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Metal-Free Oxidative C(sp^3)−H Bond Functionalization of Alkanes and Conjugate Addition to Chromones

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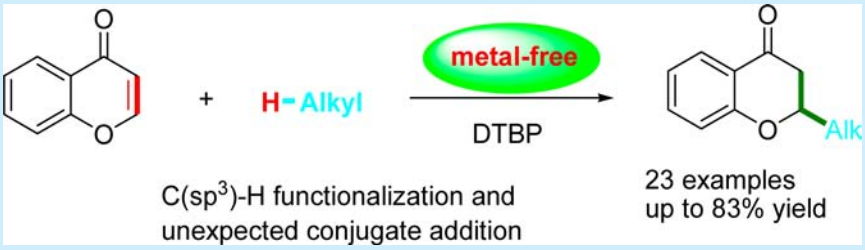
Supporting Information

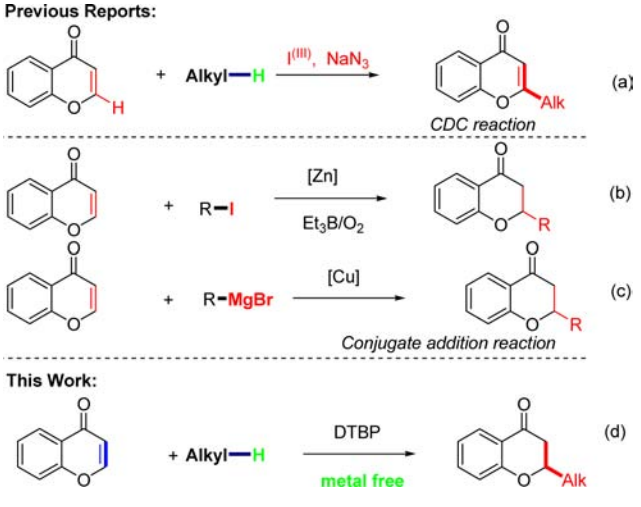


ABSTRACT: A metal-free oxidative C(sp^3)−H bond functionalization and subsequent conjugate addition reaction using di-*tert*-butyl peroxide (DTBP) as the oxidant was established, which tolerates a wide range of simple alkane substrates to react with different substituted chromones for direct preparation of 2-alkylchromanones.

Direct functionalization of C(sp^3)−H bonds, which is a great challenge due to their low reactivity and the lack of a coordination site for the metal catalyst, has been an extremely remarkable project in recent years.[1] Various methods have been reported for C(sp^3)−H bond activation adjacent to heteroatoms,[2] double bonds,[3] phenyl,[4] or electron-withdrawing groups.[5] However, selective activation of the inactive C−H bonds of simple alkanes to generate C−C bonds is a more challenging target. In the past several years, the Li group and others have developed cross-dehydrogenative-coupling (CDC) reactions forming C−C bonds by using transition metals as catalysts (such as Ru, Sc, Fe, etc.) with simple alkanes.[6] In addition, our group and others have explored transition metal catalyzed decarboxylative alkenylation of simple alkanes with arylvinyl carboxylic acids via radical addition−elimination processes.[7] Recently, the Liu group explored free-radical addition/cyclization of *N*-arylacrylamides with simple alkanes and free-radical addition/cyclization of isocyanides with simple alkanes.[8] Very recently, our group described an example of Cu-catalyzed dehydrogenation−olefination and esterification of the C(sp^3)−H bond of cycloalkanes with aromatic aldehydes in the presence of TBHP as the oxidant.[9] However, these systems were limited in the use of a transition metal as the catalyst. C(sp^3)−H bond functionalization of simple alkanes under metal-free conditions is a more challenging task and highly appreciated but scarely studied. The Li group and others have reported metal-free C(sp^3)−H bond functionalization reactions for the C(sp^2)−C(sp^3) bond formation between heteroaromatics and cycloalkanes.[10] And, our group also established a C−S cross-coupling reaction through direct C−H bond functionalization of simple alkanes with diaryl sulfides using DTBP as the oxidant without use of any metal catalyst.[11]

The chromanone skeleton is an important type of heterocycle found in a number of bioactive natural products and pharmaceutical molecules, which show a wide range of biological activities including anticancer, antitumor, antibacterial, antioxidant, and antimicrobial properties.[12] Among the derivatives of chromanone, 2-alkyl chromanone represents an extremely important type of bioactive compound.[13] However, the synthesis of chromanones bearing an aliphatic substituent at C-2 has been reported in a limited number of studies. Recently, the Antonchick group reported an elegant work on the dehydrogenative cross-coupling reaction of chromones with alkanes in the presence of hypervalent iodine (Scheme 1a).[14]

Scheme 1. Reactions for the Synthesis of 2-Alkylchromanones



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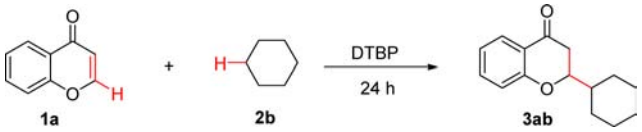
Also, two conjugate addition reactions for the catalytic synthesis of 2-alkylchromanones have been reported. In 2011, the Zimmerman group developed a $Zn(OTf)_2$-catalyzed conjugate addition of alkyl iodides to chromones for the preparation of 2-alkylchromanones via a radical process with the aid of Et_3B (Scheme 1b).[15] In 2013, the Feringa group achieved a copper catalyzed direct conjugate addition of Grignard reagents to chromones for the synthesis of 2-alkylchromanones (Scheme 1c).[16] A conjugate addition reaction generally requires the pregeneration of organometallic reagents, which lowers the synthetic efficiency and produces tremendous waste at the same time. With the recent great advances in C−H functionalization, direct sp^3 C−H functionalization of simple alkanes and subsequent conjugate addition[17] with chromones under metal-free conditions would be an ideal pathway for the synthesis of 2-alkylchromanones. Herein we report an unexpected oxidative direct C(sp^3)−H functionalization and subsequent conjugate addition reaction under metal-free conditions (Scheme 1d).

Initially, we conducted our investigation by reacting chromone **1a** (0.5 mmol) with cyclohexane **2a** (2 mL) in the presence of 2.0 equiv of DTBP at 120 °C for 24 h. The reaction proceeded and afforded the expected product of 2-cyclohexyl-chroman-4-one **3ab** in a moderate yield (51%, Table 1, entry 1). When the amount of DTBP was increased to 4.0 equiv, a substantial improvement in the yield of product **3ab** to 72% was observed (Table 1, entry 2). Further increases in the loading of the oxidant and additive did not result in any improvement (Table 1, entry 3). The reaction could not take place at all if DDQ, NaClO, $K_2S_2O_8$, BQ, or O_2 (1 atm) was employed as the oxidant (Table 1, entries 4−8). And the use of other oxidants such as H_2O_2 (30% aqueous solution), TBHP (5.5 M in decane), TBPB, BPO, or DCP did not provide better results (Table 1, entries 9−13). Almost all of the starting material **1a** remained in the reactions with these examined oxidants (entries 4−13). When the reaction was performed at 100 °C, almost no product was obtained (Table 1, entry 14). No significant effect on the yield of **3ab** was found when the reaction was conducted at 140 °C (Table 1, entry 15). When the reaction was performed under a N_2 atmosphere, it did not result in any improvement of the yield (70%, Table 1, entry 16). Notably, the addition of a metal catalyst, $Cu(OAc)_2$ (10 mol %), suppressed the transformation slightly and the yield reduced (Table 1, entry 17). In all these reactions (entries 1−17), no byprodcut of 2-cyclohexylchromen-4-one was detected.

Table 1. Optimization of Reaction Conditions[a]



1a 2b 3ab

entry	oxidant (equiv)[b]	t (°C)	yield (%)[c]
1	DTBP (2.0)	120	51
2	DTBP (4.0)	120	72
3	DTBP (6.0)	120	72
4	DDQ (4.0)	120	N.D.
5	NaClO (4.0)	120	N.D.
6	$K_2S_2O_8$ (4.0)	120	N.D.
7	BQ (4.0)	120	N.D.
8	O_2 (1 atm)	120	N.D.
9	H_2O_2[d] (4.0)	120	trace
10	TBHP (4.0)	120	trace
11	TBPB (4.0)	120	12
12	BPO (4.0)	120	22
13	DCP (4.0)	120	29
14	DTBP (4.0)	100	trace
15	DTBP (4.0)	140	73
16	DTBP (4.0)	120	70[d]
17	DTBP (4.0)	120	62[e]

[a]Catalytic conditions: **1** (0.5 mmol), cyclohexane (2 mL), oxidant, 24 h. [b]DTBP: di-*tert*-butyl peroxide. TBHP: *tert*-butyl hydroperoxide 5.5 M in decane. DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. BQ: 1,4-benzoquinone. H_2O_2: 30% aqueous solution. TBPB: *tert*-butyl peroxybenzoate. BPO: benzoyl peroxide. DCP: dicumyl peroxide. [c]Isolated yield based on **1**. [d]Under a N_2 atmosphere. [e]$Cu(OAc)_2$ (0.05 mmol) was added.

With the optimized reaction conditions in hand, a series of chromones and alkanes as the substrates were investigated (Scheme 2). First, the variation in the cycloalkanes part of the reaction was studied. The reaction was found to work well with a wide range of cycloalkanes, including cyclopentane, cyclohexane, cycloheptane, and cyclooctane. Fortunately, they work well in the system under the optimized conditions and can react with different chromones **1**, giving the corresponding products **3aa−cd** in 64−83% chemical yields. It is noteworthy that the reaction with cyclooctane showed higher efficiency than in the case with smaller cycloalkanes. After studying the scope of cycloalkanes, we turned our attention toward substituted chromones. As shown in Scheme 2, the process has a broad scope and high compatibility with functional groups, such as methyl, halo, and methoxyl functional groups. C5-, C6-, and C7-substituted chromones were well tolerated, and the reactions gave the corresponding products with moderate to good yields of 58−83% (**3aa−3gd**). The lower yields observed in the case of C5-substituted chromones were comparable to those from the C6- or C7-analogues, which is possibly due to the steric hindrance (**3eb−3gd**). In addition, 6-chloro-7-methyl-4*H*-chromen-4-one, which has two different functional groups, gave desired products in 71% yield (**3hb**). Disappointingly, the reaction did not work when chromones containing a nitro group were used as a substrate (**3ib**). Notably, highly conjugated aromatic systems, 4*H*-benzo[*h*]chromen-4-one and 1*H*-benzo[*f*]chromen-1-one, reacted smoothly with cycloalkanes to give desired products in appreciable 56−68% yields (**3jb−kd**). Interestingly, reactions of alkanes with a high boiling point also resulted in moderate yields of the products. For example, when norbornane was used, **3ae** were isolated in a yield of 64% with a ratio of C1/C2 1/1. Reaction at the tertiary sp^3 C−H position (C3) of norbornane was not observed, which is possibly due to the steric hindrance. Finally, open chain alkanes were also investigated, and the corresponding products were obtained (**3af** and **3ag**). It is noteworthy that a highly selective reaction occurred at the primary sp^3 C−H position of 2,3-dimethylbutane but cannot occur at the tertiary sp^3 C−H position of 2,3-dimethylbutane (**3af**). *n*-Hexane reacted well with chromone to form the corresponding product **3ag** as a mixture of positional isomers in the ratio C1/C2/C3 1:10:5 and a combined yield of 50%.

To understand the mechanism of this reaction, a series of experiments were carried out. Addition of the radical-trapping reagent 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) can completely inhibit the reaction, and almost no desired product was obtained; only a TEMPO−cyclohexane adduct was

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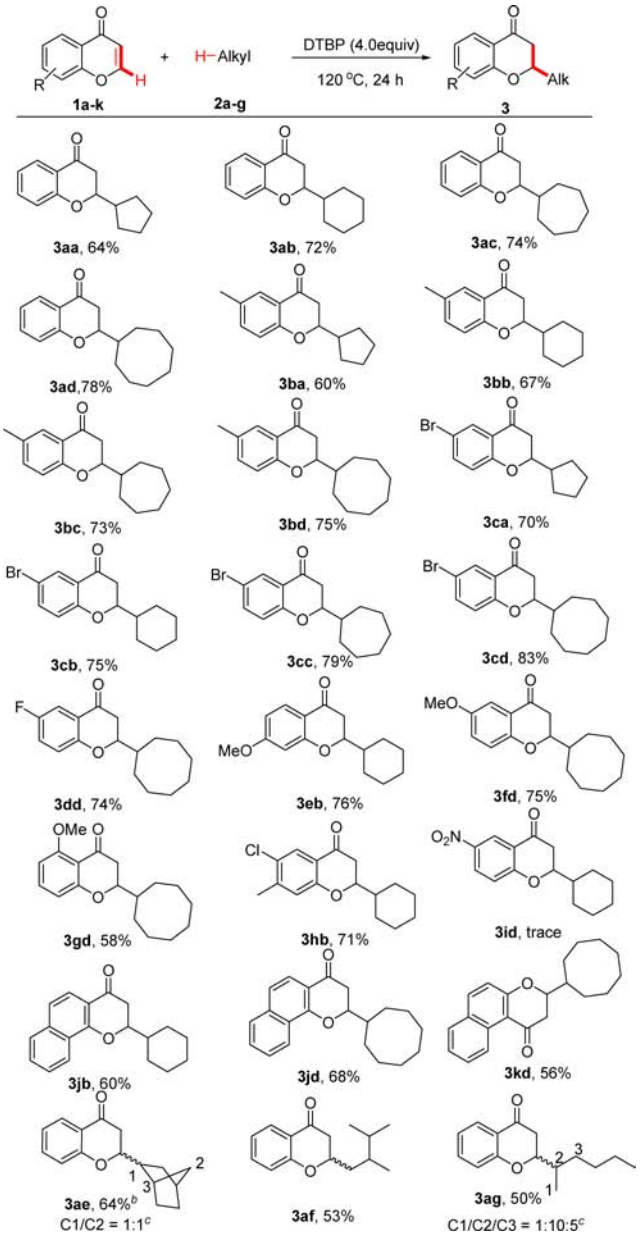
Scheme 2. Substrate Scope for the Synthesis of 2-Alkylchromanones via sp^3 C−H Functionalization[a]

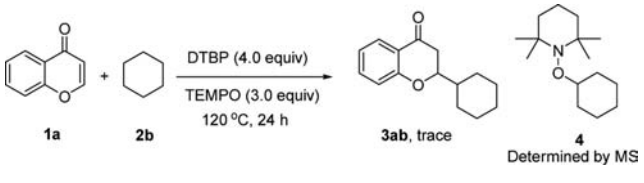


[a]Catalytic conditions: **1** (0.5 mmol), **2** (2 mL), DTBP (4.0 equiv), 120 °C, 24 h. Isolated yield based on **1**. [b] **2e** (5.0 equiv) in benzene (2.0 mL). [c] Determined by ^{1}H NMR analysis.

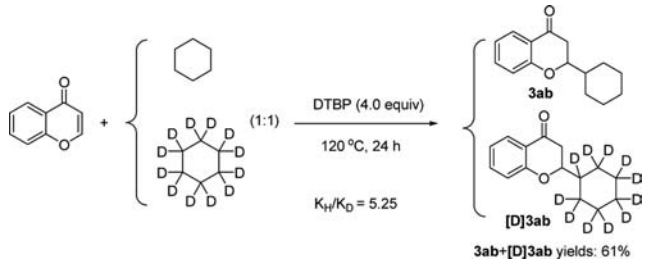
observed (Scheme 3). The results indicate that the transformation may proceed via a radical course.

In addition, an intermolecular competing kinetic isotope effect (KIE) experiment was carried out (Scheme 4). As a result, a significant KIE was observed with k_H/k_D = 5.25 (the

Scheme 3. Radical-Trapping Experiment



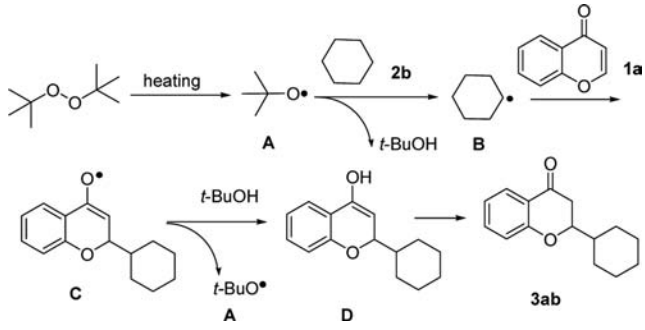
Scheme 4. KIE Studies



KIE was determined by ^{1}H NMR spectroscopy by analyzing the ratio of **3ab** and [**D**]**3ab**). This indicates that C(sp^3)−H bond cleavage may be one of the rate-determining steps of this procedure.

On the basis of the above-mentioned results and literature reports,[11,14,15] a plausible mechanism for the oxidative radical process is illustrated in Scheme 5. At the beginning, homolysis

Scheme 5. A Plausible Reaction Mechanism



of DTBP gives *tert*-butoxy radical intermediate **A** under the conditions of heating. Then, cyclohexane radical intermediate **B** is generated via reaction of intermediate **A** and cyclohexane **2b** through a C−H bond cleavage. Next, cyclohexane radical **B** adds to chromone **1a** to give intermediate radical **C**. The following step is the reaction between **C** and *t*-BuOH, affording enol form product **D** and a *tert*-butoxy radical intermediate **A**, which continues the radical cycle. Finally, enol form product **D** transformed to the final keto form product **3ab**.

In summary, we have developed an unprecedented directed oxidative sp^3 C−H functionalization and a subsequent conjugate addition reaction using DTBP as the oxidant without use of any metal catalyst. Different substituted chromones and various simple alkanes could be tolerated, affording 2-alkylchromanones in moderate to good yields. This method not only provided a simple and atom-economic route for the syntheses of 2-alkylchromanones but also represented a new strategy for selective functionalization of simple alkanes. Further investigation of this strategy focusing on selective activation of unactivated sp^3 C−H and subsequent conjugate addition by one single step, to provide a novel strategy for raising efficiency in C−H bond functionalization, is underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, full spectroscopic data for compounds **3**, and copies of ^{1}H and ^{13}C NMR spectra. This

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material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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