Domino Reactions

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Organocatalytic Domino Oxa-Michael/1,6-Addition Reactions: Asymmetric Synthesis of Chromans Bearing Oxindole Scaffolds

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Abstract: *An asymmetric organocatalytic domino oxa-Michael/1,6-addition reaction of ortho-hydroxyphenyl-substituted para-quinone methides and isatin-derived enoates has been developed. In the presence of 5 mol% of a bifunctional thiourea organocatalyst, this scalable domino reaction affords 4-phenyl-substituted chromans bearing spiro-connected oxindole scaffolds and three adjacent stereogenic centers in good to excellent yields (up to 98%) and with very high stereoselectivities (up to >20:1 d.r., >99% ee).*

The chroman skeleton is a pervasive structural moiety not only in many bioactive natural products, but also in a plethora of pharmaceuticals.[1] In particular, enantiopure 4-phenyl-substituted chroman derivatives featuring multiple stereogenic centers have received tremendous interest owing to their potential medical value and structural complexity (Figure 1). For instance, ormeloxifene, which is currently being marketed, is a selective estrogen receptor modulator.[2]

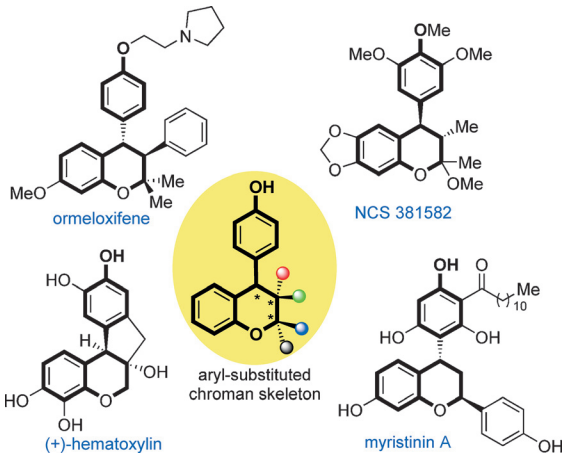

Figure 1. Pharmaceuticals and natural products containing chiral 4-aryl chroman moieties.

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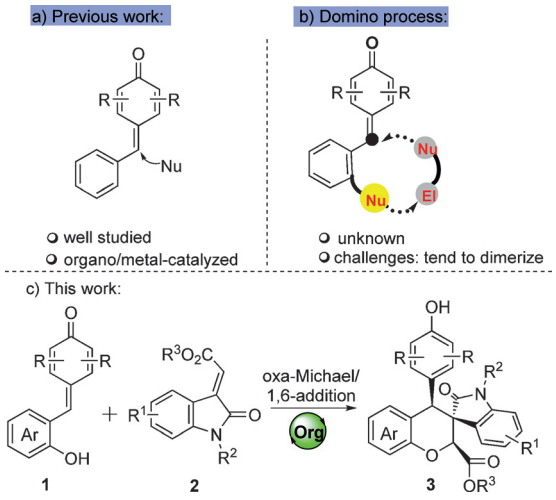
The podophyllotoxin analogue NSC 381582 exhibits antineoplastic activity;[3] (+)-hematoxylin is used as a stain in histology and is a potent protein tyrosine kinase inhibitor.[4] Myristinin A, a flavonoid isolated from *Myristica cinnamomea* and *Knema elegans*, shows antifungal and DNA polymerase β inhibitory activities.[5] Accordingly, several asymmetric reactions to approach this privileged skeleton have been developed over the years. One of these, the strategy based on *ortho*-quinone methides (*o*-QMs),[6] has been shown to be very viable and reliable by the research groups of Schneider,[7] Rueping,[8] and Shi.[9] Whereas the aforementioned reports have realized high efficiency and stereoselectivity, only limited reaction partners, such as enamides,[7a] electron-rich olefins,[8,9] and oxonium ylides,[7b] were reacted with *o*-QMs to construct aryl-substituted chroman frameworks. Therefore, developing additional methods that are not based on *o*-QM intermediates is still highly desirable.

Recently, *para*-quinone methides (*p*-QMs) have increasingly been investigated,[10] and 1,6-conjugate additions to *p*-QMs have emerged as a most prevailing method for the synthesis of highly enantioenriched diarylmethine compounds.[11] For example, the groups of Fan and Jørgensen have independently reported organocatalytic 1,6-addition reactions between *p*-QMs and malonates[11a] or aldehydes,[11b] respectively. Shortly after these reports, Sun and co-workers developed an elegant strategy in which *p*-QMs were generated in situ and then trapped with pyrroles[11d] and naphthols.[11k] Furthermore, addition reactions of bis(pinacolato)-diboron,[11c,f] thioacetic acid,[11e] 3-substituted oxindoles,[11h,i] glycine Schiff bases,[11g,l] and dicyanoolefins[11j] to *p*-QMs catalyzed by copper, chiral phosphoric acids, chiral ammonium salts, bifunctional squaramides, and thioureas have also been developed (Scheme 1 a). Surprisingly, applications of the *p*-QMs in asymmetric domino reactions have not been explored thus far despite the fact that domino reactions have been demonstrated to be efficient and powerful approaches in modern organic synthesis.[12]

Over the past decade, our group has also focused on the development of asymmetric organocatalytic domino reactions.[13] As part of an ongoing project, we envisioned that the installation of a suitable nucleophilic group could convert *p*-QMs into donor–Michael acceptor substrates, which could be used in domino processes (Scheme 1 b). However, this attempt constitutes a significant challenge owing to the potential dimerization of such species. After extensive investigations, we were pleased to find that *ortho*-hydroxyphenyl-substituted *p*-QMs **1** are ideal substrates.[14] To the best of our knowledge, there are no precedents for using this donor–Michael acceptor synthon in synthesis. To fill this gap, we thought of an unprecedented domino oxa-Michael/1,6-con-



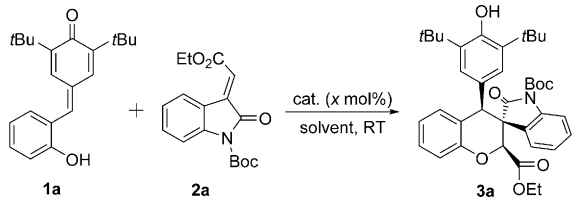
Scheme 1. a) Reported methods based on *p*-QMs. b) Our domino strategy. c) Asymmetric oxa-Michael/1,6-addition reactions to form aryl-substituted chromans with spiro-connected oxindole scaffolds.

jugate addition reaction (Scheme 1c).[15] Moreover, an asymmetric version of such a domino reaction might be developed by employing a suitable chiral organocatalyst, leading to enantioenriched highly functionalized chromans featuring not only an oxindole scaffold but also three contiguous stereogenic centers.

To examine the feasibility of the envisaged domino reaction, we chose **1a** and the isatin-derived enoate **2a**[16] as the model substrates to optimize this reaction. First, thiourea catalyst **A** was used. To our delight, the expected reaction proceeded readily, and the desired product **3a** was isolated in 45% yield with excellent enantioselectivity, albeit with poor diastereoselectivity (entry 1). The widely used squaramide catalyst **B** delivered comparable results (entry 2). Then, several bifunctional thiourea organocatalysts **C**–**H** were examined (entries 3–8), and catalyst **G** proved to be the best choice for this domino process, giving excellent efficiency and stereoselectivity (entry 7). When the catalyst loading was decreased to 10 mol% and 5 mol%, the yields slightly increased and the stereoselectivities remained excellent (entries 9 and 10). No further improvements were observed when other solvents, such as DCM, DCE, Et_2O, or $PhCF_3$, were used (entries 11–14). The best reaction conditions are those shown in entry 10, and gave **3a** in 89% yield, 99% *ee*, and 17:1 d.r.

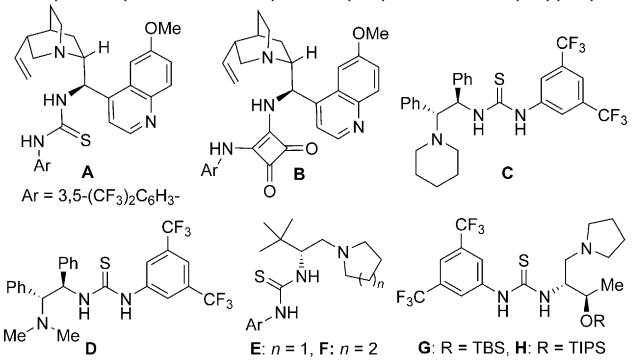
With optimized reaction conditions established (Table 1, entry 10), the substrate scope of this oxa-Michael/1,6-addition reaction was explored. First, we evaluated the generality of the olefinic oxindole component **2** (Table 2, top). In general, broad range of 3-olefinic oxindoles were viable substrates and furnished products **3a**–**3p** in 58–98% yield with excellent enantioselectivities (up to >99% *ee*). In detail, substrates bearing electron-neutral (R = H), electron-donating (R = Me, OMe), or electron-withdrawing groups (R = F, Cl, Br, I, NO_2, OCF_3) at the C5, C6, or C7 position of the oxindole ring readily underwent this domino process to afford the corresponding chroman products in good to excellent yields with

Table 1: Optimization of the reaction conditions.[a]



Entry	Cat. (mol%)	Solvent	Yield[b] [%]	d.r.[c]	*ee* [%][d]
1	**A** (20)	toluene	45	1:1.3	94
2	**B** (20)	toluene	42	1:1.5	94
3	**C** (20)	toluene	63	3:1	−45
4	**D** (20)	toluene	69	5:1	−97
5	**E** (20)	toluene	81	10:1	96
6	**F** (20)	toluene	80	8:1	83
7	**G** (20)	toluene	82	16:1	98
8	**H** (20)	toluene	trace	–	–
9	**G** (10)	toluene	88	17:1	98
10	**G (5)**	**toluene**	**89**	**17:1**	**99**
11	**G** (5)	DCM	62	4:1	95
12	**G** (5)	DCE	75	7:1	96
13	**G** (5)	Et_2O	70	6:1	99
14	**G** (5)	$PhCF_3$	81	12:1	98

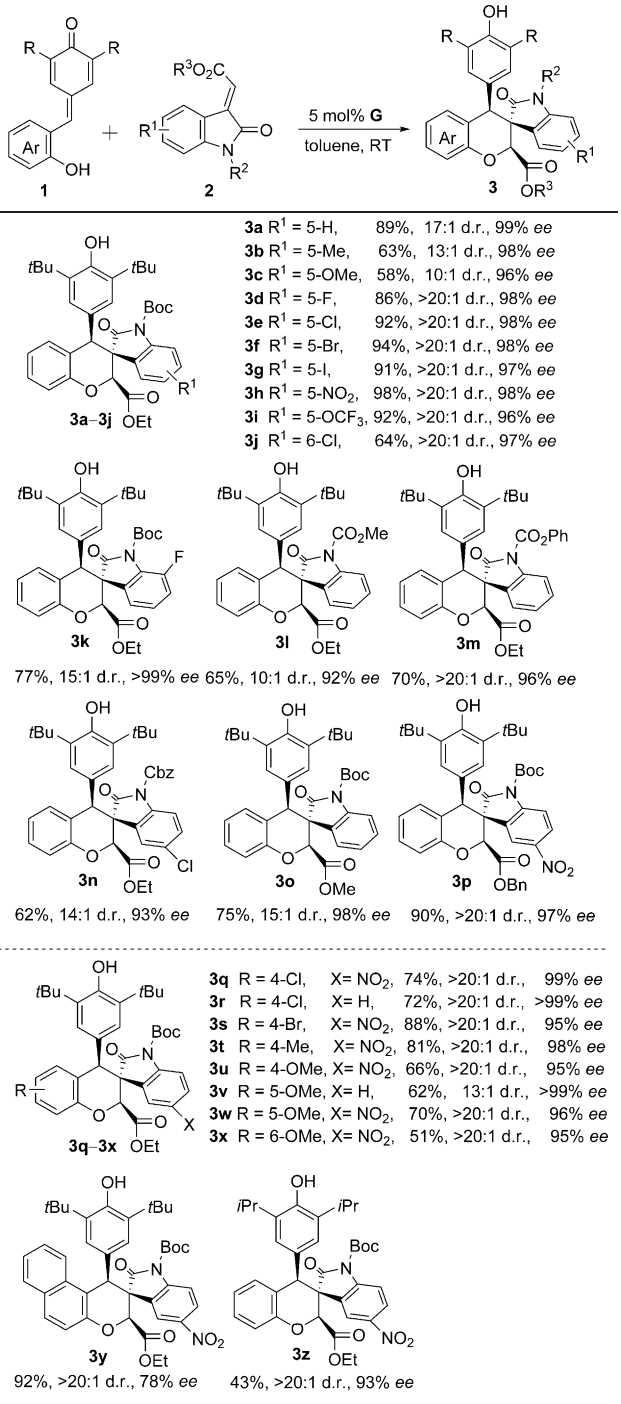
[a] All reactions were conducted with 0.2 mmol of **1a** (1 equiv), 0.24 mmol of **2a** (1.2 equiv), and 5–20 mol% of catalyst in the indicated solvent (2.0 mL) at room temperature for 48 h. [b] Yield of isolated **3a**. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.



excellent asymmetric induction (**3a**–**3k**). In addition, the substituent on the oxindole nitrogen atom could be changed from the Boc group to a methyl ester, phenyl ester, or Cbz group, and the results were still excellent (**3l**–**3n**). Furthermore, we found that the ester group (R^3) had almost no effect on the stereoselectivity, and the products **3o** and **3p** were isolated in 75% yield, 98% *ee* and 90% yield, 97% *ee*, respectively.

Next, hydroxyphenyl-substituted *p*-QMs **1** with different substituents and functional groups were investigated (**3q**–**3z**). Both electron-withdrawing substituents (Cl, Br) and electron-donating groups (Me, OMe) in the *para*, *meta*, and *ortho* positions of the aryl ring of substrates **1** were well tolerated, and the corresponding products were formed in good yields and excellent stereoselectivities (**3q**–**3x**). A naphthyl- and hydroxy-substituted *p*-QM also took part in this domino sequence and gave product **3y**. Replacing the *tert*-butyl

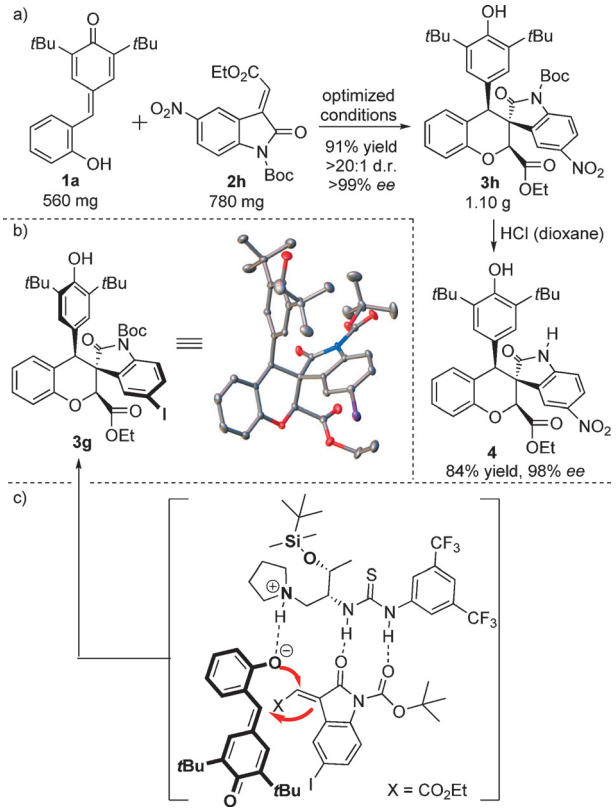
Table 2: Evaluation of the substrate scope.[a]



[a] All reactions were conducted with 0.4 mmol of **1** (1.0 equiv), 0.48 mmol of **2** (1.2 equiv), and 5 mol% of catalyst **G** in toluene (4.0 mL) at room temperature for 12–72 h. Yields of isolated products **3** after column chromatography. The diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. The enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. Cbz = benzyloxycarbonyl.

R substituents of the *p*-QM by isopropyl groups did not influence the stereoselectivity of this reaction (**3z**).

To evaluate the robustness and practical utility of this oxa-Michael/1,6-addition reaction, a gram-scale reaction of **1a** and **2h** was run under the standard conditions. As shown in Scheme 2a, the desired product **3h** was obtained in 91% yield, >20:1 d.r., and virtually enantiopure (>99% *ee*). Moreover, removal of the *N*-Boc group to form **4** was easily achieved without any erosion of the stereoisomeric purity. Notably, the absolute configuration of the adduct **3g** was unambiguously determined by X-ray crystallography,[17] and the configurations of the other chroman derivatives were assigned by analogy (Scheme 2b, left). Furthermore, a plausible transition state[18] is proposed to explain the stereochemical outcome of this oxa-Michael/1,6-addition sequence (Scheme 2c). Taking the reaction between **1a** and **2g** as an example, the bifunctional catalyst **G** activates the olefinic oxindole **2g** through hydrogen-bonding interactions while its tertiary amino group activates *p*-QM **1a**. The *Si* face of **2g** is attacked by the phenolic oxygen atom in an oxa-Michael addition; subsequent intramolecular 1,6-addition delivers the final product **3g**.



Scheme 2. a) Gram-scale synthesis of compound **3h** followed by deprotection to **4**. b) X-ray structure of **3g**. c) Proposed transition state.

In conclusion, we have described the highly stereoselective synthesis of densely functionalized chromans with an oxindole motif through an organocatalytic oxa-Michael/1,6-addition domino reaction. In this process, three vicinal stereogenic centers, including an all-carbon spiro center,[19] were efficiently constructed, delivering a series of chroman

derivatives in high yields and with excellent diastereo- and enantioselectivities. We have thus successfully explored highly reactive hydroxyphenyl-substituted *p*-QMs as bifunctional substrates in organocatalytic domino reactions.

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Keywords: chromans · domino reactions · organocatalysis · oxa-Michael addition · *para*-quinone methides

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