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Exploring the Reactivity of Nitro-Activated 1,3-Enynes in an Organocatalytic One-Pot, Three-Component Coupling Reaction: A Tandem Catalytic Approach to a Novel 3-Nitrochroman Scaffold

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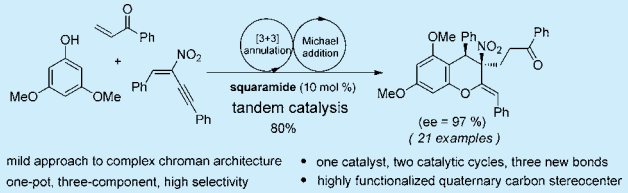
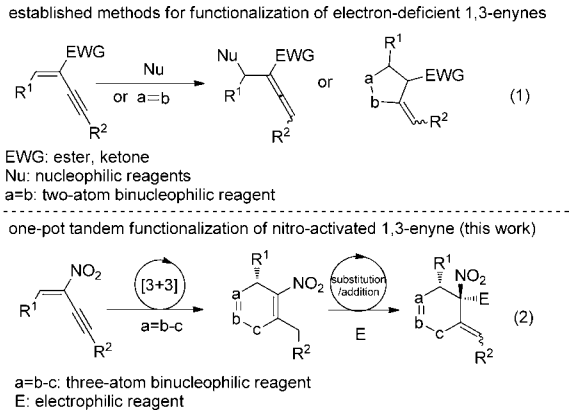
Supporting Information

ABSTRACT: A tandem catalytic strategy enabling one-pot, three-component couplings of electron-rich phenols, 2-nitro 1,3-enynes, and vinyl ketones was achieved. This chemistry combined mechanistically distinct [3 + 3]-annulation and nitro-Michael addition using a single squaramide catalyst, leading to the construction of novel chiral quaternary 3-nitrochromane architecture with high chemo-, regio-, and stereoselectivity.



The development of efficient and selective protocols enabling rapid generation of value-added complex molecules from readily accessible starting materials remains a major focus in modern organic synthesis.[1] With electron-deficient conjugated 1,3-enynes,[2] novel and elegant transformations triggered by nucleophilic conjugate addition have emerged to produce highly functionalized allenes and heterocyclic compounds over the past decade (Scheme 1, eq 1).[3] In this context, asymmetric catalytic processes of ester- or ketone-activated 1,3-enynes, which are of particular significance, have also been achieved with organocatalysis[4] and transition-metal-complex catalysis.[5] However, the application of nitro-activated conjugated 1,3-enyne in asymmetric catalysis has been underdeveloped, even though nitroolefin-involved transformation was one of the most fruitful areas since the renaissance of organocatalysis.[6,7] On the other hand, the tandem catalysis, whereby one or more catalysts promote two or more distinct chemical transformations in a single reactor, has received growing attention due to its wide success in the efficient assembly of structurally and stereochemically diverse molecules.[8] Considering the high propensity of the nitro group toward catalyst activation with hydrogen-bond donor organocatalysts, we envisioned that a one-pot, three-component tandem catalytic process would be feasible to enable the sequential functionalization of nitro-activated 1,3-enynes with suitable nucleophiles and electrophiles using a bifunctional hydrogen donor organocatalyst: (1) a double addition of three-atom binucleophiles to nitro-activated 1,3-enynes would lead to six-membered cyclic nitroolefins,[7] and (2) the resulting nitroolefin would further undergo nucleophilic addition or substitution with appropriate electrophiles to form a quaternary carbon-containing six-membered ring system (Scheme 1, eq 2).[9] Furthermore, when chiral bifunctional catalysts were used, this tandem reaction would provide a powerful tool for preparing chiral complex cyclic architecture with a quaternary carbon stereocenter from simple acyclic precursors.

Scheme 1. Nucleophilic Addition-Triggered Transformations of Electron-Deficient Conjugated 1,3-Enynes



Flavanoid and chromanoid scaffolds are prevalent in natural products and biologically active molecules[10] (Scheme 2, a). Despite various synthetic methods established,[11] the asymmetric synthesis of this privileged architecture via a one-pot multicomponent reaction in a tandem catalytic fashion, which will be straightforward and highly efficient, is still highly desirable. Based on the asymmetric synthesis of functionalized chromans by means of organocatalytic cascade reactions developed in our laboratory,[12] herein we report our discovery that this intriguing scaffold could be achieved by a bifunctional squaramide-promoted[13] one-pot, three-component coupling reaction of electron-rich phenols, nitro-activated 1,3-enynes, and vinyl ketones.[14] The desired reaction proceeded via a

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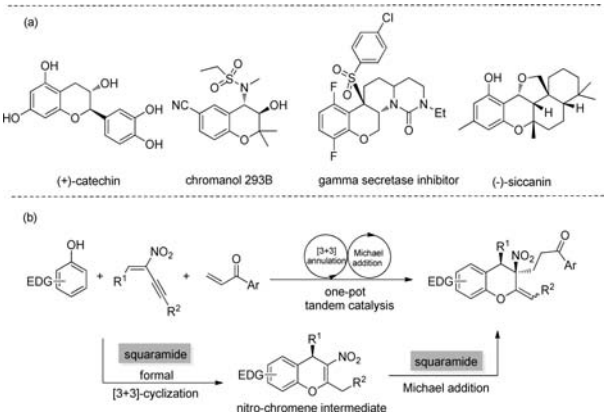
Scheme 2. (a) Representative Examples of Natural Products and Bioactive Molecules Containing Chroman Scaffold; (b) One-Pot Three-Component Coupling Reaction toward Complex Chroman Scaffold Based on Tandem Catalysis



Friedel–Crafts alkylation[15]/annulation and a subsequent nitro-Michael addition via a nitro-chromene intermediate, and the products could be produced directly from the starting materials in satisfactory yield with high enantioselectivity (Scheme 2, b). This chemistry provides an efficient alternative way toward novel complex chroman synthesis and complements the current knowledge of α-branched nitroolefin chemistry.

The study was initiated by testing the model reaction of 3,5-dimethoxyphenol (**1a**) and 2-nitro-1,3-enyne (**2a**) in a 1.2:1 ratio in the presence of bifunctional tertiary amine–hydrogen donor catalysts (Figure 1). With thiourea **I** as the catalyst and

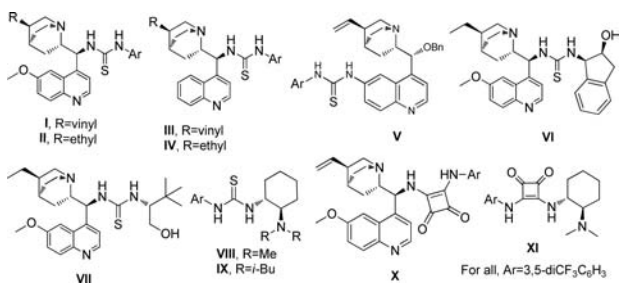
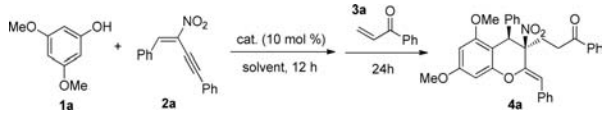


Figure 1. Catalysts investigated.

DCE as the solvent, it was found that after the consumption of **2a**, the addition of vinyl ketone **3a** to the reaction mixture under reflux gave rise to the desired quaternary 3-nitro-chromane **4a** in moderate yield with excellent stereoselectivity (Table 1, entry 1). A variety of tertiary amine–hydrogen bond donor bifunctional organocatalysts were then screened, and it was found that bifunctional squaramide **X** provided the best results (Table 1, entries 1–11). Further solvent screening revealed that CH_2Cl_2 was the solvent of choice, giving satisfactory results in terms of yield and selectivity (Table 1, entries 12–16). Adjusting the amount of vinyl ketone in hopes of improving the yield revealed that 2.0 equiv of **3a** would give better results (Table 1, entry 17–20). However, prolonging the reaction time of the nitro-Michel addition had an unfavorable effect (Table 1, entry 21).

Under the optimized reaction conditions, the one-pot, three-component tandem reactions of a variety of electron-rich phenols, 2-nitro 1,3-enynes, and vinyl ketones with different electronic and steric properties were investigated, and the

Table 1. Optimization of the Reaction Conditions for One-Pot, Three-Component Cascade Reactions[a]



entry	catalyst	solvent	dr[b]	ee[c] (%)	yield[d] (%)
1	**I**	DCE	>25:1	19	30
2	**II**	DCE	>25:1	15	32
3	**III**	DCE	>25:1	11	25
4	**IV**	DCE	>25:1	17	27
5	**V**	DCE			trace
6	**VI**	DCE			trace
7	**VII**	DCE			trace
8	**VIII**	DCE	>25:1	−37	26
9	**IX**	DCE			trace
10	**X**	DCE	>25:1	93	51
11	**XI**	DCE	>25:1	−85	20
12	**X**	THF	>25:1	78	22
13	**X**	CH_3CN	>25:1	87	16
14	**X**	CH_2Cl_2	>25:1	93	66
15	**X**	EA	>25:1	85	32
16	**X**	toluene			trace
17[e]	**X**	CH_2Cl_2	>25:1	97	74
18[f]	**X**	CH_2Cl_2	>25:1	97	80
19[g]	**X**	CH_2Cl_2	>25:1	97	79
20[h]	**X**	CH_2Cl_2	>25:1	97	80
21[i]	**X**	CH_2Cl_2	>25:1	88	70

[a]Unless otherwise noted, the reaction was carried out for the indicated time with substituted phenol **1** (0.12 mmol), 2-nitro-1,3-enyne **2** (0.1 mmol), Michael acceptor **3a** (0.1 mmol), and bifunctional catalyst (0.01 mmol) in dry CH_2Cl_2 (0.5 mL). For detailed experimental procedures, see the SI. [b]Determined by ^{1}H NMR analysis of the crude product. [c]Determined by chiral HPLC analysis. [d]Isolated yield. [e]1.5 equiv of **3a** was added. [f]2.0 equiv of **3a** was added. [g]3.0 equiv of **3a** was added. [h]4.0 equiv of **3a** was added. [i]2.0 equiv of **3a** was added, and the second step was for 36 h.

results are outlined in Table 2. In general, the reaction proceeded under mild conditions to give rise to the desired products, and the electronic nature and the position of the substituents of the reactants had no obvious influence on the enantioinduction yet a pronounced effect on the yield (Table 2, entries 1–18). Notably, satisfactory results with respect to the yield and the enantioselectivity were achieved with sterically demanding substrates (Table 2, entries 5 and 12). In addition, satisfactory results were also obtained with the 2-nitro 1,3-enyne with multiple substituted substrates (Table 2, entry 6). For the electron-rich phenols, in addition to **1a**, the reactivity of **1b–e** was also investigated, and all of them delivered the corresponding substituted chromans in high enantioselectivities (Table 2, entries 15–18). With regard to vinyl ketones **3**, it was found that methyl-substituted (Table 2, entry 19) and halogen-incorporated vinyl ketones (Table 2, entries 20 and 21) are also competent substrates, delivering the substituted 3-nitrochromans with moderate to high yields and excellent selectivities.

To further demonstrate the practicality of the current chemistry, the one-pot, three-component reaction with all of the starting materials **1–3** added simultaneously was also tested, and the product **4** was obtained with comparable selectivity, albeit with decreased reactivity (Scheme 3, eq 1). Furthermore, when the reaction was amplified to the gram scale, both of the ee and yield of the product were maintained,

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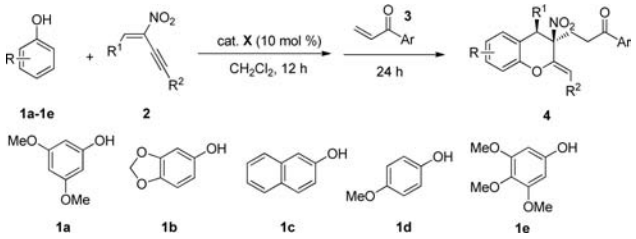
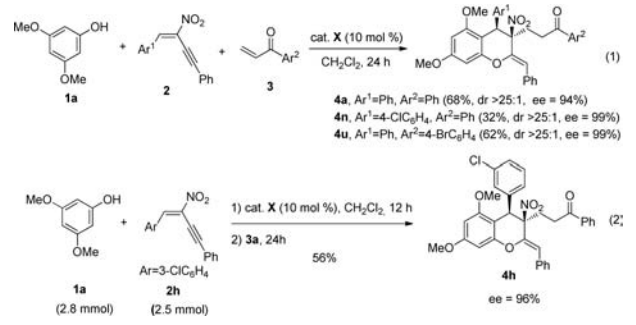
Table 2. Substrate Scope of One-Pot, Three-Component Reaction[a]



entry	1	$R^1/R^2/Ar$	dr[b]	ee[c] (%)	4, yield[d] (%)
1	**1a**	Ph/Ph/Ph	>25:1	97	**4a**, 80
2	**1a**	2-MeC_6H_4/Ph/Ph	>25:1	95	**4b**, 36
3	**1a**	3-MeC_6H_4/Ph/Ph	>25:1	98	**4c**, 46
4	**1a**	4-MeC_6H_4/Ph	>25:1	97	**4d**, 90
5	**1a**	4-*t*BuC_6H_4/Ph/Ph	>25:1	98	**4e**, 60
6	**1a**	3,4-diMeC_6H_3/Ph/Ph	>25:1	97	**4f**, 64
7	**1a**	2-ClC_6H_4/Ph/Ph	>25:1	97	**4g**, 83
8	**1a**	3-ClC_6H_4/Ph/Ph	>25:1	94	**4h**, 64
9	**1a**	4-ClC_6H_4/Ph/Ph	>25:1	97	**4i**, 75
10	**1a**	4-BrC_6H_4/Ph/Ph	>25:1	96	**4j**, 87
11	**1a**	4-FC_6H_4/Ph/Ph	>25:1	97	**4k**, 59
12	**1a**	2-naphthyl/Ph/Ph	>25:1	96	**4l**, 68
13	**1a**	Ph/4-MeC_6H_4/Ph	>25:1	99	**4m**, 28
14	**1a**	Ph/4-ClC_6H_4/Ph	>25:1	99	**4n**, 78
15	**1b**	Ph/Ph/Ph	>25:1	99	**4o**, 78
16	**1c**	Ph/Ph/Ph	>25:1	95	**4p**, 27
17	**1d**	Ph/Ph/Ph	>25:1	97	**4q**, 20
18	**1e**	Ph/Ph/Ph	>25:1	99	**4r**, 53
19	**1a**	Ph/Ph/4-MeC_6H_4	10:1	97	**4s**, 52
20	**1a**	Ph/Ph/4-ClC_6H_4	>25:1	97	**4t**, 74
21	**1a**	Ph/Ph/4-BrC_6H_4	>25:1	99	**4u**, 78

[a]Unless otherwise noted, the reaction was carried out for the indicated time with substituted phenol **1** (0.12 mmol), 2-nitro-1,3-enyne **2** (0.1 mmol), Michael acceptor **3** (0.2 mmol), and catalyst **X** (0.01 mmol) in dry CH_2Cl_2 (0.5 mL). For detailed experimental procedures, see the SI. [b]Determined by ^1H NMR analysis of the crude product. [c]Determined by chiral HPLC analysis. [d]Isolated yield.

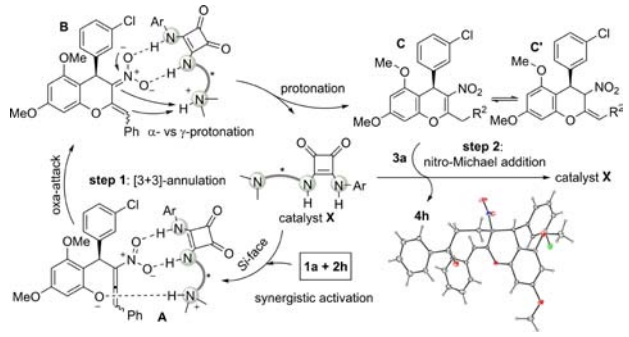
Scheme 3. One-Pot Reaction and Gram-Scale Synthesis



further demonstrating the synthetic value of this reaction (Scheme 3, eq 2).

On the basis of our experimental results and previous reports, the reaction pathway of the current one-pot tandem reaction was proposed. As depicted in Scheme 4, first, the phenol **1a** and 2-nitro 1,3-enyne **2a** are synergistically activated by the bifunctional squaramide **X** to form the reactive nitro-activated allene intermediate **A**,[16] which then rapidly undergoes annulation to form allylic nitronate **B**. This species could be trapped by protonated catalyst producing nitro-chromene **C**

Scheme 4. Proposed Reaction Pathway



and its exocyclic isomer **C′** to finish catalytic cycle 1.[17] Subsequent nitro-Michael addition of **C** and **C′** to vinyl ketone **3a** selectively gave the quaternary product **4h** and ultimately released the catalyst to terminate cycle 2. Since the reaction also proceeded with the three reactants added in a true one-pot fashion, the direct trapping of intermediate **B** by **3a** through a classical cascade mode cannot be ruled out at the current stage. The absolute configuration of the product was assigned by X-ray crystallographic analysis.[18]

In summary, we have developed a one-pot, three-component cascade reaction through the efficient combination of the bifunctional squaramide-catalyzed [3 + 3]-annulation and nitro-Michael addition. This tandem catalysis strategy provides a straightforward access to the intriguing 3-nitrochroman architecture with a highly functionalized quaternary carbon stereocenter directly from electron-rich phenols, nitro-activated 1,3-enynes, and vinyl ketones with elegant chemo-, regio-, and stereocontrol. Notably, the cascade nucleophilic and electrophilic functionalization of nitro-activated 1,3-enynes was readily achieved through sequential trappings of the in situ generated nitro-activated allene and the vinylogous nitronate species, complementing and extending our current knowledge of the α-branched nitroolefin and electro-deficient conjugated 1,3-enyne chemistry. The results presented here are expected to have a potential impact on the novel reaction design and the development of novel organocatalytic one-pot multicomponent reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03073.

X-ray crystal structure data for compound **4h** (CIF)
Additional optimization of the reaction parameters, experimental procedures, and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(18) CCDC 1481885 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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