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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 reactions[3] catalyzed by aminocatalysts,[4] thiourea organocatalysts[5] 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-CF_3-nitroolefins to yield CF_3-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]

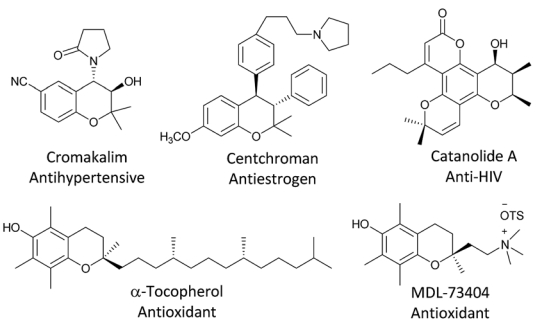

Fig. 1 Selected biologically active compounds.

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

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

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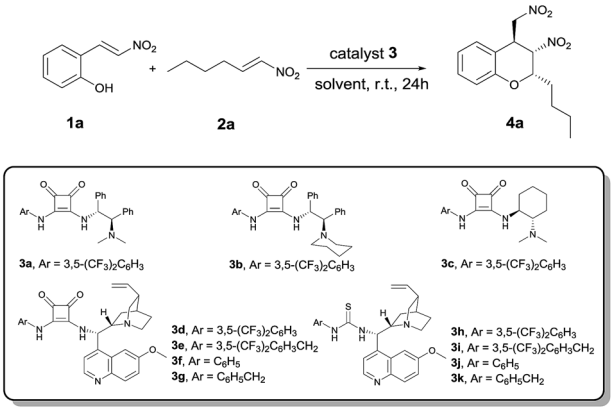
Table 1 Screening of reaction conditions[a]

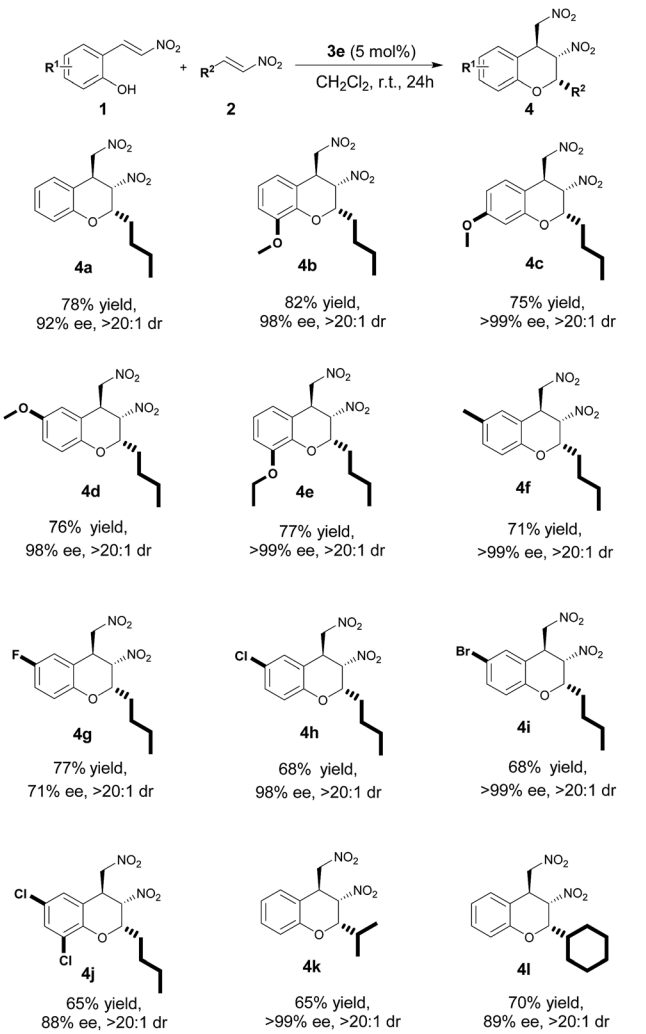


Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)	dr[c]
1	**3a**	CH_2Cl_2	47	5	>20 : 1
2	**3b**	CH_2Cl_2	Trace	N.D.[d]	N.D.
3	**3c**	CH_2Cl_2	42	−39	>20 : 1
4	**3d**	CH_2Cl_2	73	80	>20 : 1
5	**3e**	$\mathbf{CH_2Cl_2}$	**78**	**92**	**>20 : 1**
6	**3f**	CH_2Cl_2	65	43	>20 : 1
7	**3g**	CH_2Cl_2	71	85	>20 : 1
8	**3h**	CH_2Cl_2	69	75	>20 : 1
9	**3i**	CH_2Cl_2	75	79	>20 : 1
10	**3j**	CH_2Cl_2	67	58	>20 : 1
11	**3k**	CH_2Cl_2	68	69	>20 : 1
12	**3e**	$CHCl_3$	65	93	>20 : 1
13	**3e**	$ClCH_2CH_2Cl$	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_2O	Trace	N.D.	N.D.
18	**3e**	CH_3CN	61	27	>20 : 1
19	**3e**	Toluene	77	81	8 : 1
20	**3e**	Cyclohexane	49	38	10 : 1

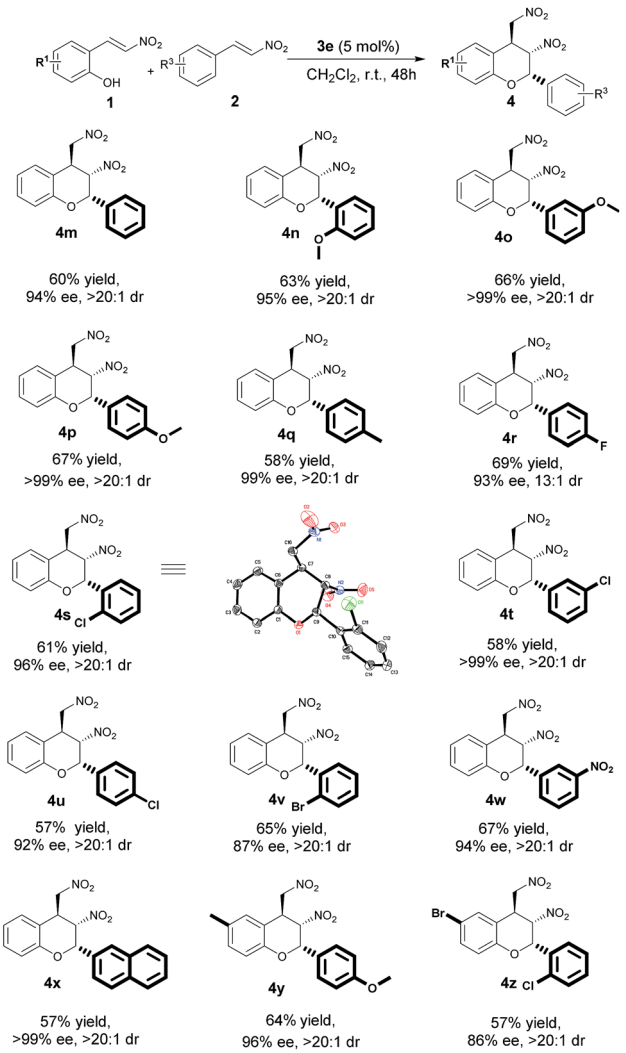
[a] All the reactions were conducted with **1a** (0.2 mmol), **2a** (0.24 mmol), and solvent (2 mL) in the presence of 5 mol% organocatalyst **3** at room temperature with vigorous stirring for 24 h. [b] Isolated yield of **4a**. [c] Determined by chiral HPLC using an OJ–H column. [d] N.D. = Not determined.

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 CH_2Cl_2 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 (R^1 = OMe, OEt, Me) or electron-withdrawing groups (R^1 = 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 (R^2 = i-Pr) and cycloaliphatic group (R^2 = cyclohexyl) were further explored,



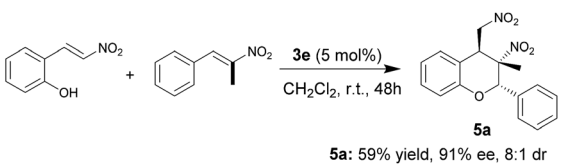
Scheme 1 Scope of 2-alkyl chromans.



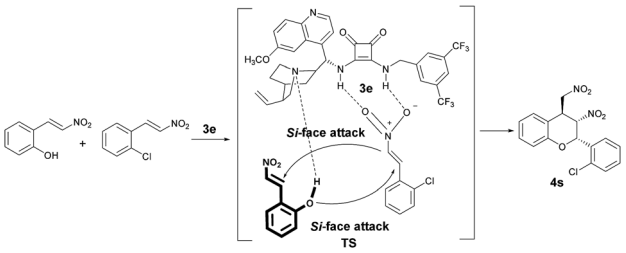
Scheme 2 Scope of 2-aryl chromans.

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 (R^3 = 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**.‡