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Asymmetric synthesis of polysubstituted chiral chromans *via* an organocatalytic oxa-Michael-nitro-Michael domino reaction†‡

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A catalytic asymmetric method for the synthesis of polysubstituted chromans *via* an oxa-Michael-nitro-Michael reaction has been developed. The squaramide-catalyzed domino reaction of 2-hydroxynitrostyrenes with *trans*- β -nitroolefins produced chiral chromans with excellent enantioselectivities (up to 99% ee), diastereoselectivities (up to >20 : 1 dr), and moderate to good yields (up to 82%).

Chromans play an essential role in natural products and pharmaceutical molecules (Fig. 1).¹ Given the biological relevance and diverse applications of this indispensable structural motif, numerous valuable methods for building chiral chromans have been developed.² Rapid, direct, and highly atom-economical asymmetric strategies to construct optically active chromans are the first choice.

In the past several years, considerable effort has been made to build chiral chroman derivatives with multichiral centers *via* asymmetric domino reactions³ catalyzed by aminocatalysts,⁴ thiourea organocatalysts⁵ squaramide organocatalysts,⁶ and other organocatalysts.⁷ Among these approaches, the addition to nitroolefins is a simple but highly efficient route to obtain

chiral chromans containing nitro-group, and the nitro group can often lead to changes in chemical and physical properties.^{4d-h,4j,5b-d} In 2013, Zhu *et al.* reported the organocatalytic oxa-Michael-Michael cascade strategy for the construction of spiro [chroman/tetrahydroquinoline-3,3'-oxindole] scaffolds from 2-hydroxynitrostyrenes and N-Boc-protected methyleneindolinones using a squaramide-cinchona bifunctional catalyst.^{6a} Peng *et al.* disclosed the highly efficient synthesis of polysubstituted 4-amino-3-nitrobenzopyrans from 2-hydroxyaryl-substituted α -amido sulfones and nitroolefins mediated by chiral squaramides.^{6b} Furthermore, Yan and Wang's group developed the squaramide-catalyzed cascade reaction of 2-hydroxychalcones with β -CF₃-nitroolefins to yield CF₃-containing heterocyclic compounds with a quaternary stereocenter.^{6c} Notably, a general strategy for the synthesis of chiral chromans bearing two nitro moieties was never reported, especially for 2-alkyl-substituted chromans. In 2003, an easy and efficient method for the synthesis of 3-nitrochromans *via* the reaction of 2-hydroxynitrostyrenes and *trans*- β -nitroolefins in the presence of DABCO was reported.⁸ Motivated by our previous work concerning the asymmetric synthesis of chromans,^{4i,9} this paper presents a highly efficient asymmetric method for the synthesis of polysubstituted chiral chroman derivatives, especially 2-alkyl-substituted chiral types, from 2-hydroxynitrostyrenes and *trans*- β -nitroolefins using a chiral bifunctional squaramide organocatalyst.^{10,11}

Given these considerations and previous work, the organocatalytic oxa-Michael-nitro-Michael reaction was performed with 2-hydroxynitrostyrene **1a** and aliphatic *trans*- β -nitroolefin **2a** as model substrates to examine the feasibility of our approach. Different parameters (Table 1), such as the catalyst and solvent, were studied. Efficient bifunctional squaramide organocatalysts possessing both H-bonding (thiourea, squaramide) and basic/nucleophilic moieties (tertiary amine), which act cooperatively, have been developed by several research

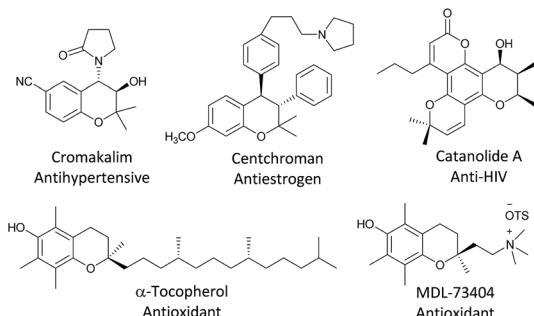


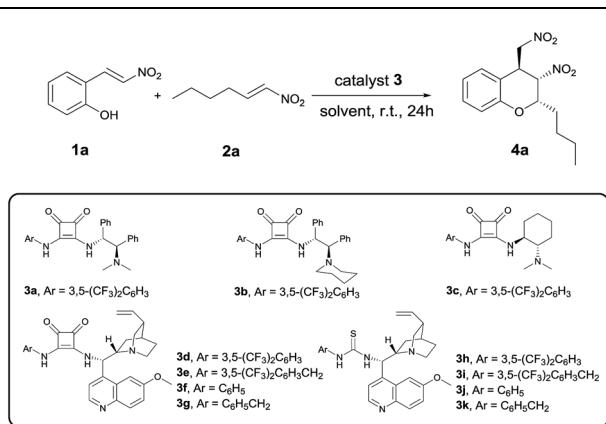
Fig. 1 Selected biologically active compounds.

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† Dedicated to Professor Zhen-Yuan Xu on the occasion of his 80th birthday.

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Table 1 Screening of reaction conditions^a

Entry	Catalyst	Solvent	Yield ^b (%)	ee ^c (%)	dr ^c
1	3a	CH ₂ Cl ₂	47	5	>20 : 1
2	3b	CH ₂ Cl ₂	Trace	N.D. ^d	N.D.
3	3c	CH ₂ Cl ₂	42	-39	>20 : 1
4	3d	CH ₂ Cl ₂	73	80	>20 : 1
5	3e	CH ₂ Cl ₂	78	92	>20 : 1
6	3f	CH ₂ Cl ₂	65	43	>20 : 1
7	3g	CH ₂ Cl ₂	71	85	>20 : 1
8	3h	CH ₂ Cl ₂	69	75	>20 : 1
9	3i	CH ₂ Cl ₂	75	79	>20 : 1
10	3j	CH ₂ Cl ₂	67	58	>20 : 1
11	3k	CH ₂ Cl ₂	68	69	>20 : 1
12	3e	CHCl ₃	65	93	>20 : 1
13	3e	CH ₂ CH ₂ Cl	77	88	>20 : 1
14	3e	EtOAc	71	57	>20 : 1
15	3e	THF	32	87	3 : 1
16	3e	1,4-Dioxane	Trace	N.D.	N.D.
17	3e	Et ₂ O	Trace	N.D.	N.D.
18	3e	CH ₃ CN	61	27	>20 : 1
19	3e	Toluene	77	81	8 : 1
20	3e	Cyclohexane	49	38	10 : 1

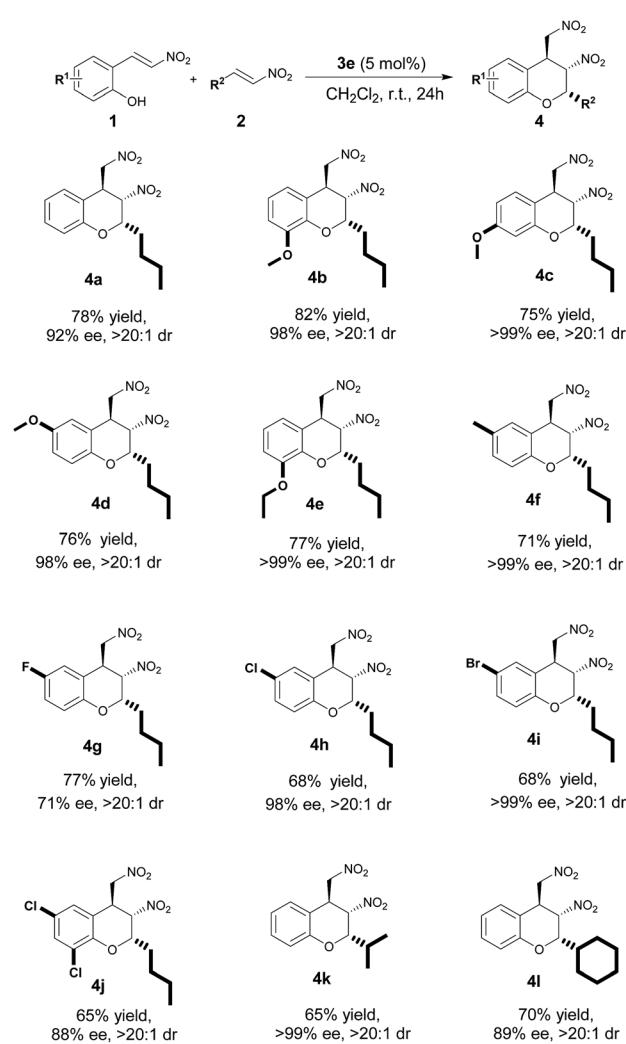
^a All the reactions were conducted with 1a (0.2 mmol), 2a (0.24 mmol), and solvent (2 mL) in the presence of 5 mol% organocatalyst 3 at room temperature with vigorous stirring for 24 h. ^b Isolated yield of 4a.

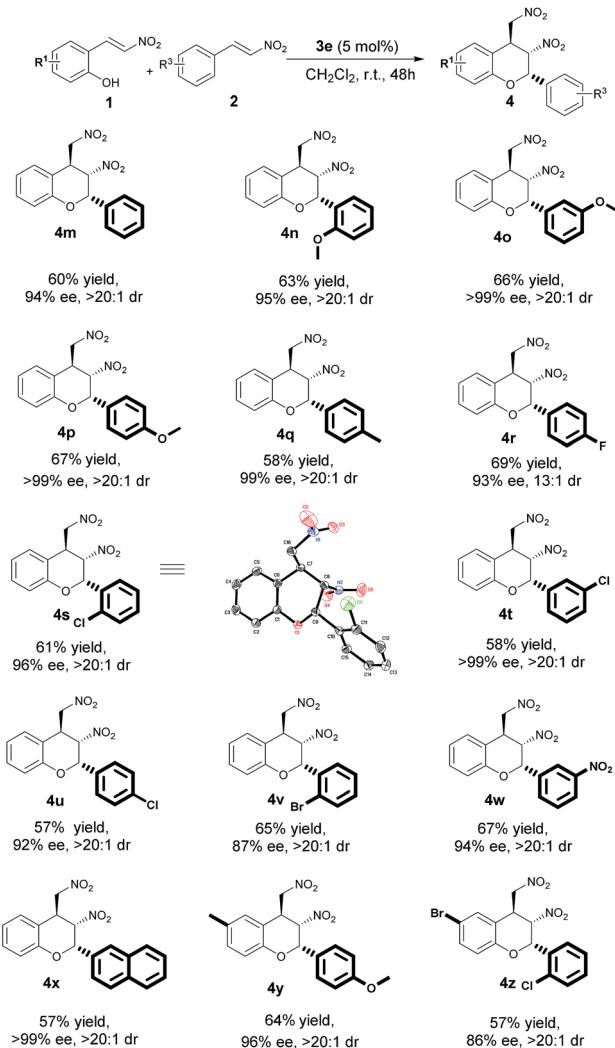
^c Determined by chiral HPLC using an OJ-H column. ^d N.D. = Not determined.

groups for a broad range of enantioselective transformations.^{5c,d} An appropriate basic/nucleophilic moiety is critical to this kind of reaction. Under this consideration, chiral 1,2-diphenylethylenediamine, cyclohexanediamine, and quinine were selected as scaffolds. After a preliminary study, the quinine scaffold revealed excellent stereoinduction for the asymmetric synthesis of the chiral chroman 4a when paired with the squaramide unit (Table 1, entries 1–4). Therefore, the influence of the quinine-derived catalysts should be studied systematically. Among the quinine-derived thiourea and squaramide organocatalysts 3d–3k, the squaramide catalyst 3e could promote the efficient formation of 4a with increased enantioselectivities (up to 92% ee) (entries 4–11). A series of solvents was tested, and the performance of dichloromethane was satisfactory to afford 4a in 78% yield, 92% ee, and >20 : 1 dr (Table 1, entries 5 and 12–20).

Consequently, the best conditions were found with 5 mol% of catalyst 3e loading in CH₂Cl₂ at room temperature.

The reaction scope was determined under the optimal conditions. To investigate the versatility of the catalytic system, we first explored the universality of 1-nitro-1-hexene 2a in this squaramide-catalyzed domino reaction. The reaction was tolerant to a range of substituents, such as OMe, OEt, Me, F, Cl, and Br, on the aromatic ring of 2-hydroxynitrostyrenes. The results revealed that the current transformation was a general and efficient strategy for the asymmetric synthesis of n-Bu group-substituted chiral chromans in the 2-position with three contiguous stereogenic centers. More specifically, when the substrates bore electron-donating groups (R¹ = OMe, OEt, Me) or electron-withdrawing groups (R¹ = F, Cl, Br) at the 6-, 7-, and 8-positions of the benzene ring, the target products achieved 68–82% yields with excellent diastereoselectivities (>20 : 1 dr) and enantioselectivities (71–99% ee). The targeted products with electron-donating groups resulted in high yields (Scheme 1, 4b, 4c, 4d, 4e, 4f versus 4g, 4h, 4i, 4j). In particular, other aliphatic nitroolefins substituted by branched chain aliphatic group (R² = i-Pr) and cycloaliphatic group (R² = cyclohexyl) were further explored,

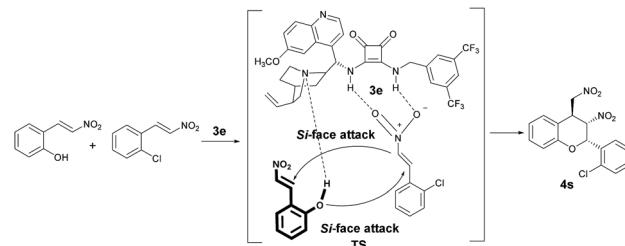




Scheme 2 Scope of 2-aryl chromans.

and these compounds delivered products with good asymmetric inductions (99% and 89% ee, >20 : 1 dr).

In-depth study of the current situation revealed that the enantioselectivities and diastereoselectivities of the chromans with 2-alkyl substituted groups were satisfactory. Therefore, further exploration of aromatic nitroolefins in the oxa-Michael-Michael domino reaction was necessary. Scheme 2 shows that nitroolefins incorporating electron-withdrawing groups and electron-donating groups at the aryl substituents in the 2-position could be successfully employed under these conditions, resulting in final adducts with high to excellent enantioselectivities (86–99% ee), high-to-excellent diastereoselectivities (up to >20 : 1 dr),



Scheme 4 Proposed transition state for this reaction.

and moderate yields (57–69%). In general, nitroolefins with OMe and Me as substituent R³ groups yielded products in excellent 95–99% ee (Scheme 2, 4n–4q, 4y), which were superior to nitroolefins incorporating electron-withdrawing groups (R³ = F, Cl, Br, NO₂). However, product 4t was an interesting special case with 99% ee. The absolute configuration of product 4s was determined to be (2S, 3S, 4S) by single-crystal X-ray diffraction analysis (Scheme 3).¹²

To further demonstrate the synthetic utility of this reaction, we tested *trans*-α-Me-β-nitroolefin. As listed in Scheme 4, *trans*-α-Me-β-nitroolefin was suitable for this reaction and afforded the product 5a with an all-carbon quaternary stereocenter in the 3-position in 59% yield, 91% ee, and 8 : 1 dr.

On the basis of the X-ray crystallographic analysis of the absolute configuration of adduct 4s, we proposed a transition state model (Scheme 4). 2-Chloro-nitrostyrene 1a was activated well through the hydrogen-bonding interaction between the nitro group of 2-chloro-nitrostyrene and the N-H of squaramide catalyst 3e. Meanwhile, 2-hydroxynitrostyrene 1a was activated through a hydrogen-bonding interaction between the hydroxyl group of 1a and the basic/nucleophilic moiety of 3e. Therefore, the hydroxyl group of 1a attacked the β-carbon of the activated 2-chloro-nitrostyrene from the Si face under the control of the catalyst 3e. Subsequently, the α-carbon of activated 2-chloro-nitrostyrene attacked the β-carbon of 1a from the Si face to yield the major stereoisomer of chiral chroman 4s with the configuration of (2S, 3S, 4S).

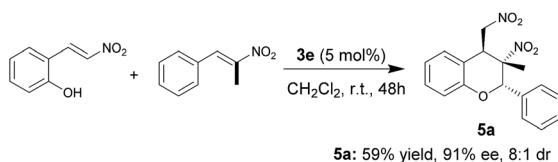
In conclusion, the first enantioselective, organocatalytic oxa-Michael-Michael domino reaction of 2-hydroxynitrostyrenes with *trans*-β-nitroolefins was successfully demonstrated. The new domino reaction provided an easy and efficient approach to construct 2-alkyl-substituted chiral chroman derivatives bearing three contiguous stereogenic centers with two nitro moieties. This strategy was also suitable for the asymmetric synthesis of 2-aryl-substituted chiral derivatives. Furthermore, this methodology could be used to construct chiral chromans with an all-carbon quaternary stereocenter in the 3-position. Further applications of this organocatalytic system are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Scheme 3 Further investigation of the substrate scope.



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12 CCDC 1031452 contains the supplementary crystallographic data for the compound **4s**.[‡]

