

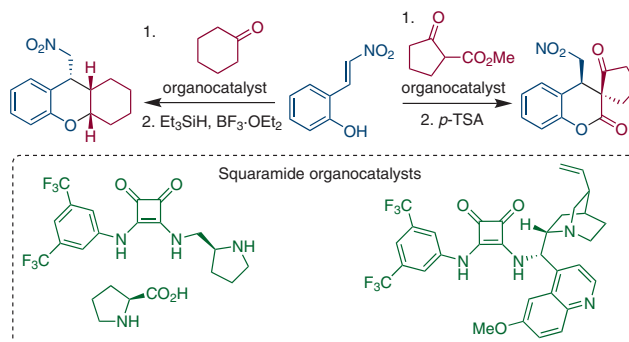
# Asymmetric Sequential Michael Addition and Cyclization Reactions of 2-(2-Nitrovinyl)phenols Catalyzed by Bifunctional Amino-Squaramides

Eva Veverková

Pavína Molnosiová

Radovan Šebesta\*

Comenius University in Bratislava, Faculty of Natural Sciences,  
Department of Organic Chemistry, Mlynská dolina, Ilkovičova 6,  
842 15 Bratislava, Slovakia  
radovan.sebesta@uniba.sk



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**Abstract** In this work, we describe the Michael addition–cyclization reaction of 2-(2-nitrovinyl)phenol with two different reactive Michael donors, which lead to chiral benzopyran derivatives. Specifically, bifunctional amino-squaramides with one or two chiral units in the side chains were evaluated as catalysts in these transformations. Furthermore, the utility of selected green solvents as reaction media for these processes was also tested. The best result was achieved with methyl-cyclopentanone-2-carboxylate as the Michael donor in ethyl (–)-l-lactate with quinine-based amino-squaramide as catalyst (yield 72%, dr >99:1, ee 99%).

**Key words** asymmetric catalysis, organocatalysis, amino-squaramides, Michael cyclization reaction

Asymmetric organocatalysis have become one of the pillars of asymmetric catalysis, allowing the efficient, user-friendly, and environmentally benign synthesis of many important chiral compounds.<sup>1,2</sup> Organocatalytic domino or cascade sequences have often been successfully employed for the asymmetric synthesis of bioactive natural products as well as enantioenriched compounds for therapeutic use.<sup>3</sup> Therefore, investigation of cascade or tandem reactions is an important direction of development in organocatalysis, which allows the rapid construction of structurally complex molecules from simple and readily available starting materials.<sup>4–8</sup> Asymmetric organocatalytic cascade or sequential reactions are most commonly catalyzed by chiral amines, but over the past decade a number of hydrogen-bonding catalysts such as ureas/thioureas,<sup>9–13</sup> guan-

dines,<sup>14,15</sup> cinchona alkaloids,<sup>16,17</sup> and chiral phosphoric acids<sup>18,19</sup> have applied to promote a wide array of useful asymmetric sequential reactions.

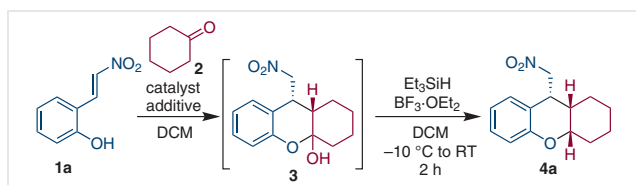
Ramachary and co-workers described the asymmetric sequential reaction of 2-(2-nitrovinyl)phenols with cyclopentanone-2-carboxylates.<sup>20</sup> The desired spiro-dihydrocoumarins with a quaternary stereocenter were isolated in good yields in the presence of quinine-thiourea catalysts combined with *para*-toluene sulfonic acid. Also, Enders explored this kind of sequence with thiourea catalysts.<sup>21</sup> Later, the Ramachary group successfully exploited a combination of quinine-thiourea with amino acids as efficient chiral catalysts for the synthesis of hexahydroxanthenols<sup>22</sup> and tetrahydroquinolines from simple substrates.<sup>23</sup> Similar transformations were explored also by Andres, Pedrosa, and co-workers using polystyrene-immobilized squaramide organocatalysts.<sup>24</sup>

Chiral amino-squaramides are powerful hydrogen-bonding, often bifunctional, organocatalysts applicable in a variety of transformations.<sup>25–28</sup> Squaramides are not only useful for promoting simple carbon–carbon and carbon–heteroatom bond formations but also for assisting in various domino/cascade reactions.<sup>29</sup> Recently, amino-squaramides were applied in a variety of cascade or sequential reactions utilizing Michael addition as a key step for building complex heterocyclic scaffolds.<sup>30–36</sup>

Part of our research program focuses on the applications of squaramide organocatalysts in the syntheses of chiral heterocyclic compounds. Within this area, we have recently described amino-squaramides as efficient catalysts for Michael additions/hemiketalization of hydroxycoumarins with unsaturated ketones and keto esters.<sup>37</sup> Squaramides were also effective in a related transformation with nitroalkenes.<sup>38</sup> We have also explored the construction of nitrogen heterocycles via formal cycloaddition reactions catalyzed by squaramide catalysts.<sup>39</sup> As squaramides have

emerged as an effective alternative to thiourea-based organocatalysts, we decided to investigate the catalytic effect of a series of amino-squaramides on the course of the above-mentioned sequential reactions between 2-(2-nitrovinyl)phenol and Michael acceptors.

Our research started with an examination of the amino-squaramide-catalyzed domino reaction between 2-(2-nitrovinyl)phenol (**1a**) and cyclohexanone (**2**). The initial formation of lactol **3a** was followed by a reductive etherification to obtain a more stable hexahydro-1*H*-xanthen **4a** (Scheme 1).



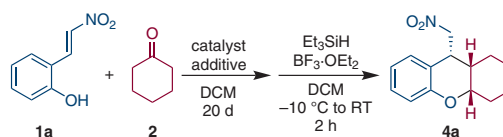
**Scheme 1** Squaramide-catalyzed asymmetric Michael reaction of cyclohexanone with 2-(2-nitrovinyl)phenol followed by reductive etherification

We decided to test several squaramide catalysts, which possess various stereoinducing moieties as well as diverse additional activating groups (Figure 1). Catalysts **C1** and **C2** comprise a primary amino group. Squaramides **C3–C5** possess secondary amine moieties and catalysts **C6–C9** tertiary amino functionalities.

In comparison with catalysis by tertiary amino-thioureas,<sup>22</sup> the first step of the reaction proceeded slowly

when squaramide catalysts were used. Long reaction times were required even if (*S*)- or (*R*)-proline were used as co-catalysts. For comparison of the results, all experiments were carried out with the same reaction time (20 d). Synthetically relevant yields were obtained with squaramides **C1**, and **C3** (Table 1, entries 1, 2 and 5, 6). Considerably higher yields and diastereomeric purities of product **4a** were obtained with organocatalysts **C5** and **C6**. In the presence of (*R*)-proline as a co-catalyst, diastereoselectivities were high, but the enantioselectivity was only low to moderate (26–40% ee, Table 1, entries 1–4). On the other hand, (*S*)-proline improved the enantioselectivity in comparison with its enantiomer, especially in combination with secondary amino-squaramides **C3** and **C5**. Product **4a** was obtained with 78% and 68% ee, respectively, even though the yields were only 26% and 40% (Table 1, entries 6 and 7). Interestingly, a significant increase in the yield up to 83% was achieved when the basic additive, sodium acetate, was added to the catalytic system **C3**/*S*-proline. Furthermore, the enantioselectivity of the reaction increased to 86% ee (Table 1, entry 9). Catalyst **C3** in the absence of (*S*)-proline gave product **4a** with excellent diastereomeric and enantiomeric purity (>99:1 dr, 91% ee) but only in 30% yield (Table 1, entry 10). The acidic additive (4-nitrobenzoic acid), in combination with **C3** or catalytic system **C3**/*S*-proline afforded

**Table 1** Asymmetric Michael/Cyclization Reaction of 2-(2-Nitrovinyl)phenol (**1a**) with Cyclohexanone **2**



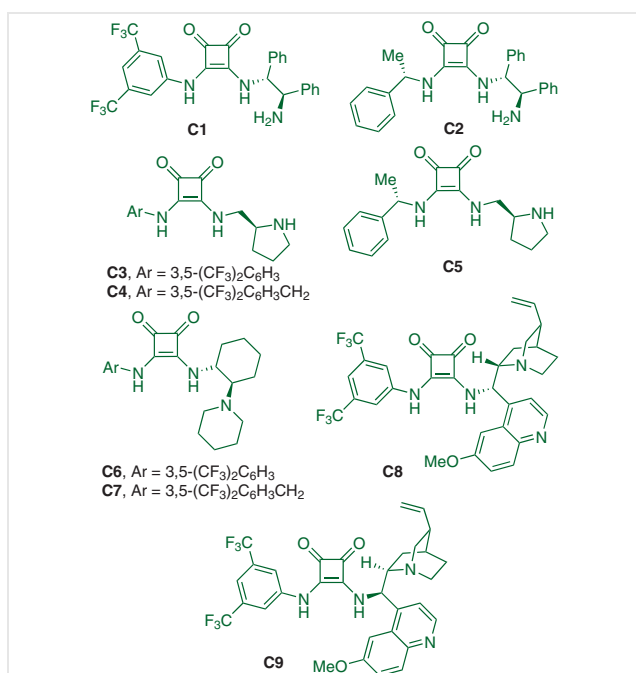
Entry	Catalysts	Additive	Yield of <b>4a</b> (%) <sup>a</sup>	dr <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>C1</b> / <i>R</i> -Pro	–	54	92:8	32 <sup>d</sup>
2	<b>C3</b> / <i>R</i> -Pro	–	44	98:2	40
3	<b>C5</b> / <i>R</i> -Pro	–	92	90:10	30
4	<b>C6</b> / <i>R</i> -Pro	–	79	82:12	26
5	<b>C1</b> / <i>S</i> -Pro	–	31	98:2	40
6	<b>C3</b> / <i>S</i> -Pro	–	26	90:10	78
7	<b>C5</b> / <i>S</i> -Pro	–	40	98:2	68
8	<b>C6</b> / <i>S</i> -Pro	–	59	92:8	34
9	<b>C3</b> / <i>S</i> -Pro	NaOAc	83	99:1	86
10	<b>C3</b>	NaOAc	30	>99:1	91
11	<b>C3</b> / <i>S</i> -Pro	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	53	84:15	68
12	<b>C3</b>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	42	>99:1	64

<sup>a</sup> Yield refers to column chromatography purified product after two steps.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture after the second step.

<sup>c</sup> Enantiomeric excess of major diastereomer.

<sup>d</sup> Opposite enantiomer.



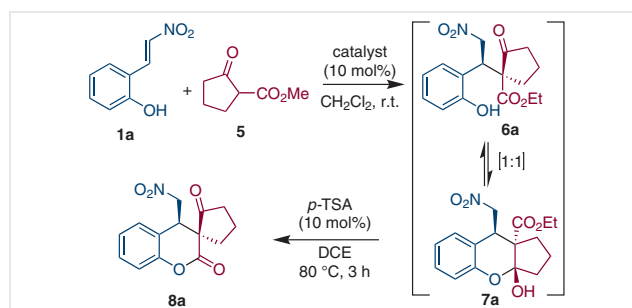
**Figure 1** Amino-squaramide organocatalysts used in this study

the product in lower yield and worse stereoselectivity in comparison to sodium acetate (Table 1, entries 12 and 11).

Replacement of harmful and environmentally undesirable solvents with better alternatives is an important goal of the green chemistry movement. In addition to their better health and environmental profile, green solvents often have a significant effect on reaction rate, yield, and selectivity.<sup>40</sup> Therefore, we screened several green solvents in the first step of the reaction of 2-(2-nitrovinyl)phenol (**1a**) with cyclohexanone (**2**). All experiments were allowed to proceed for same time of 8 d. We started evaluation of green solvents with cyclopentyl(methyl)ether (CpOME) and 2-methyltetrahydrofuran (2-MeTHF) as greener alternatives to ethereal solvents.<sup>41</sup> This choice stemmed from our previous positive experience with these solvents in the organocatalytic synthesis of warfarin using amino-squaramide catalysts.<sup>37</sup> When CPME was used, product **4a** was isolated in only medium yields in the presence of both basic as well as acidic additives. Interestingly, diastereoselectivity (93:7 dr) and enantioselectivity (69% ee) were higher when acidic additive was used (Table 2, entries 1 and 2). In 2-MeTHF, product **4a** was obtained in rather low yield and enantiomeric purity (30% ee) with NaOAc as an additive. The acidic additive was again more effective, and the product **4a** was isolated in 53% yield and with higher enantiomeric purity (76% ee, Table 2, entries 3 and 4). The reaction in chiral (–)-L-ethyl lactate, an environmentally benign solvent comparable to petroleum-based solvents,<sup>42</sup> afforded **4a** in 70% yield with the basic additive but in only 18% yield in the presence of the acidic additive. In both cases, the diastereoselectivity was comparably high (95:5 and 97:3 dr, respectively) and enantiomeric purity was also quite good (66% and 74% ee, respectively, Table 2, entries 5, 6). Nontoxic, in-

expensive, thermally stable, and recoverable ethylene glycol<sup>43</sup> in combination with 4-nitrobenzoic acid was one of the best solvents in view of diastereoselectivity (>99:1 dr). The enantioselectivity was also increased when an acidic additive was employed (25% vs. 74% ee, Table 2, entries 7 vs. 8).

In the second part of our study, we examined the amino-squaramide-catalyzed reaction of 2-(2-nitrovinyl)phenol (**1a**) with more reactive methyl cyclopentanone-2-carboxylate (**5**). The primary product of this transformation is the Michael adduct **6a**, which is in equilibrium with the corresponding lactol **7a**. We then transformed this to a more stable and readily purifiable spiro-dihydrocoumarin *cis*-**8a** using a literature procedure (Scheme 2).<sup>7</sup>



**Scheme 2** Domino Michael addition–cyclization between nitroalkene **1a** and keto ester **5**

At the outset, we again tested amino-squaramide catalysts with primary, secondary, and tertiary amino groups **C2** and **C4–C9**. As shown in Table 3, the higher reactivity of Michael donor **5** led to a reduction of reaction time without any co-catalyst or additives, in the case of tertiary amino-

**Table 2** Screening of Solvents and Additives by Using Catalytic System **C3**/(S)-Proline



Entry	Solvent	Additive	Yield of <b>4</b> (%) <sup>a</sup>	dr <sup>b</sup>	ee (%) <sup>c</sup>
1	CpOME	NaOAc	40	76:24	52
2	CpOME	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COOH	36	93:7	69
3	2-MeTHF	NaOAc	37	79:27	30
4	2-MeTHF	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COOH	53	96:4	76
5	(–)-L-ethyl lactate	NaOAc	70	95:5	66
6	(–)-L-ethyl lactate	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COOH	18	97:3	74
7	diglyme	NaOAc	72	79:20	25
8	diglyme	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COOH	61	>99:1	74

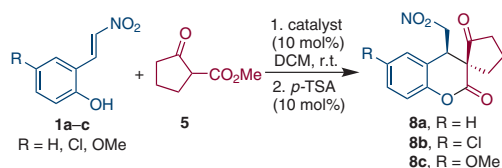
<sup>a</sup> Reaction time 8 d. Yield refers to the column chromatography purified product after two steps.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture after the second step.

<sup>c</sup> Enantiomeric excess of major diastereomer.

squaramides (**C6–C8**) down to 1 d. High diastereoselectivities (de >99%) were observed with all tested catalysts, and very good enantioselectivities were achieved with primary (**C2**) and tertiary amino-squaramides (**C6–C9**, Table 3, entries 1 and 4–7). The catalysts with the secondary amino group (**C4, C5**) surprisingly gave only a racemic product (Table 3, entries 2, 3). The best result was achieved with cinchona-derived catalyst **C8**, which afforded product **8a** in 66% yield and enantiomeric purity of 98% ee (Table 3, entry 6).

**Table 3** Asymmetric Michael/Cyclization Reaction of 2-(2-Nitrovinyl)phenols **1** with Methyl Cyclopentanone-2-carboxylate (**5**)



Entry	Catalyst	Time (d)	Yield of <b>8</b> (%) <sup>a</sup>	dr <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>C2</b>	12	<b>8a</b> 16	>99:1	(+) 87
2	<b>C4</b>	7	<b>8a</b> 22	>99:1	rac
3	<b>C5</b>	12	<b>8a</b> 18	>99:1	rac
4	<b>C6</b>	1	<b>8a</b> 36	>99:1	(+) 89
5	<b>C7</b>	1	<b>8a</b> 45	>99:1	(+)72
6	<b>C8</b>	1	<b>8a</b> 66	>99:1	(-) 98
7	<b>C9</b>	6	<b>8a</b> 43	>99:1	(+) 92
8	<b>C8</b>	1	<b>8b</b> 43	>99:1	(-) 99
9	<b>C8</b>	2.5 <sup>d</sup>	<b>8c</b> 55	>99:1	(-) 98

<sup>a</sup> Yield refers to column chromatography purified product after two steps.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture after the second step.

<sup>c</sup> Enantiomeric excess of major diastereomer.

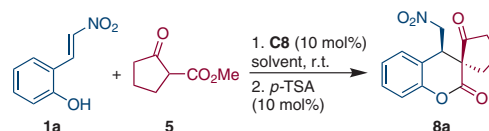
<sup>d</sup> Time in hours.

Then, we explored two additional 2-(2-nitrovinyl)phenols with 4-chloro and 4-methoxy substituents, using the most effective organocatalyst **C8**. Enantiomeric purities of products **8b** and **8c** were excellent (99% and 98% ee) and were not affected by the electronic nature of the substituents on the benzene ring (Table 3, entries 8 and 9), although they influenced reactivity in a predictable fashion. The electron-donating methoxy group led to a significantly shortened reaction time (2.5 h, Table 3, entry 9).

Then, we applied amino-squaramide catalyst **C8** to investigate the effect of selected green solvents (Table 4). The reaction proceeded with very high diastereoselectivity (>99% de) and excellent enantioselectivity (up to >99% ee) in all tested solvents, with reaction being fastest in 2-MeTHF. Only 5 h were necessary for complete conversion of nitroalkene **1a**, but the product **8a** was isolated in only a moderate 50% yield (Table 4, entry 1). (–)-L-Ethyl lactate was found to be the best solvent as product **8a** was obtained

in a preparatively interesting 72% yield after 3 d; whereas diglyme and cyclopentyl(methyl)ether provided the product in somewhat lower yields after comparable times (Table 4, entry 4 vs. entries 2, 3). Using diastereoisomeric catalyst **C9**, the opposite enantiomer of product **8a** was obtained in 50% yield, and slightly lower enantioselectivity (90% ee) in (–)-L-ethyl lactate (Table 4, entry 5).

**Table 4** Screening of Solvents by Using Catalyst **C8**



Entry	Solvent	Time (d)	Yield of <b>8a</b> (%) <sup>a</sup>	dr (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	2-MeTHF	5 <sup>d</sup>	50	>99:1	(-) 98
2	diglyme	3	60	>99:1	(-) 98
3	CpPMe	5	36	>99:1	(-) 98
4	(–)-L-ethyl lactate	3	72	>99:1	(-) >99
5	(–)-L-ethyl lactate	3	50	>99:1	(+) 90 <sup>e</sup>

<sup>a</sup> Yield refers to column-purified product after two steps.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture after the second step.

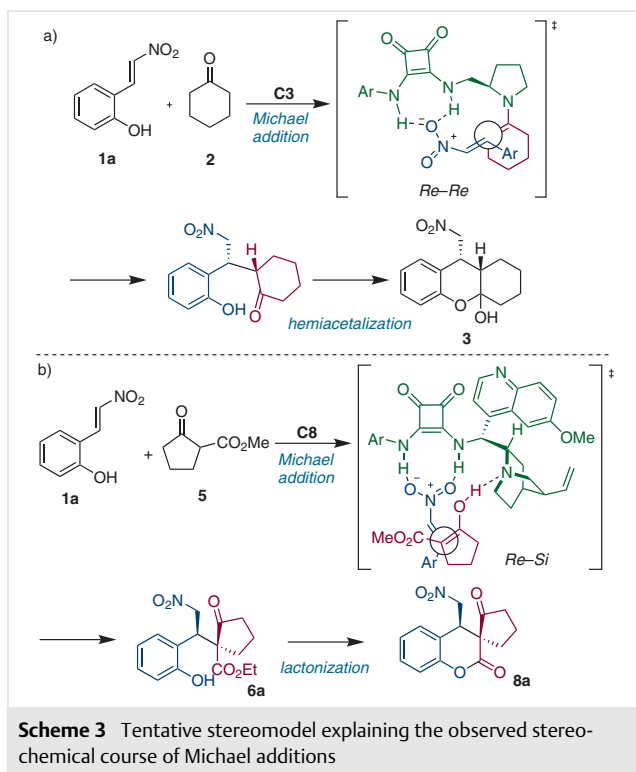
<sup>c</sup> Enantiomeric excess of major diastereomer.

<sup>d</sup> Time in hours.

<sup>e</sup> Catalyst **C9**.

Configurations of products were assigned by comparison of chiral HPLC and specific rotation data with literature values.<sup>20,22</sup> A plausible pathway of the reaction with the most effective squaramide catalyst **C3** is depicted in Scheme 3a. Presumably, squaramide **C3** operates via dual enamine–hydrogen bonding activation. In this way, it orients reagents for the preferred *Re–Re* approach to each other, which affords the major stereoisomer of product **4**. On the other hand, amino-squaramide **C8** probably activates the keto ester via the formation of an enol or enolate bound to the quinuclidine nitrogen (Scheme 3b). In this case, the nitroalkene moiety is probably also attached via hydrogen bonding to the squaramide NH groups. The preferred orientation of reagents in this reaction is *Re–Si*, which leads to the observed major stereoisomer of spirocyclic product **8**.

In conclusion, we have evaluated the suitability of squaramide organocatalysts for Michael addition–cyclization cascades. We found that, from a series of chiral amine-squaramide catalysts, the secondary amino-squaramide **C3** was an effective catalyst in asymmetric Michael reaction of 2-(2-nitrovinyl)phenol (**1a**) with cyclohexanone (**2**) followed by reductive etherification. This reaction worked best under basic conditions and with (*S*)-proline as a co-catalyst. (–)-L-Ethyl lactate with a basic additive and 2-methyltetrahydrofuran with acidic additive can be used as suitable green solvents in an environmentally more friendly version of this reaction. Next, the quinine-derived squar-



amide **C8** was successfully applied to catalyze the related asymmetric sequential Michael–lactonization reaction of keto ester **5** with 2-(2-nitrovinyl)phenol **1**. The product **8a** was obtained in excellent yield (72%) and enantiomeric purity (>99%), when the green solvent (–)-L-ethyl lactate was used.

Solvents were purified by standard methods. NMR spectra were recorded on Varian NMR System 300 and 600 instruments (300 or 600 MHz for  $^1\text{H}$ , 151 MHz for  $^{13}\text{C}$ ). Chemical shifts ( $\delta$ ) are given in ppm relative to tetramethylsilane. Specific rotations were measured on a Jasco P-2000 polarimeter and are given in  $\text{deg cm}^3 \text{g}^{-1} \text{dm}^{-1}$ . Column chromatography was performed on Merck silica gel 60. Thin-layer chromatography was performed on Merck TLC plates coated with silica gel 60, F-254. Enantiomeric excesses were determined by HPLC using Chiralpak OJ-H and OD-H (Daicel Chemical Industries) columns with *n*-hexane/propan-2-ol as a mobile phase and UV detection at 254 nm. The squaramide organocatalysts **C1**,<sup>44</sup> **C3**,<sup>45</sup> **C4**,<sup>46</sup> **C6**,<sup>46</sup> **C7**,<sup>47</sup> **C8**,<sup>48</sup> and **C9**<sup>48</sup> were synthesized according to literature procedures. The Michael acceptors **1a–c** were prepared according to the published method.<sup>49</sup> Racemic products **4a**,<sup>22</sup> and **8a–c** were prepared according to the published methods.<sup>20</sup>

#### Typical Procedure for Squaramide-Catalyzed Asymmetric Michael Reaction of Cyclohexanone with 2-(2-Nitrovinyl)phenol Followed by Reductive Etherification

To a mixture of 2-(2-nitrovinyl)phenol (**1a**, 82.5 mg, 0.50 mmol) and cyclohexanone (245 mg, 2.5 mmol) in DCM (1.0 mL) was added the squaramide catalyst (0.025 mmol), co-catalyst (0.025 mmol), and ad-

ditive (10 mol%), and the solution was stirred at room temperature. The catalyst, co-catalyst, additive, and reaction time are specified in Tables 1 and 2. Then, the reaction mixture was diluted with DCM (15 mL) and quenched with aqueous  $\text{NH}_4\text{Cl}$  solution. The aqueous layer was extracted with EtOAc ( $3 \times 20 \text{ mL}$ ), and the combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered, and concentrated. Purification of the residue by column chromatography ( $\text{SiO}_2$ , EtOAc/hexanes = 1:5) afforded lactol **3a**. Then  $\text{Et}_3\text{SiH}$  (0.24 mL, 1.5 mmol) and  $\text{BF}_3 \cdot \text{OEt}_2$  (0.12 mL, 1.0 mmol) were added to a solution of lactol **3a** in DCM (1.0 mL) at  $-10^\circ\text{C}$ , and the mixture was stirred for 30 min at the same temperature and another 60 min at room temperature. After this time, the mixture was quenched with saturated aqueous  $\text{NaHCO}_3$  (10 mL) and extracted with DCM ( $2 \times 30 \text{ mL}$ ). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered, and concentrated. Pure product **4a** was obtained as a colorless solid.

#### (4aS,9R,9aS)-9-(Nitromethyl)-2,3,4,4a,9,9a-hexahydro-1H-xanthene (**4a**)

Mp  $78\text{--}80^\circ\text{C}$  (lit.<sup>22</sup>  $68^\circ\text{C}$ ),  $[\alpha]_{\text{D}}^{20} -9.16$  (*c* 0.9,  $\text{CHCl}_3$ , 94% ee); lit.<sup>22</sup>  $[\alpha]_{\text{D}}^{20} -124.2$  (*c* 0.4,  $\text{CHCl}_3$ , >99% ee).

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.19\text{--}7.14$  (m, 1 H), 6.95–6.92 (m, 1 H), 6.88–6.84 (m, 2 H), 4.94 (dd,  $J = 12.7, 5.8 \text{ Hz}$ , 1 H), 4.56 (dd,  $J = 12.7, 9.8 \text{ Hz}$ , 1 H), 4.30 (br s, 1 H), 3.97–3.94 (m, 1 H), 2.17–1.17 (m, 9 H).  $^1\text{H}$  NMR data are consistent with those in the literature.<sup>22</sup>

Enantiomeric purity 91% (Table 1, entry 10) was determined by HPLC (Daicel Chiralpak OJ-H, hexane/*i*-PrOH (90:10), flow rate 0.8 mL/min,  $\lambda = 254 \text{ nm}$ ):  $t_{\text{R}} = 11.8 \text{ min}$  (major), 13.5 min (minor).

#### Typical Procedure for Squaramide-Catalyzed Sequential Asymmetric Michael Lactonization Reaction of Methyl Cyclopentanone-2-carboxylate with 2-(2-Nitrovinyl)phenol

To a mixture of methyl cyclopentanone-2-carboxylate (**5**, 56 mg, 0.4 mmol) and 2-(2-nitrovinyl)phenol **1** (0.3 mmol) in solvent (1 mL) was added the squaramide catalyst (0.025 mmol), and the solution was stirred at room temperature. The catalyst, solvent, and reaction time are specified in Tables 3 and 4. Then, the reaction mixture was diluted with DCM (15 mL) and filtered through a silica gel column. After concentration, dry DCE (4 mL) and *p*-TSA (5.2 mg, 0.03 mmol, 10 mol%) were added to the residue, and the solution was stirred at  $80^\circ\text{C}$  for 3 h. Then, the cooled reaction mixture was quenched with aqueous  $\text{NaHCO}_3$ , and the aqueous layer was extracted with DCM ( $3 \times 10 \text{ mL}$ ). The combined extracts were dried ( $\text{MgSO}_4$ ), filtered, concentrated, and the residue was purified by column chromatography ( $\text{SiO}_2$ , EtOAc/hexanes = 1:7 to 1:3) to afford the desired product **8**. Yields and enantiomeric excess data are summarized in Tables 3 and 4.

#### (3S,4R)-4-(Nitromethyl)spiro(chroman-3,1'-cyclopentane)-2,2'-dione (**8a**)

Mp  $145\text{--}147^\circ\text{C}$  (lit.<sup>20</sup>  $143\text{--}145^\circ\text{C}$ ),  $[\alpha]_{\text{D}}^{20} -58.9$  (*c* 0.15,  $\text{CHCl}_3$ , >99% ee); lit.<sup>20</sup>  $[\alpha]_{\text{D}}^{20} -36.5$  (*c* 0.34,  $\text{CHCl}_3$ , >99% ee).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta = 7.40\text{--}7.37$  (m, 1 H), 7.20–7.12 (m, 3 H), 5.55 (dd,  $J = 13.6, 4.9 \text{ Hz}$ , 1 H), 4.40 (dd,  $J = 13.5, 10 \text{ Hz}$ , 1 H), 3.77 (dd,  $J = 10.1, 4.9 \text{ Hz}$ , 1 H), 2.72–2.66 (m, 1 H), 2.50–2.44 (m, 1 H), 2.20–2.19 (m, 1 H), 2.07–1.98 (m, 3 H).  $^1\text{H}$  NMR data in agreement with literature.<sup>20</sup>

Enantiomeric purity > 99% (Table 4, entry 4) was determined by HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH (80:20), flow rate 1.0 mL/min,  $\lambda = 254 \text{ nm}$ ):  $t_{\text{R}} = 21.3 \text{ min}$  (major), 25.3 min (minor).

**(3R,4S)-4-(Nitromethyl)spiro(chroman-3,1'-cyclopentane)-2,2'-dione (8a)**

$[\alpha]_{\text{D}}^{20} +39.3$  (c 0.2, CHCl<sub>3</sub>, 92% ee); lit.<sup>20</sup>  $[\alpha]_{\text{D}}^{20} +28.7$  (c 0.42, CHCl<sub>3</sub>, 98% ee).

Enantiomeric purity 90% (Table 4, entry 5) was determined by HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH (80:20), flow rate 1.0 mL/min,  $\lambda = 254$  nm):  $t_{\text{R}} = 21.8$  min (minor), 25.3 min (major).

**(3S,4R)-6-Chloro-4-(nitromethyl)spiro(chroman-3,1'-cyclopentane)-2,2'-dione (8b)**

Mp 118–120 °C (lit.<sup>20</sup> 116–118 °C),  $[\alpha]_{\text{D}}^{20} -47.8$  (c 0.15, CHCl<sub>3</sub>, >99% ee); lit.<sup>20</sup>  $[\alpha]_{\text{D}}^{20} -12.1$  (c 0.28; CHCl<sub>3</sub>, >87% ee).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta = 7.35$  (dd,  $J = 8.7, 2.5$  Hz, 1 H), 7.20 (d,  $J = 2.4$  Hz, 1 H), 7.07 (d,  $J = 8.7$  Hz, 1 H), 5.55 (dd,  $J = 13.9, 4.8$  Hz, 1 H), 4.40 (dd,  $J = 13.9, 10.0$  Hz, 1 H), 3.74 (dd,  $J = 9.9, 4.8$  Hz, 1 H), 2.72–2.67 (m, 1 H), 2.50–2.44 (m, 1 H), 2.20–2.16 (m, 1 H), 2.09–1.96 (m, 3 H). <sup>1</sup>H NMR data in agreement with literature.<sup>20</sup>

Enantiomeric purity >99% (Table 3, entry 8) was determined by HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH (80:20), flow rate 1.0 mL/min,  $\lambda = 254$  nm):  $t_{\text{R}} = 30.1$  min (major).

**(3S,4R)-6-Methoxy-4-(nitromethyl)spiro(chroman-3,1'-cyclopentane)-2,2'-dione (8c)**

$[\alpha]_{\text{D}}^{20} -5.7$  (c 1.5, CHCl<sub>3</sub>, >99% ee); lit.<sup>20</sup>  $[\alpha]_{\text{D}}^{20} -35.2$  (c 0.3, 84% ee).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta = 7.04$  (d,  $J = 8.7$  Hz, 1 H), 6.88 (dd,  $J = 8.9, 2.9$  Hz, 1 H), 6.69 (d,  $J = 2.9$  Hz, 1 H), 5.55 (dd,  $J = 13.7, 4.9$  Hz, 1 H), 4.39 (dd,  $J = 13.7, 10.1$  Hz, 1 H), 3.78 (s, 3 H), 3.72 (dd,  $J = 10.1, 4.9$  Hz, 1 H), 2.71–2.66 (m, 1 H), 2.49–2.43 (m, 1 H), 2.21–2.17 (m, 1 H), 2.07–1.96 (m, 3 H). <sup>1</sup>H NMR data in agreement with literature.<sup>20</sup>

Enantiomeric purity 98% (Table 3, entry 9) was determined by HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH (80:20), flow rate 1.0 mL/min,  $\lambda = 254$  nm):  $t_{\text{R}} = 28.5$  min (minor), 38.1 min (major).

## Conflict of Interest

The authors declare no conflict of interest.

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## Supporting Information

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