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Phosphine Sequentially Catalyzed Domino 1,6-Addition/Annulation: Access to Functionalized Chromans and Tetrahydroquinolines with an Ethynyl-Substituted All-Carbon Quaternary Center

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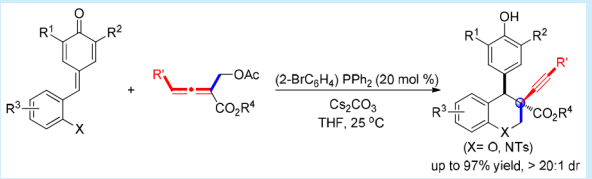
Supporting Information

ABSTRACT: A novel phosphine sequentially catalyzed domino 1, 6-addition/annulation process has been developed using *p*-quinone methides (*p*-QMs) and α-substituted allenoates which generates a series of chroman and tetrahydroquinoline derivatives containing an ethynyl-substituted all-carbon quaternary center with up to 97% yield and 20:1 dr. value. In this reaction, allenoates act as C2 synthons.



Chroman and tetrahydroquinoline skeletons exist in a number of natural products and pharmaceuticals, which possess diverse biological properties (Figure 1).[1] Meanwhile,

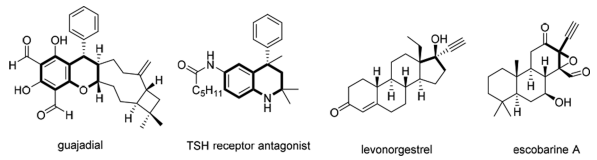
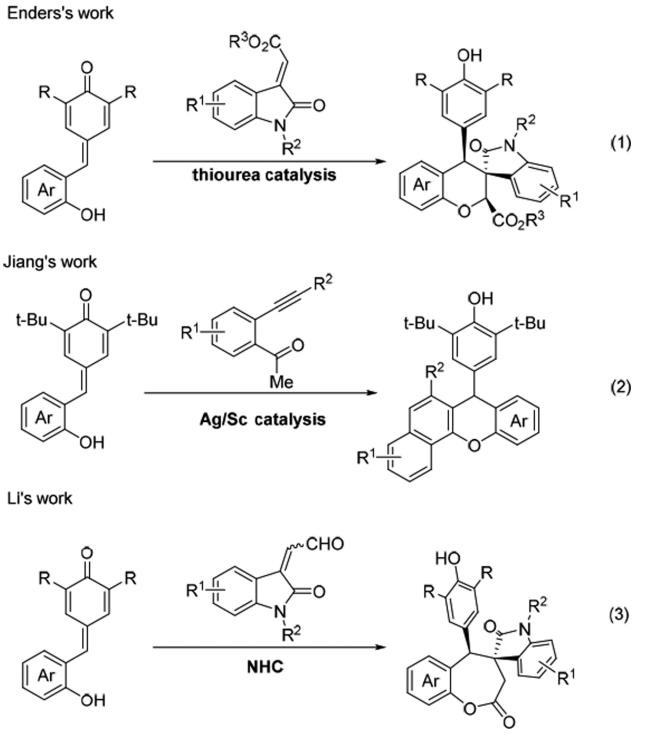


Figure 1. Natural products and bioactive molecules featuring chroman/tetrahydroquinoline scaffolds and ethynyl-substituted all-carbon quaternary centers.

ethynyl-substituted all-carbon quaternary center represent an important structural motif featured in bioactive molecules (Figure 1).[2] Furthermore, acetylene can be easily converted into many other functional groups in organic chemistry and also has broad applications in click chemistry.[3] It is evident that the development of efficient strategies for the construction of alkynyl-containing motifs is highly desirable. There are some efficient methods to construct all-carbon α-alkynyl quaternary center such as strong base-promoted direct alkynylation,[4] phase-transfer-catalyzed acetylenic substitution,[5] decarboxylative α-alkynylation,[6] radical−radical coupling,[7] and alkynylation with ethynyl benziodoxolone (EBX) reagents.[8] Despite these achievements, most of those methods require a large number of additives and costly catalysts, and those methods access the new alkynyl quaternary carbon based on an existing alkynyl substrate. Therefore, the development of a new and versatile strategy for the in situ generation of ethynyl-substituted quaternary carbon center is of great value.

Recently, *p*-quinone methides (*p*-QMs) have been widely employed as effective Michael acceptor for 1,6-addition reactions with a wide range of nucleophiles.[9] In 2016, Enders converted *p*-QMs into donor−Michael acceptor synthons by installing a hydroxyl group and achieved an asymmetric organocatalytic domino oxa-Michael/1,6-addition reaction to construct functionalized chromans featuring an spiro-oxindole scaffold (Scheme 1, eq 1).[10] In 2017, Jiang described the

Scheme 1. Examples of Intermolecular Catalyzed Cyclization Based on *p*-QM Derivatives



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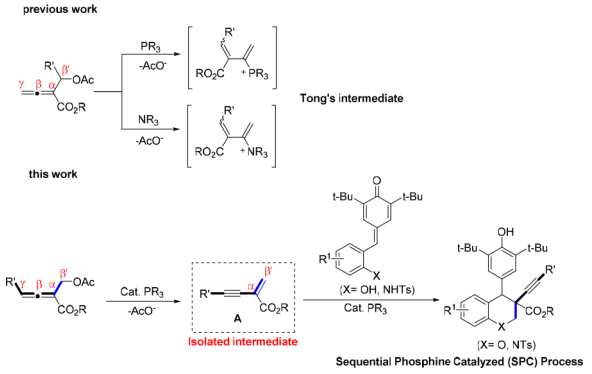
$AgTFA/Sc(OTf)_3$ co-catalyzed bicyclization processes of β-alkynyl ketones and *p*-QMs for the synthesis of tetracyclic benzo[*c*]xanthenes (Scheme 1, eq 2).[11] Next, Fan reported that chiral amine−phosphines catalyzed the intramolecular vinylogous Rauhut−Currier reaction of *p*-QMs, delivering coumarin and quinolinone derivatives.[12] Then Shi realized the construction of chromene and xanthene scaffolds using *p*-QMs and ynones or benzyne.[13] Very recently, Li and Enders independently discovered an NHC-catalyzed [4 + 3] annulation of enals with *o*-quinone methides for the synthesis of spirocyclic oxindole-ε-lactones (Scheme 1, eq 3).[14] We herein report the first phosphine-catalyzed intermolecular annulation of *p*-QMs, which provides a new family of chroman and tetrahydroquinoline derivatives bearing an alkynyl-substituted all-carbon quaternary center.

Since the first example of phosphine-catalyzed [3 + 2] cycloaddition reported by Lu in 1995,[15] a wide variety of nucleophilic phosphine-catalyzed annulation reactions of allenoates has emerged as a powerful method for constructing synthetically valuable carbo- and heterocycles.[16,17] Among them, the Tong group has realized several Lewis base catalyzed annulations of β'-acetoxy allenoates via introduction an acetate group at the β'-position of 2,3-butadienoate.[17e,18] In these cases, β'-acetoxy allenoate can be converted into a 2-phosphonium diene or 2-aminium diene intermediate via an addition−elimination process under phosphine catalysis or amine catalysis (Scheme 2), allowing for the achievement of

Scheme 2. Novel Reaction Mode of Allenoates

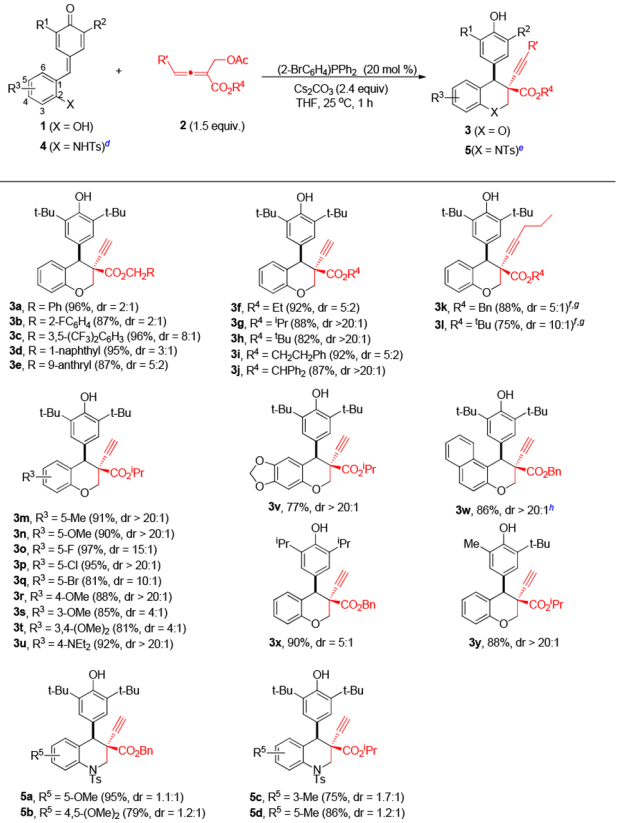


biselectrophilic reactivity of allenoates. Here, we report our studies on the development of a novel sequential phosphine catalyzed process of β'-acetoxy allenoates with *p*-QMs, In this manner, enyne intermediate **A** is first formed in situ under the phosphine catalyst, and then phosphine catalysis can promote 1,6-addition/annulation of *p*-QMs with intermediate **A** to construct chroman and tetrahydroquinoline skeletons bearing an all-carbon α-alkynyl quaternary center (Scheme 2). It is the first time that α-substituted allenoates act as C2 synthons and the α- and β'-carbon of α-substituted allenoates participate in the [4 + 2] cycloaddition.

We first tested the feasibility of our proposed [4 + 2] annulation process (see Table S1). Toward this end, *p*-QMs **1a** and β'-acetoxy allenoate **2a** were treated with PPh_3 as the catalyst in the presence of 1.2 equiv of Na_2CO_3 at 25 °C, providing initial disappointing results. Significantly, when the amount of Na_2CO_3 was increased to 2.4 equiv, the product **3a** was obtained in 41% yield along with 2:1 dr within 1 h. To further improve the yield, other bases such as K_2CO_3, Cs_2CO_3, K_3PO_4, and EtONa were investigated, among which Cs_2CO_3 was found to be the most efficient, with the yield of **3a** being improved to 75%. Subsequent screening of phosphine catalysts showed that as the nucleophilicity of the phosphine catalyst increases the yield decreases gradually. Next, other catalysts with electron-withdrawing and -donating groups on the aromatic ring were tested. To our great delight, **3a** could be isolated with 96% yield when $(2\text{-}BrC_6H_4)PPh_2$ was used as catalyst. Finally, the screening of solvents indicated that THF was the optimal choice. Based on these results, the best reaction condition was using $(2\text{-}BrC_6H_4)PPh_2$ (20 mol %) as catalyst, Cs_2CO_3 (2.4 equiv) as base, and carrying out the reaction at 25 °C in THF for 1 hour.

With the optimized reaction conditions in hand, we set out to explore the scope of this [4 + 2] annulation (Scheme 3).

Scheme 3. Substrate Scope for Synthesis of Products 3[a−c]



[a]The reactions were carried out with **1** (0.1 mmol), **2** (0.15 mmol), $(2\text{-}BrC_6H_4)PPh_2$ (20 mol %), and Cs_2CO_3 (0.24 mmol) in 1.0 mL of THF at 25 °C for 1 h. [b]Total isolated yield of two diastereomers. [c]The dr values were determined by ^1H NMR analysis. [d]1.2 equiv of Cs_2CO_3 was used. [e]The two diastereomers can be separated by column chromatography. [f]4.8 equiv of Cs_2CO_3 was used. [g]The reaction time was 24 h. [h]The reaction time was 4 h.

First, different ester groups on allenoates were investigated. Various aromatic ring at the ester group of allenoates **2** including benzyl, *o*-fluorobenzyl, and 3,5-bis-trifluoromethyl-benzyl and heteroaryls such as 1-naphthyl and 9-anthryl were found to be well tolerated, and the desired products **3a−e** were isolated in high to excellent yields with moderate dr values. Furthermore, starting allenes containing an alkyl substituent were also suitable; the alkyl groups can be linear, branched, or aryl bearing, and the corresponding **3f−j** were obtained in high yields. It is noteworthy that the allenoates with the more

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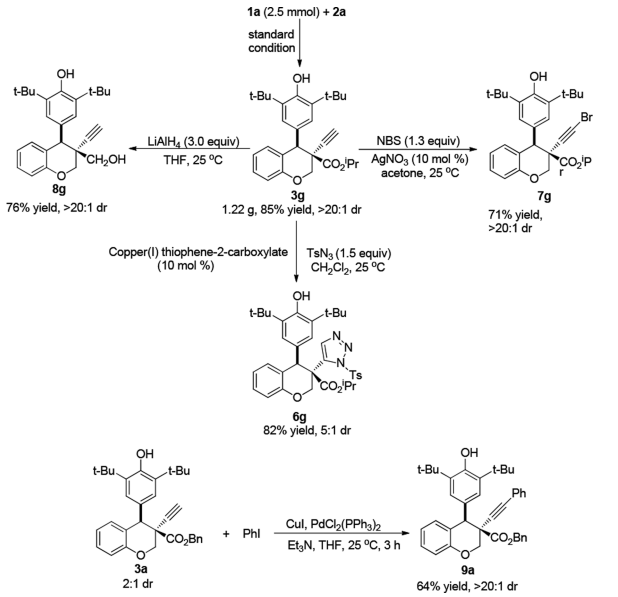
hindered isopropyl and *tert*-butyl generated the corresponding products **3g** and **3h** as a single diastereomer, respectively, and did not have a significant influence on the outcomes. Importantly, this domino process was also suitable for the directly synthesis of internal alkynes by using γ-substituted allenes as the reaction substrates without loss of reactivity (**3k** and **3l**). In general, both internal and terminal alkynes are easily accessible through this strategy.

Next, a series of variations to the *p*-QMs were tested. Various substituents including electron-rich (Me, OMe, NEt_2) groups and electron-deficient (F, Cl and Br) groups in the *para*, *meta*, and *ortho* position of the aromatic rings of substrates **1** were well tolerated, furnishing the corresponding **3m**−**u** in high yields (81−97%). However, when substituents were on the 3-position of aromatic rings, the dr values decreased obviously (**3s** and **3t**). Further investigation showed that *p*-QMs **1** bearing a piperonyl or 1-naphthyl group were also efficient for the transformation (**3v** and **3w**). Changing *tert*-butyl group to an isopropyl or methyl *tert*-butyl group did not influence the outcome of this reaction (**3x** and **3y**). To further broaden the scope of the reaction, *p*-QMs amides **4** were also subjected to the reaction. Using 1.2 equiv of Cs_2CO_3, **5a**−**d** were obtained in good yields and moderate dr values. The structures of **3w** and **5aa** were unambiguously assigned by single-crystal X-ray analysis (see the Supporting Information).[19,20]

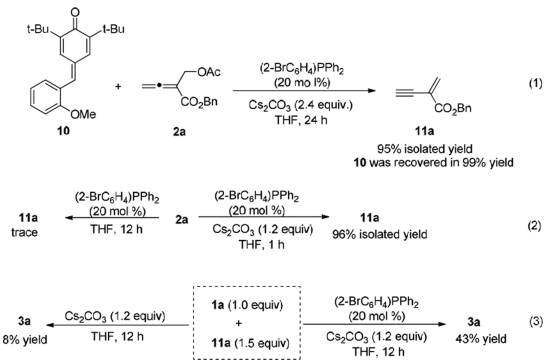
To demonstrate the practicality of the terminal alkyne-substituted chroman derivatives, a gram-scale synthesis of **3g** and some transformations were then conducted. Under the optimized reaction conditions, *p*-QMs **1a** (0.775 g, 2.5 mmol) and allenoate **2g** (0.923 g, 3.0 mmol) reacted smoothly, giving 1.22 g (85% yield) of the product **3g** with >20:1 dr (Scheme 4). Derivatizations on the terminal alkyne moeity of **3g** were conducted by a click reaction with tosyl azide and bromination with NBS catalyzed by $AgNO_3$, furnishing the corresponding products **6g** and **7g**, respectively. Alternatively, the ester group could be easily reduced to produce the corresponding **8g** in 76% yield. Furthermore, the product **9a** can be obtained in good yield via Sonogashira coupling of **3a** and phenyl iodide and the diastereoselectivity can be improved in this process, giving a single diastereomer (Scheme 4). The preliminary asymmetric version of this new domino reaction was carried out by using several chiral phosphine catalysts; unfortunately, poor enantioselectivity was obtained (see Table S2).

To explore the reaction mechanism, the following control experiments were carried out. First, using a methyl-protected *p*-QM derivative **10** did not realize the subsequent cyclization process, leading to alkyne product **11a** (Scheme 5, eq 1).

Scheme 4. Gram-Scale Synthesis and Further Transformation of the Product



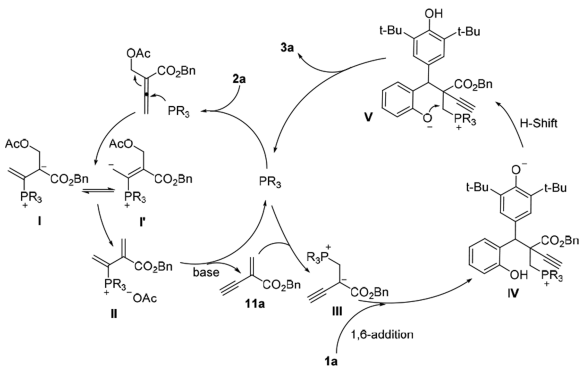
Scheme 5. Control Experiments



Furthermore, **11a** could be isolated in 96% yield when (2-BrC_6H_4)PPh_2 (20 mol %) and Cs_2CO_3 (1.2 equiv) were added to **2a** in THF, but no product could be obtained under the catalysis of phosphine (Scheme 5, eq 2). It implies that base plays a crucial role in the first catalytic process. We then put **11a** instead of **2a** into the reaction system. We found that when only the base was present, the final product could only be obtained in 8% yield. In the presence of a phosphine catalyst in the system, the target product **3a** was obtained with 43% yield (Scheme 5, eq 3), indicating that the entire annulation reaction is achieved by a sequential phosphine-catalyzed process, while **11a** is a key intermediate for the entire reaction.

On the basis of these results, a plausible mechanism involving a sequential catalytic process was proposed (Scheme 6). The reaction is initiated by the nucleophilic attack of the phosphine catalyst on the allenoate **2a** to form intermediates **I** and **I′**. Subsequent elimination of an acetate group gives Tong's intermediate **II**. Then **11a** was obtained by elimination of phosphine under basic conditions. Next, a recatalyzed process begins. Nucleophilic addition of phosphine to **11a**

Scheme 6. Plausible Reaction Mechanism



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generates intermediate **III**. This is followed by 1,6-conjugate addition of **1a** to **III** to form intermediate **IV**, which then undergoes a proton-transfer process to give intermediate **V**. Finally, intermediate **V** undergoes cyclization to furnish the desired chroman derivative **3a** with a terminal alkyne-substituted quaternary carbon and releases the phosphine catalyst.

In summary, we have disclosed a novel phosphine sequentially catalyzed domino [4 + 2] cycloaddition of *p*-QMs and α-substituted allenoates, affording a series of chroman and tetrahydroquinoline derivatives bearing an alkynyl-substituted quaternary carbon in high to excellent yields. It is noteworthy that this is the first time that the α-carbon and β'-carbon of α-substituted allenoates have participated in the [4 + 2] cycloaddition. Both internal and terminal alkynes could be constructed at the quaternary carbon center of products. The newly constructed terminal alkynyl group can be applied to the Sonogashira coupling and click reaction. More mechanistic details and further work on the asymmetric version of the present reaction are currently being investigated by our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03819.

Experimental details, characterization data for new compounds, copies of NMR spectra and X-ray crystal structure (PDF)

Accession Codes

CCDC 1831405−1831406 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to 100th anniversary of Nankai University and Dedicated to the 100th anniversary of the birth of Academician Ruyu Chen.

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(19) CCDC 1831405 contains the supplementary crystallographic data for **3w**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(20) Compound **5aa** is the anti-isomer of **5a**. CCDC 1831406 contains the supplementary crystallographic data for **5aa**. 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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