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## RESEARCH ARTICLE

## An Organocatalytic and Stereoselective Vinylogous Domino Process Towards Thiochromans

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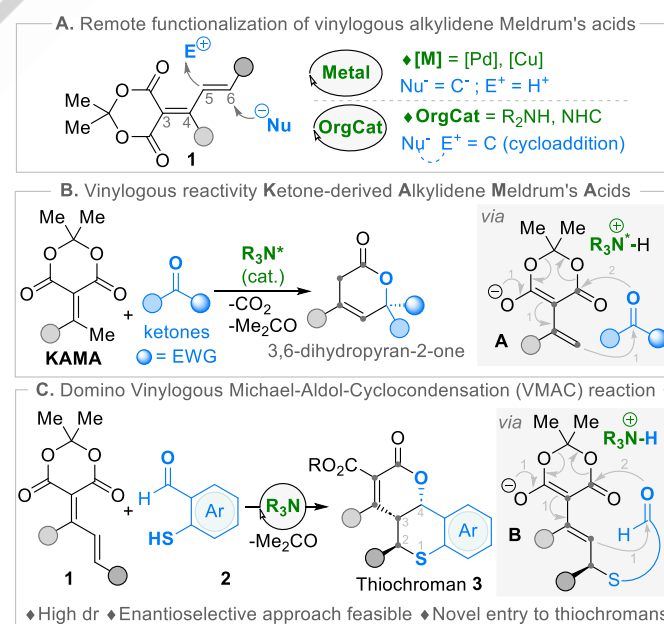
**Abstract:** A highly diastereoselective organocatalyzed domino Vinylogous sulfa-Michael-Aldol-Cyclocondensation (VMAC) reaction has been developed using alkylidene Meldrum's acid as dienes highlighting two vinylogous steps, an unprecedented sulfa-1,6-conjugate addition and a diastereoselective aldol reaction triggering a formal (4+2) cycloaddition. This work opens a new route towards bio-relevant and original tricyclic thiochroman derivatives.

## Introduction

The catalytic vinylogous hetero-Michael addition reaction allows a valuable remote 1,6-functionalization sequence of electron-poor dienes, which affords various opportunities for subsequent stereoselective domino or stepwise transformations of the remaining 3,4- or 4,5-enone motif towards chemical diversity.<sup>[1]</sup> The vinylogous alkylidene Meldrum's acids (MA) **1** proved to be reactive platform molecules,<sup>[2]</sup> undergoing facile catalytic 1,6-addition of carbon-nucleophiles in the presence of a catalytic amount of metal complexes<sup>[3]</sup> and organocatalysts<sup>[4]</sup> (1 example in each publications), in a racemic or enantioselective fashions (Scheme 1A). However, the catalytic 1,6-conjugate addition of hetero-nucleophiles remains to be developed starting from **1**,<sup>[2]</sup> and the subsequent transformation of the remaining valuable alkylidene Meldrum's acid motif has been rarely investigated and only in a stepwise manner.<sup>[2],[3]b,[5]</sup>

We recently discovered a unique vinylogous reactivity of ketone-derived alkylidene Meldrum's acid (**KAMA**) under organocatalytic asymmetric conditions (Scheme 1B).<sup>[6],[7]</sup> Subsequent to the deprotonation of **KAMA** with a tertiary amine, the resulting transient vinylogous enolate species **A** led to a formal stepwise (4+2) cycloaddition to activated ketones, giving rise to formation of 3,6-dihydropyran-2-ones as the kinetic product.<sup>[6],[7]</sup> Aiming at exploring further this original organocatalytic reactivity, we reasoned that a suited bifunctional nucleophile, like 2-carboxaldehyde thiophenol **2**, may lead to a selective 1,6-sulfa-Michael process generating enolate **B** which could trigger a diastereoselective formal (4+2) cycloaddition towards novel and

valuable tricyclic thiochromans **3** (Scheme 1C). While tricyclic C3-C4-fused thiochroman derivatives have been shown to be valuable compounds in medicinal chemistry, their synthesis usually requires multi-step process endeavors.<sup>[8],[9]</sup> The recent work of Li and colleagues is noteworthy in opening up a straightforward catalytic domino sulfa-Michael-aldol reaction towards the construction of thiochromans flanked by a five-membered isotetronic acid ring fused at C3-C4.<sup>[10]</sup> Although, a great deal of work has been done in domino 1,4-sulfa-Michael-aldol reactions with bifunctional nucleophiles such as 2-mercapto benzaldehyde,<sup>[10],[11],[12]</sup> the organocatalytic domino vinylogous 1,6-sulfa-Michael-aldol reaction remains sparingly described and the work of Albrecht on dienones and dienals to be pointed out.<sup>[13]</sup>



Scheme 1. Catalytic vinylogous transformations of alkylidene Meldrum's acids.

We are delighted to report hereby, the original domino Vinylogous sulfa-Michael-Aldol-Cyclocondensation (VMAC) reaction which

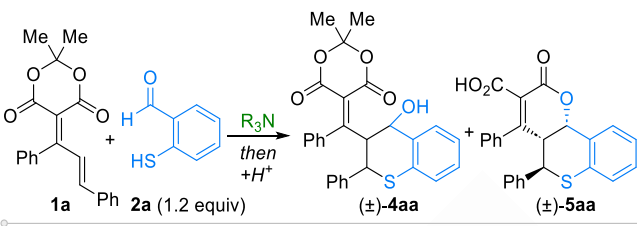
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encompasses unprecedented achievements related to the transformation of vinylogous alkylidene MA derivatives **1**: (1) an efficient 1,6-sulfa-Michael to dienes **1** (2) highlighting a double vinylogous conjugate addition-aldol reactions as key steps (3) in a highly diastereoselective manner (control of three stereocenter C\* through the concomitant C-S, C-C and C-O bonds formation) which, eventually, (4) opens a new entry to medicinally valuable Csp<sup>3</sup>-rich thiochroman derivatives, with an original 3-fused 6-membered-ring backbone.

## Results and Discussion

Our investigation commenced with the reaction between vinylogous alkylidene MA **1a** and 2-mercapto benzaldehyde **2a** (Table 1). To our delight, in the presence of 20 mol% of quinuclidine and 2 equivalents of Na<sub>2</sub>CO<sub>3</sub> in toluene/brine mixture, the tricyclic thiochroman **5aa** was obtained in only 2 hours in high NMR yield of 99%, as a carboxylic acid after an acidic work-up (entry 1). We essentially observed one diastereoisomer by <sup>1</sup>H NMR (95:5 diastereoisomeric ratio - dr), which highlighted the excellent relative stereocontrol of three-contiguous stereocenters. When quinuclidine was changed for Et<sub>3</sub>N, *i*-Pr<sub>2</sub>EtN or DABCO organocatalysts (entries 2-4), lower yields were obtained (60-86%) with a by-product postulated as the uncyclized compound **4aa**. While the lack of stability of **4aa** prevented its isolation and full characterization, <sup>1</sup>H NMR and mass spectrometry analyses were performed on the crude mixture and pointed towards the proposed structure (see SI). Stronger DBU and TBD bases provided essentially the tricyclic product **5aa** (entries 5-6), although with a lower dr. It was demonstrated that a slow reaction occurred in the absence of base, providing **5aa** in 11% NMR yield after 5 hours (entry 7). This background reaction was suppressed by means of water instead of brine but a significant hydrolysis process of the starting material **1a** was observed. Importantly, the transformation was significantly accelerated by quinuclidine organocatalyst, which also turned out to be particularly competent to favor the cyclization event on the 1,3-dioxan-4,6-dione (25% of **4aa** left without quinuclidine, entry 8). This is in agreement with previous observations showing the importance of the nature of the organic base to promote this type of cyclocondensation sequence.<sup>[6],[14]</sup> Importantly, the use of 20 mol% of an organic base alone, without an excess of a mineral base, led to a complex mixture (see SI), likely due to the formation of a non-catalytic tertiary ammonium carboxylate intermediate. Additionally, Na<sub>2</sub>CO<sub>3</sub> used as a solid led to a worse outcome (entry 9). Toluene as organic solvent turned out to be the best option (entries 10-11). At that stage, two observations have to be pointed out. First, the VMAC sequence was achieved with aldehydes, contrariwise to the previous vinylogous addition of **KAMA**, which only occurred with activated ketones (see Scheme 1B). Next, the 5,6-dihydropyran-2-one **5aa** with a conjugated C-C double bond was obtained from **1a** without a decarboxylative event, in sharp contrast with our previous report.<sup>[6],[7]</sup> Geometric constraint within tricyclic structure **5aa** might retard the C-C double bond shift (see SI).

**Table 1.** Optimization of the domino VMAC reaction.



Entry	Variation of conditions	Yield (%) <sup>[a]</sup> <b>4aa</b> ; <b>5aa</b>	dr <sup>[b]</sup>
1	none	0; 99	95:5
2	Et <sub>3</sub> N instead of quinuclidine	10; 86	95:5
3	<i>i</i> -Pr <sub>2</sub> EtN instead of quinuclidine	30; 61	92:8
4	DABCO instead of quinuclidine	24; 60	95:5
5	DBU instead of quinuclidine	0; 70	90:10
6	TBD <sup>[c]</sup> instead of quinuclidine	0; 90	87:13
7	No base	21; 11 <sup>[d]</sup>	-
8	Without quinuclidine	25; 29 <sup>[e]</sup>	95:5
9	Na <sub>2</sub> CO <sub>3</sub> solid in toluene	18; 54 <sup>[f]</sup>	95:5
10	CH <sub>2</sub> Cl <sub>2</sub> or THF instead of PhMe	0; 75-76	95:5
11	PhCF <sub>3</sub> instead of PhMe	0; 85	94:6

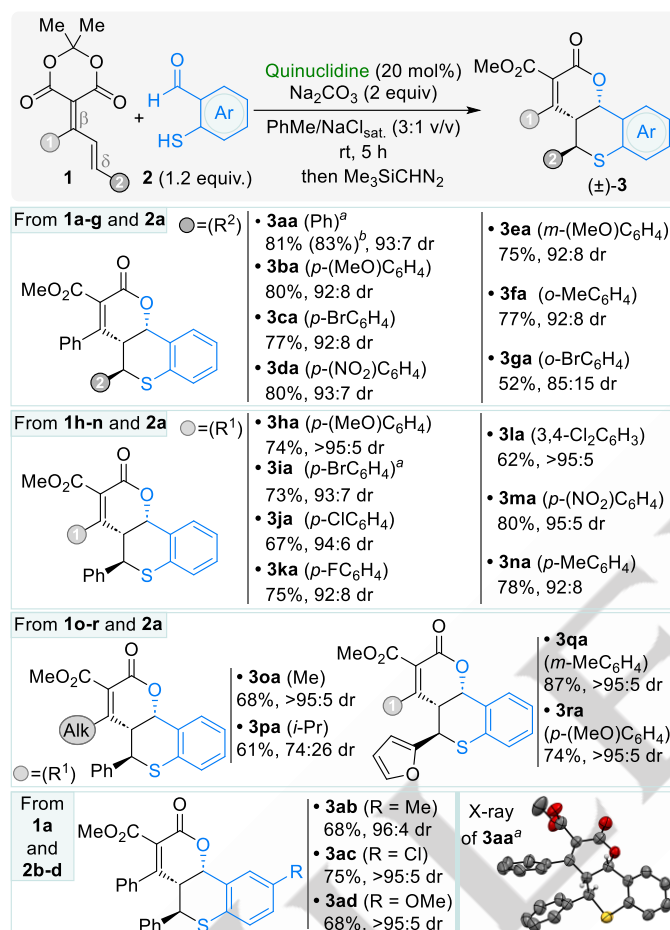
Reaction performed at 0.1 M (versus **1a**) on 0.1 mmol scale of **1a**. [a] NMR yield of both diastereoisomers determined by <sup>1</sup>H NMR using an internal standard. [b] Diastereoisomeric ratio (dr) of **5aa** determined on the crude by <sup>1</sup>H NMR. [c] TBD: triazabicyclodecene. [d] Carried out in 5 hours (58% **1a** left); and no product formation in PhMe/water. [e] In 5 hours. [f] With Cs<sub>2</sub>CO<sub>3</sub> instead (64% **5aa**, 85:15 dr).

With these organocatalytic conditions in hands, the scope of the domino VMAC reaction was investigated with 2-mercapto benzaldehyde **2a** in 5 hours of reaction (Scheme 2). Importantly, from the model **1a**, the acid product **5aa** (Table 1) proved to be unstable for longer reaction time (or upon heating) in the presence of a base, leading to a C-O elimination reaction (see SI). Thus, we implemented a simple esterification protocol with Me<sub>3</sub>SiCHN<sub>2</sub> to afford the corresponding stable methyl ester **3aa**, with the major diastereoisomer isolated in 81% yield (83% on 1 mmol scale) after purification by column chromatography. Moreover, the relative stereochemistry was ascertained by X-ray analyses for **3aa** (as well as for **3ia** *vide infra*). We probed the reactivity of various vinylogous alkylidenes **MA 1** flanked by aryl moieties at β- and δ-position which are platform molecules poorly investigated in the literature.<sup>[2a, 2b],[3],[4]</sup> To our delight, dienes with *para*- (**1b-d**), *meta*- (**1e**) and the more sterically hindered *ortho*-substituted aryl pendants (**1f**) at the δ-position (with R<sup>1</sup> = Ph) were easily transformed into their corresponding products **3aa-fa** in good yields ranging from 75% to 81% and excellent dr between 92:8 and 93:7. A slightly more moderate outcome was observed with the *ortho*-bromo derivative **1g** giving the major stereoisomer **3ga** in 52% yield and 85:15 dr. As long as dienes variously substituted at β-position are concerned (**1h-n**, with R<sup>2</sup> = Ph), the electronics of the aryl moiety had little influence on the reaction outcome allowing the formation of thiochromans **3ha-na** with 62-80% yields and more than 92:8 dr. Eventually, tricyclic structures with either an heteroaromatic furan (**3qa-ra**, 74-87%, >95:5 dr) or a



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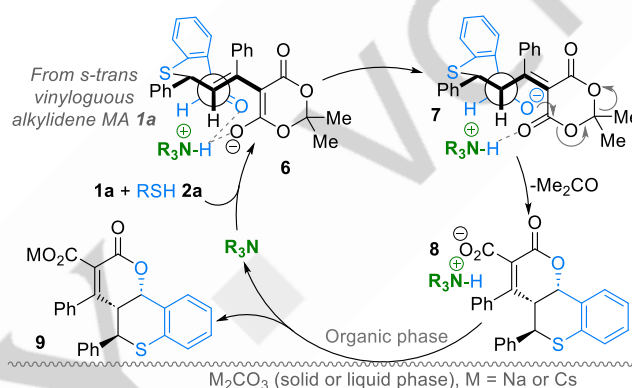
methyl pendant (**30a**, 68%, >95:5 dr) were easily synthesized in the same conditions. Contrariwise to the excellent diastereoselectivity observed thus far, the more sterically encumber *iso*-propyl ( $R^1$ ) derivative **1p** gave a crude mixture with 74:36 dr but the main stereoisomer **3pa** was successfully isolated in 61% yield. Eventually, the domino VMAC reaction was successfully achieved with three different thiol derivatives **2b-d** to afford the corresponding tricyclic thiochromans **3ab-3ad** with good 68-75% yields and excellent dr > 95:5.



**Scheme 2.** Scope of the domino VMAC reaction. Reaction performed at 0.1 M (versus **1**) on 0.2 mmol scale; isolated yields (%) of the major diastereoisomer after purification by column chromatography, and diastereoisomeric ratio (dr) determined on the crude by <sup>1</sup>H NMR before esterification. [a] Structures **3aa** and **3ia** were ascertained by X-ray analyses. [b] Carried out on 1 mmol scale (92:8 dr).

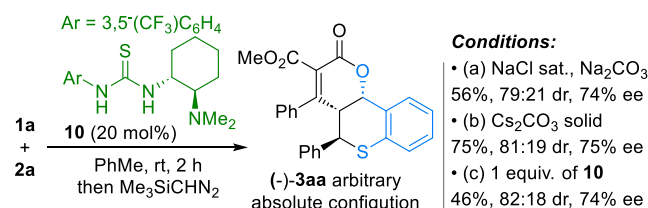
As long as the mechanism is concerned (Scheme 3), we proposed that an organocatalyzed vinylogous sulfa-Michael of thiol **2a** occurred regioselectively on the likely more stable *s*-trans alkylidene Meldrum's acid **1a** to provide enolate intermediate **7** (only one enantiomer arbitrary shown). The significant nucleophilic character of the thiolate ammonium intermediate is probably important for the conjugate addition as long as no reaction was observed with the 2-carboxaldehyde phenol analogue. Next, according to our previous observations,<sup>[6],[14]</sup> hydrogen bonding events, involving the protonated amine **R<sub>3</sub>N<sup>+</sup>**

**H**, are likely key for the reactivity and stereoselectivity issues. First of all, (1) the diastereoselectivity of the subsequent vinylogous aldol would be secured by H-bonds shared between the two oxygen atoms of **6** (i.e. the aldehyde and the enolate moieties) to afford alkoxide **7** as the major stereoisomer. Next, (2) **R<sub>3</sub>N<sup>+</sup>-H** would assist the cyclocondensation cascade on **7** towards the formation of ammonium carboxylate **8**. The release of acetone during the cyclization step likely prevents the otherwise equilibration of the sulfa-Michael to take place, as testified by the instability of the putative intermediate **4aa** (see Scheme 1). A cation exchange would take place at the liquid/liquid or liquid/solid interface to afford sodium carboxylate **9** while recycling the organocatalyst **R<sub>3</sub>N** after deprotonation by the carbonate base.



**Scheme 3.** Catalytic cycle and induction model.

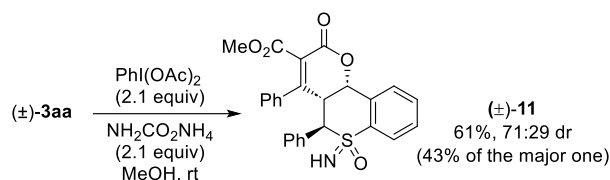
With this efficient domino sulfa-Michael based protocol in hands, we wondered whether an organocatalytic enantioselective process could be feasible (Scheme 4). After a significant screening of conditions and catalysts (see SI), the Takemoto catalyst **10** (20 mol%) was found to promote the construction of tricyclic thiochromane **3aa** in 56% yield and with a satisfactory 74% ee. By means of Cs<sub>2</sub>CO<sub>3</sub> in a solid/liquid biphasic media, an improved yield of 75% was obtained with the same enantioselectivity. The efficacy of the organocatalyst **10** was proven as long as one equivalent of **10** led to a similar ee of 74% showing that the racemic background reaction did not compete under these conditions. At that stage, it is difficult to precisely describe the role of a chiral **R<sub>3</sub>N<sup>+</sup>** such as Takemoto's bifunctional organocatalyst. One can imagine that after the enantiodetermining sulfa-Michael step giving **6**, the subsequent aldol event (**6** to **7**) would be altered by hydrogen bonding which could also stabilize the addition to the other face of the aldehyde leading to the lower diastereoselectivity (79:21-82:18 dr) compared to the racemic conditions (see Scheme 2).



**Scheme 4.** An enantioselective domino VMAC reaction.

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We further highlighted the versatility of the new tricyclic thiochroman structure **3aa** by synthesizing the corresponding sulfoximine **11**, which is a known valuable motif present within a series of pharmaceutically active compounds.<sup>[15]</sup> Thanks to recent straightforward protocols,<sup>[16]</sup> the sulfoximine **11** was synthesized in one step in 61% yield as a mixture of separable *S*-epimers with a ratio of 71:29 (Scheme 5).



Scheme 5. Product transformation.

## Conclusion

In conclusion, we have demonstrated a new type of transformation of valuable alkylidene Meldrum's acids **1** as dienes highlighting a highly stereoselective domino VMAc reaction which encompasses two vinylogous steps, i.e., a sulfa-Michael and an aldol reaction, prior to the final cyclocondensation sequence. A promising enantioselective version of this protocol was also demonstrated affording **3aa** in 75% ee. This approach not only opens a route to bio-relevant and original tricyclic thiochromans but paves the way to the development of other domino process towards construction of chemical diversity in Csp<sup>3</sup>-rich heterocycles from platform diene-molecules **1**.

## Experimental Section

**Representative procedure for the synthesis of methyl 2-oxo-4a,10b-dihydro-2H,5H-thiochromeno[4,3-b]pyrane-3-carboxylate (3).** Vinylogous alkylidene Meldrum's acid **1a** (0.2 mmol, 1.0 equiv) and thioaldehyde **2a** (0.24 mmol) were dissolved in anhydrous PhMe (2.0 mL, 0.1 M) in a sealable tube under inert atmosphere. Quinuclidine (0.04 mmol, 0.2 equiv, 1 M in anhydrous PhMe) was added under stirring at room temperature, followed by a solution of Na<sub>2</sub>CO<sub>3</sub> (42.4 mg, 0.4 mmol, 2.0 equiv) in a saturated solution of NaCl (0.8 mL). The tube was sealed, and the resulting heterogeneous mixture was vigorously stirred at room temperature for 5 h under inert atmosphere. The reaction was quenched by dropwise addition of HCl (2 mL, 1 M in H<sub>2</sub>O) and diluted with EtOAc (4 mL). The organic phase was washed twice with HCl 1 M (2 × 3 mL) and the combined aqueous phases were extracted twice with EtOAc (2 × 3 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The diastereoselectivity was measured by <sup>1</sup>H NMR and the resulting crude product was directly engaged without further purification in the methylation step. A solution of the crude carboxylic acid **5aa** in PhMe/MeOH (1.0 mL, 80:20 v/v) was cooled down to 0 °C with an iced bath under inert atmosphere. Trimethylsilyldiazomethane (0.4 mL, ca 8 equiv, 2 M in hexane) was added dropwise. The reaction mixture was stirred at room temperature for 30 min. Then the

excess of TMSCHN<sub>2</sub> was quenched by dropwise addition of acetic acid at 0 °C. The mixture was stirred at 0 °C for 5 min, then at room temperature for 10 min. The resulting solution was concentrated under reduced pressure and the crude product was purified by flash column chromatography to isolate the major methyl ester product **3aa** (see Scheme 2 for the results).

## Conflict of interest

The authors declare no conflict of interest.

## Supporting Information

The data that support this investigation are available in the supplementary material.

## Acknowledgements

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**Keywords:** Meldrum's acid • Michael addition • organocatalysis • sulfur heterocycles • thiochromenone • vinylogy

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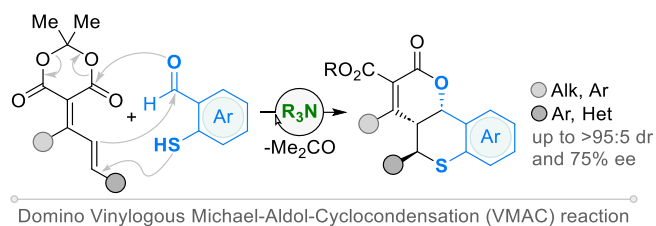
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