same protocol.<sup>6</sup> The research groups of Li<sup>7</sup> and Wang<sup>8</sup> also described the asymmetric synthesis of tricyclic chromanes via quadruple domino reactions using  $\alpha,\beta$ -unsaturated aldehydes, respectively. Despite the previous progress for the construction of valuable tricyclic chromanes, some extensions are still required in terms of substrate scope and reaction selectivities, and hence, the development of further protocols are desirable. Very recently, our group described a new protocol for the stereoselective synthesis of highly functionalized

**Received:** January 17, 2018

tricyclic chromane scaffolds via a triple domino reaction between aliphatic aldehydes, nitrochromenes, and enals.<sup>9</sup>

Based on our recent efforts in the development of asymmetric domino reactions for the construction of complex polycyclic compounds<sup>10,11</sup> and the pioneering work of Gong and co-workers on oxa-Michael initiated domino reaction,<sup>12</sup> we herein report a one-pot quadruple domino reaction involving an oxa-Michael/Michael/Michael/aldol condensation sequence for the asymmetric synthesis of tricyclic chromanes bearing three contiguous stereogenic centers (Scheme 1).

### Scheme 1. Retrosynthetic Analysis of Tricyclic Chromanes 5 Based on a One-Pot, Four-Component Quadruple Domino Sequence



We began our investigation to discover suitable reaction conditions for this quadruple domino sequence. First, we carried out the reaction between nitrochromene **1a**, acrolein (**2a**), and methanol (**3a**) in the presence of benzoic acid as additive (25 mol %) and organocatalysts **4A–F** in chloroform to afford the tricyclic chromane product **5a** (Table 1). It turned out that (*S*)-proline **4A** and 1-(pyrrolidin-2-ylmethyl)pyrrolidine **4B** completely failed to provide the desired product (entries 1 and 2), whereas diphenylprolinol **4c** furnished trace amounts of chromane **5a** (entry 3). The (*S*)-TMS-diarylprolinol catalyst **4D** provided the desired chromane product **5a** in 37% with excellent stereoselectivities (>99% ee and >20:1 dr, entry 4), whereas other proline-derived catalysts **4E** and **4F** gave inferior results in terms of product yields with unchanged stereoselectivities (entries 5–6). After finding the suitable catalyst **4D**, we performed a screening of different solvents to increase the yield of the product **5a**; however, no significant improvement was observed in the yield of the desired product **5a**, whereas the stereoselectivities remained excellent (entries 7–12). We found comparable results in terms of yield and stereoselectivities when benzoic acid was replaced with *o*-fluorobenzoic acid as additive (entry 13). To our surprise, when we used 5 Å molecular sieves (50 mg) with benzoic acid, it not only provided an increased yield of the chromane product **5a** but also reduced the reaction time for completion to within 24 h with 45% yield and excellent stereoselectivities (>99% ee and >20:1 dr, entry 14). We found similar results when we tested 4 Å molecular sieves to further increase the yield of product **5a** (entry 15). When the amount of catalyst **4D** was decreased to 5 mol %, the reaction was complete in 36 h but the yield of the domino product dropped dramatically, whereas increasing the amount of catalyst **4D** from 10 to 20 mol % gave no significant improvement in the yield of product **5a** (entries 16 and 17). Finally, we achieved the optimal reaction conditions for this quadruple domino sequence including 10 mol % of catalyst **4D**, 25 mol % of benzoic acid, and 50 mg of 5 Å molecular sieves in chloroform at 0 °C.

Having established the optimal reaction conditions for the asymmetric oxa-Michael/Michael/Michael/aldol condensation sequence, we shifted our focus to explore the substrate scope. First, we explored the scope of the nitrochromenes **1** with

Table 1. Optimization of the Reaction Conditions<sup>a</sup>

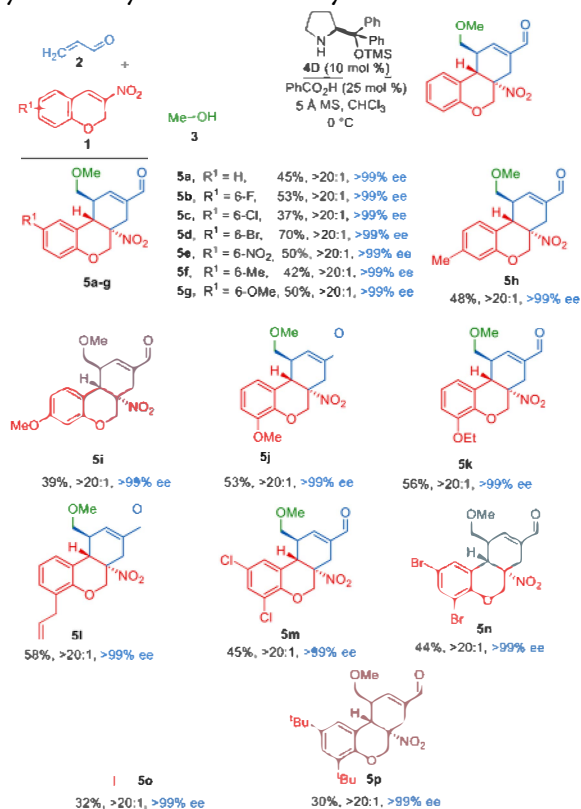
entry	cat. (x mol %)	solvent	yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>d</sup> (%)
1	<b>4A</b> (10)	CHCl <sub>3</sub>			
2	<b>4B</b> (10)	CHCl <sub>3</sub>			
3	<b>4C</b> (10)	CHCl <sub>3</sub>	trace		
4	<b>4D</b> (10)	CHCl <sub>3</sub>	37	>20:1	99
5	<b>4E</b> (10)	CHCl <sub>3</sub>	20	>20:1	99
6	<b>4F</b> (10)	CHCl <sub>3</sub>	16	>20:1	99
7	<b>4D</b> (10)	THF	10	>20:1	99
8	<b>4D</b> (10)	MTBE	17	>20:1	99
9	<b>4D</b> (10)	1,4-dioxane	8	>20:1	99
10	<b>4D</b> (10)	DCE	10	>20:1	99
11	<b>4D</b> (10)	toluene	20	>20:1	99
12	<b>4D</b> (10)	DCM	32	>20:1	99
13 <sup>e</sup>	<b>4D</b> (10)	CHCl <sub>3</sub>	36	>20:1	99
14 <sup>f</sup>	<b>4D</b> (10)	CHCl <sub>3</sub>	45	>20:1	99
15 <sup>g</sup>	<b>4D</b> (10)	CHCl <sub>3</sub>	42	>20:1	99
16 <sup>f</sup>	<b>4D</b> (5)	CHCl <sub>3</sub>	32	>20:1	99
17 <sup>f</sup>	<b>4D</b> (20)	CHCl <sub>3</sub>	40	>20:1	99

<sup>a</sup>All reactions were carried out with 0.3 mmol of **1a** (1 equiv), 0.9 mmol of **2a** (3.0 equiv), 0.45 mmol of **3a** (1.5 equiv), 25 mol % of benzoic acid, and 5–20 mol % of the catalyst in the indicated solvent (2.0 mL) at 0 °C for 1–2 d. <sup>b</sup>Yield of isolated product **5a**. <sup>c</sup>Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>d</sup>Determined by HPLC using a chiral stationary phase. <sup>e</sup>2-Fluorobenzoic acid (25 mol %) was used as additive. <sup>f</sup>5 Å M.S. (50 mg) were used with benzoic acid. <sup>g</sup>4 Å M.S. were used with benzoic acid.

acrylaldehyde (**2a**) and methanol **3a** (Scheme 2). The nitrochromenes **1** bearing electron-neutral (H) and electron-withdrawing groups (F, Cl, Br, NO<sub>2</sub>) at the C6 position of the 3-nitro-2*H*-chromene smoothly transformed to the corresponding chromane products **5a–e** in moderate to good yields with high diastereoselectivities and virtually complete enantioselectivities, whereas the nitrochromenes bearing electron-donating groups (Me, OMe) at the C6 position also gave good yields of the products **5f,g**. The presence of a methyl group at the C7 position of 3-nitro-2*H*-chromene furnished the chromane **5h** in 48% yield, whereas a methoxy group at the same position led to a lower 39% yield of **5i** with excellent diastereo- and enantioselectivities (>20:1 dr and >99% ee).

Substrates bearing a methoxy, ethoxy, or allylic group at the C8 position all reacted in a satisfactory way, providing the corresponding chromane products (**5j–l**) in moderate yields with excellent asymmetric inductions. Dihalo-substituted substrates (Cl, Br, and I) at the C6 and C8 position all reacted smoothly, providing the corresponding products (**5m,n**) in 45–44% yield and **5o** in a slightly lower 32% yield with >20:1 dr and >99% ee.

## Scheme 2. Substrate Scope of the Nitrochromenes for the Asymmetric Synthesis of the Tricyclic Chromanes 5<sup>a-d</sup>



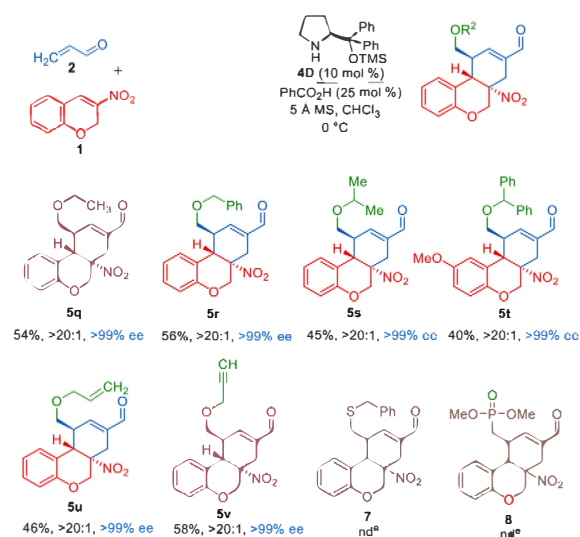
<sup>a</sup>All reactions were performed with 0.4 mmol of **1** (1.0 equiv), 1.2 mmol of **2** (3.0 equiv), 0.6 mmol of **3** (1.5 equiv), 10 mol % of catalyst **4D**, 25 mol % of PhCO<sub>2</sub>H, and 5 Å M.S. in CHCl<sub>3</sub> (3.0 mL) at 0 °C for 24–36 h. <sup>b</sup>Yields of isolated products **5** after column chromatography. <sup>c</sup>The diastereomeric ratios were determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup>The enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

When a 3-nitro-2*H*-chromene bearing two *tert*-butyl groups at the C6 and C8 positions was used, the chromane product **5p** was obtained in a lower yield of 30% with excellent stereoselectivities. To increase the scope of electrophiles, we replaced the 3-nitro-2*H*-chromene by methyl (*E*)-2-(2-oxoindolin-3-ylidene)acetate and 2*H*-chromene-3-carbonitrile under the optimized conditions; however, these substrates did not work under this protocol.<sup>13</sup>

Next we investigated the scope of the alcohols **3** used as nucleophiles for the oxa-Michael step in this quadruple domino reaction (Scheme 3). Simple aliphatic alcohols such as ethanol and benzyl alcohol reacted smoothly to provide the corresponding products (**5q** and **r**) in moderate yields with excellent diastereo- and enantioselectivities (>20:1 dr, and >99% ee). Secondary alcohols, for example, 2-propanol and diphenylmethanol, also worked well, leading to the desired products **5s** and **5t** in good yield with high diastereo- and virtually complete enantioselectivity.

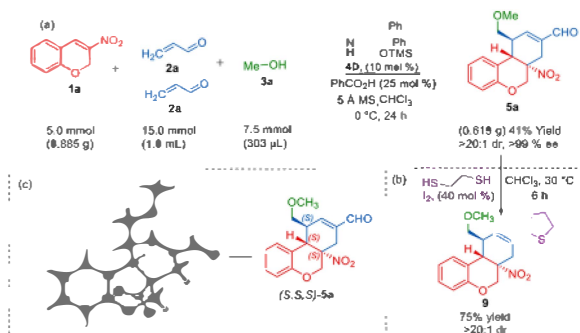
When functionalized alcohols such as allyl alcohol and propargyl alcohol were used, the corresponding chromane products **5u,v** were isolated in moderate to good yields with excellent asymmetric inductions. We also tested benzylthiol and dimethyl phosphite to increase the scope of nucleophiles; however, we could not identify the target products **7** and **8** even after 6 days.

## Scheme 3. Substrate Scope of the Alcohols for the Asymmetric Synthesis of the Tricyclic Chromanes 5<sup>a-d</sup>



<sup>a</sup>All reactions were performed with 0.4 mmol of **1** (1.0 equiv), 1.2 mmol of **2** (3.0 equiv), 0.6 mmol of **3** (1.5 equiv), 10 mol % of catalyst **4D**, 25 mol % of PhCO<sub>2</sub>H, and 5 Å M.S. in CHCl<sub>3</sub> (3.0 mL) at 0 °C for 24–36 h. <sup>b</sup>Yields of isolated products **5** after column chromatography. <sup>c</sup>The diastereomeric ratios were determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup>The enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. <sup>e</sup>No domino products were formed after 6 days.

To demonstrate the synthetic utility of the (*S*)-TMS-protected diphenylprolinol-catalyzed oxa-Michael/Michael/Michael/aldol condensation sequence, we performed a scale-up synthesis of **5a** between **1a**, **2a**, and **3a** under the optimized conditions. The chromane product **5a** was obtained in 41% yield with excellent diastereo- and enantioselectivity (Figure 2a). The chromane **5a**



**Figure 2.** (a) Scale-up synthesis of **5a**. (b) Transformation of **5a** to the mercaptal **9**. (c) X-ray crystal structure of **5a**.

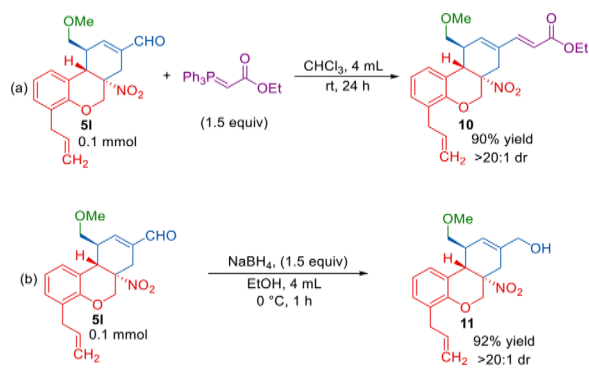
was further transformed to the mercaptal **9** using ethanedithiol in the presence of iodine in 75% yield (Figure 2b). Moreover, the functionalization of product **5l** via Wittig olefination afforded the enolate **10** whereas a chemoselective reduction of **5l** gave the alcohol **11** using sodium borohydride in ethanol (Scheme 4).

The absolute configuration of the tricyclic chromane **5a** was assigned as (*S,S,S*) by X-ray crystal structural analysis (Figure 2c). The absolute configurations of all tricyclic chromanes shown in Schemes 2 and 3 were assigned by analogy.

In conclusion, an efficient one-pot, four-component asymmetric organocatalytic quadruple domino reaction for the



**Scheme 4. (a) Transformation of the  $\alpha,\beta$ -Unsaturated Aldehyde 5I to the Enolate 10. (b) Selective Reduction of Aldehyde 5I to the Alcohol 11**



construction of tricyclic chromane scaffolds has been developed. This protocol includes an oxa-Michael/Michael/Michael/aldol condensation sequence that leads to the formation of four new bonds and three consecutive stereogenic centers, including a tetrasubstituted one in very good domino yields under virtually complete asymmetric inductions.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.8b00175](https://doi.org/10.1021/acs.orglett.8b00175).

Experimental procedures, optimization details, data for all new compounds, NMR spectra, and HPLC data (PDF)

### Accession Codes

CCDC 1816580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

Financial support from the European Research council (ERC Advanced Grant 320493 "DOMINOCAT") is gratefully acknowledged.

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