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

 Cheng-Ke Tang,^{ID} Kai-Xiang Feng, Ai-Bao Xia,^{ID} * Chen Li, Ya-Yun Zheng, Zhen-Yuan Xu and Dan-Qian Xu*

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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 methyl-eneindolinones 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

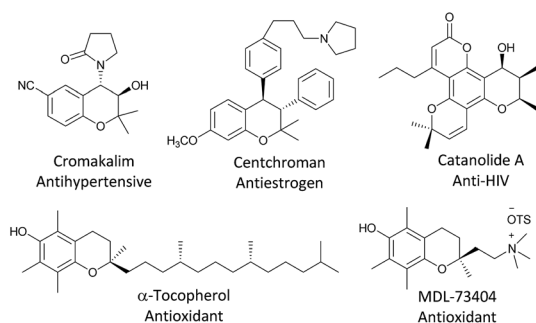


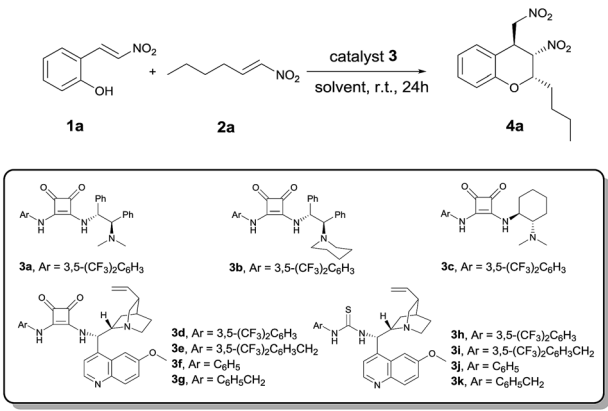
Fig. 1 Selected biologically active compounds.

Catalytic Hydrogenation Research Centre, State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou, 310014, China. E-mail: xiaaibao@zjut.edu.cn; chrc@zjut.edu.cn

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

‡ Electronic supplementary information (ESI) available. CCDC 1031452. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra13525d



Table 1 Screening of reaction conditions^a


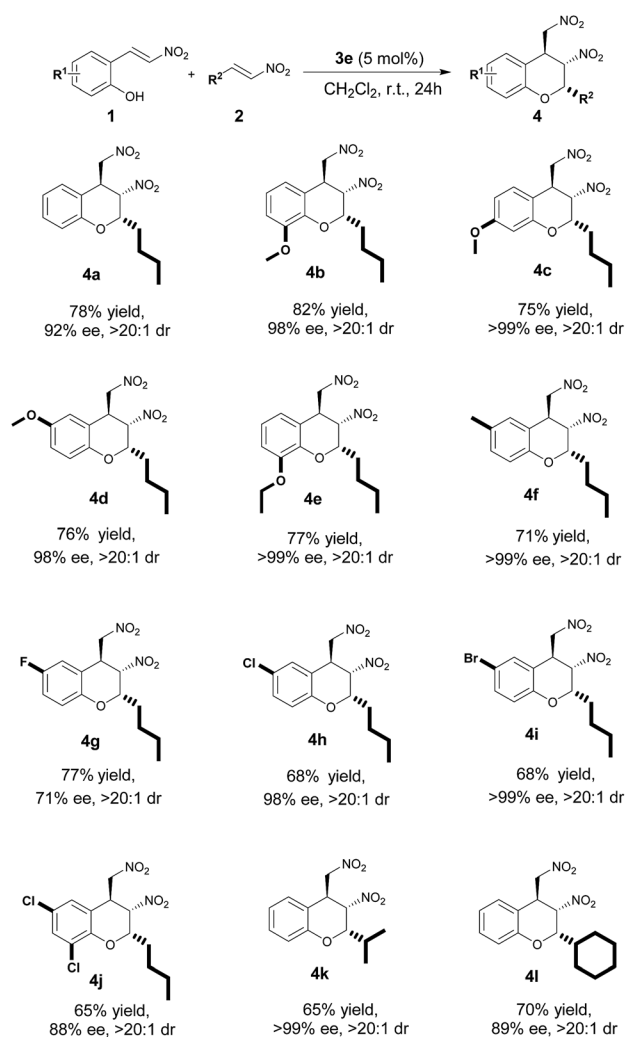
Entry	Catalyst	Solvent	Yield ^b (%)	ee ^c (%)	dr ^c
1	3a	CH ₂ Cl ₂	47	5	>20 : 1
2	3b	CH ₂ Cl ₂	Trace	N.D. ^d	N.D.
3	3c	CH ₂ Cl ₂	42	–39	>20 : 1
4	3d	CH ₂ Cl ₂	73	80	>20 : 1
5	3e	CH ₂ Cl ₂	78	92	>20 : 1
6	3f	CH ₂ Cl ₂	65	43	>20 : 1
7	3g	CH ₂ Cl ₂	71	85	>20 : 1
8	3h	CH ₂ Cl ₂	69	75	>20 : 1
9	3i	CH ₂ Cl 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	ClCH 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).

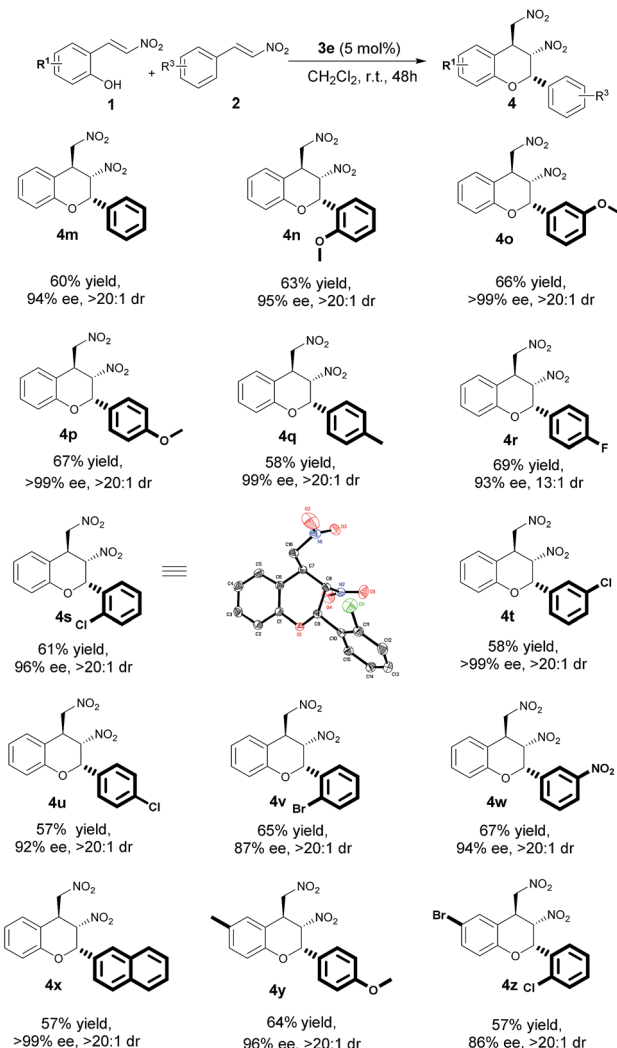
Consequently, the best conditions were found with 5 mol% of catalyst **3e** loading in CH₂Cl₂ at room temperature.

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 1 Scope of 2-alkyl chromans.

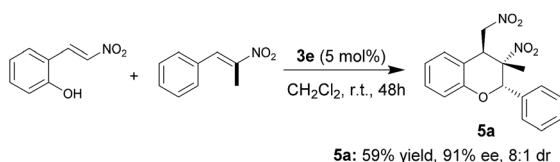




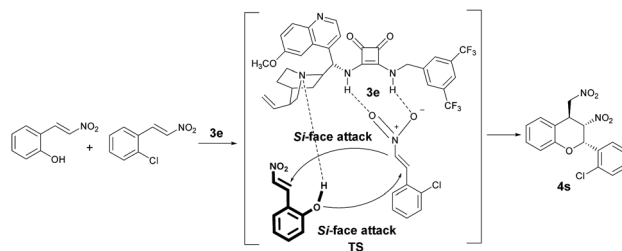
Scheme 2 Scope of 2-aryl chromans.

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-nitro-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 3 Further investigation of the substrate scope.



Scheme 4 Proposed transition state for this reaction.

and moderate yields (57–69%). In general, nitroolefins with OMe and Me as substituent R^3 groups yielded products in excellent 95–99% ee (Scheme 2, **4n–4q**, **4y**), which were superior to nitroolefins incorporating electron-withdrawing groups ($\text{R}^3 = \text{F}$, Cl , Br , NO_2). However, product **4t** was an interesting special case with 99% ee. The absolute configuration of product **4s** was determined to be (2*S*, 3*S*, 4*S*) 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-nitroolefin was activated well through the hydrogen-bonding interaction between the nitro group of 2-chloro-nitroolefin 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-nitroolefin from the Si face under the control of the catalyst **3e**. Subsequently, the α -carbon of activated 2-chloro-nitroolefin attacked the β -carbon of **1a** from the Si face to yield the major stereoisomer of chiral chroman **4s** with the configuration of (2*S*, 3*S*, 4*S*).

In conclusion, the first enantioselective, organocatalytic oxa-Michael-nitro-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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- 12 CCDC 1031452 contains the supplementary crystallographic data for the compound **4s**.[†]

