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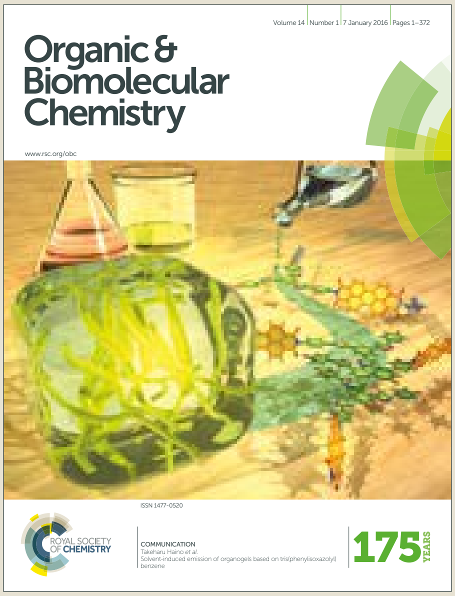

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PAPER

Copper-Promoted Direct C–H Alkoxylation of *S*,*S*-Functionalized Internal Olefins with Alcohols

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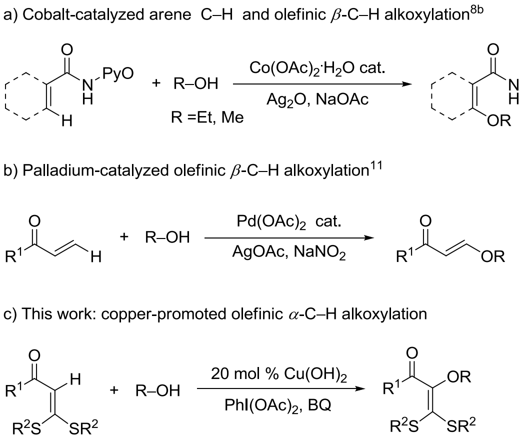
Copper-promoted direct C–H alkoxylation of *S*,*S*-functionalized internal olefins, that is, *α*-oxo ketene dithioacetals, was efficiently achieved with alcohols as the alkoxylating agents, (diacetoxyiodo)benzene ($PhI(OAc)_2$) as the oxidant, and benzoquinone (BQ) as the co-oxidant. The alkoxylated olefins were thus constructed and applied for the synthesis of alkoxylated *N*–heterocycles. Polarization of the olefinic carbon-carbon double bond by the electron-donating dialkylthio and electron-withdrawing α-oxo functionalities plays a crucial role in rendering such C–H alkoxylation reactions to undergo under mild conditions. Mechanistic studies implicate a single-electron-transfer (SET) reaction pathway involved in the overall catalytic cycle.

Introduction

Carbon-oxygen bond is one of the most important chemical bonds and it is abundant in many synthetic and natural products. Various synthetic methods have been developed to construct a C–O bond.[1] Recently, transition metal-catalyzed direct C–H functionalization has been paid more and more attention for the formation of different chemical bonds in diverse organic transformations due to the high atom economy and simplicity of the synthetic C–H activation protocols.[2] In this regard, C–H alkoxylation has aroused much interests[3] although aryl ethers can be traditionally synthesized from the reactions of aryl halides with alkali metallic alkoxides,[4] *pseudo*-halides such as aryl boronic esters[5] and hypervalent iodine derivatives[6] with alcohols, or by other methods.[7] Direct arene $C(sp^2)$–H alkoxylation has been extensively investigated with alcohols as the alkoxylating agents to access aryl alkyl ethers by means of various transition metal catalysts.[8] Plenty of examples of aliphatic $C(sp^3)$–H alkoxylation with alcohols have also been documented to prepare dialkyl ethers.[8d,9] Unfortunately, direct olefinic $C(sp^2)$–H alkoxylation with alcohols has been rarely reported although enol ethers can be used as useful synthetic building blocks in organic synthesis and enol ether motifs exist in many biologically active molecules.[10] To date, only a limited number of examples have been illustrated in cobalt-catalyzed C–H alkoxylation of olefinic carboxamides with ethanol and methanol (Scheme 1a),[8b] and palladium-catalyzed C–H alkoxylation of α,β-unsaturated carbonyls with alcohols (Scheme 1b).[11] Very recently, photocatalytic dehydrogenative cross-coupling of olefins with alcohols was reported.[12] However, in the three above-mentioned cases only the *β*-C–H bond of an *α*,*β*-unsaturated carbonyl compound or indene substrate could undergo the alkoxylation reaction with an alcohol, which suggests that olefinic *α*-C–H alkoxylation of such functionalized olefins is very challenging because the *in situ* generated alkoxy–metal intermediates in the catalytic cycle prefer to undergo reductive *β*-elimination to form the *β*-alkoxylated products and the alkanol substrates tend to be oxidized to their corresponding aldehydes or ketones under the oxidative reaction conditions.[4b,8b,13]



Scheme 1 C–H alkoxylation of olefins with alcohols.

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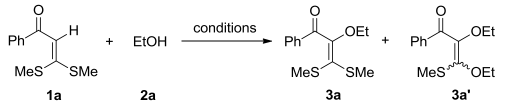
We recently became interested in the direct C–H functionalization of internal olefins.[14] In order to enhance the reactivity of an internal olefinic C–H bond, two electron–donating alkylthio moieties and one electron-withdrawing carbonyl group are introduced to the two ends of an olefinic C=C bond to construct polarized olefin substrates, that is, *α*-oxo ketene dithioacetals, which were readily prepared from various methyl ketones by the reported methods.[14a,15] On the basis of the electronic and structural features, *α*-benzoyl ketene di(methylthio)acetal (**1a**) was tentatively reacted with ethanol (**2a**) under copper catalysis. To our delight, the desired *α*-C–H alkoxylation reaction occurred to form the target alkoxylated olefin product. Herein, we report efficient copper-promoted direct C–H alkoxylation of *S*,*S*-functionalized internal olefins *α*-oxo ketene dithioacetals (Scheme 1c).

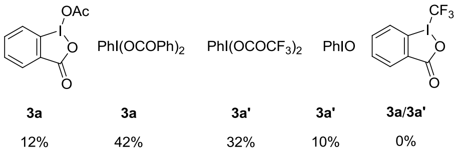
Results and discussion

Table 1 Screening of the reaction conditions[a]



Entry	PhI(OAc)$_2$ (equiv)	Additive (equiv)	Solvent	Temp (°C)	Yield[b] of **3a**
1	1.5		EtOH	25	35
2	1.5	BQ (0.2)	EtOH	25	40
3	1.5	BQ (0.5)	EtOH	25	50
4	1.5	BQ (1.0)	EtOH	25	44
5	1.5	BQ (2.0)	EtOH	25	43
6	1.5	O_2 (1 atm)	EtOH	25	11
7	2.0	BQ (0.5)	EtOH	25	56
8	2.0	BQ (0.5)	EtOH	50	79 (71)[c]
9	2.0	BQ (0.5)	THF[d]	50	34
10	2.0	BQ (0.5)	DMF[d]	50	36
11	2.0	BQ (0.5)	DCE[d]	50	56
12	2.0	BQ (0.5)	DMSO[d]	50	23
13	2.0	BQ (0.5)	toluene[d]	50	63
14	2.0	BQ (0.5)	toluene[e]	50	50
15	2.0	BQ (0.5)	toluene[f]	50	36

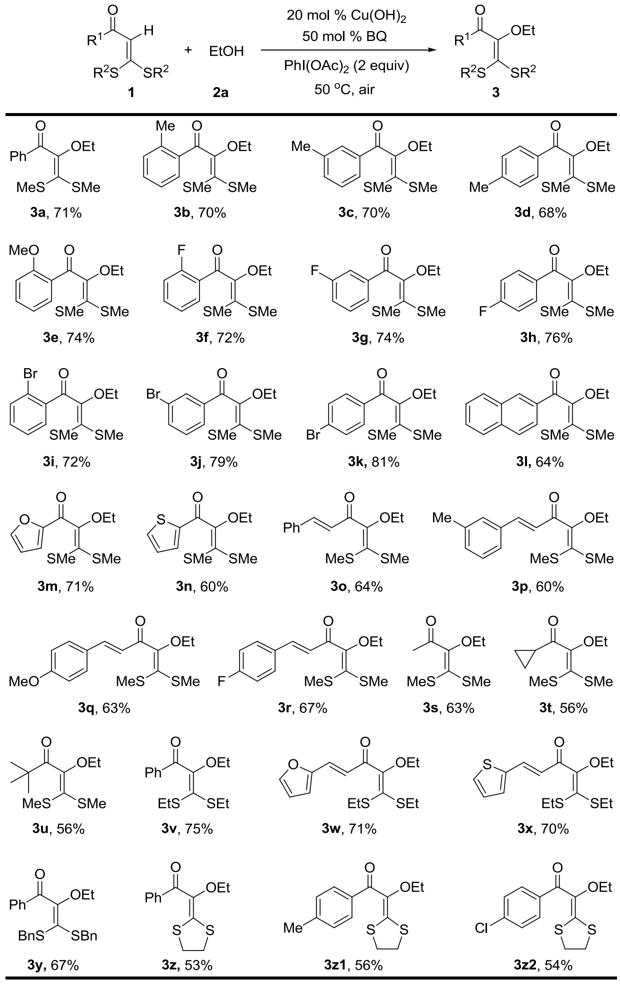
[a] Conditions: **1a** (0.3 mmol), Cu(OH)$_2$ (0.06 mmol), solvent (3 mL), air, 24 h. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yield given in parentheses. [d] Using 10 equiv EtOH. [e] Using 5 equiv EtOH. [f] Using 2 equiv EtOH.



Scheme 2 Effect of the I(III) reagents.

Initially, the reaction of *α*-benzoyl ketene di(methylthio)-acetal (**1a**) with ethanol (**2a**) was conducted to screen the reaction conditions (Table 1). In the presence of 20 mol % Cu(OH)$_2$ and PhI(OAc)$_2$ (1.5 equiv), **1a** was reacted with EtOH in air at ambient temperature for 24 h. The target *α*-C–H alkoxylation product **3a** was formed in 35% yield (Table 1, entry 1). Addition of 50 mol% benzoquinone (BQ) obviously improved the reaction efficiency (Table 1, entries 2-5), while an oxygen atmosphere deteriorated the yield to 11% (Table 1, entry 6). Elevating the reaction temperature to 50 °C with increasing the loading of PhI(OAc)$_2$ to two equivalents remarkably enhanced the product yield, leading to **3a** in 71% isolated yield (Table 1, entry 8). Use of temperature at 80-100 °C lowered the product yield (53-63%). Applying 10 equiv of EtOH in a solvent such as THF, DMF, 1,2-dichloroethane (DCE), or DMSO lessoned the reaction efficiency, and only in the case of using toluene as the solvent **3a** could be formed in a comparative yield (Table 1, entries 9-13). It was noted that large excess of ethanol facilitated the desired reaction in toluene solvent more effectively (Table 1, entries 13-15). Various copper sources, e. g., CuCl$_2$, CuBr$_2$, CuI, CuOAc, and Cu(OTf)$_2$, did not efficiently promote the reaction (see the Supporting Information for details). Other hypervalent iodine reagents were also tested as the oxidants (Scheme 2). 1-Acetoxy-1,2-benziodoxol-3-(1H)-one and (dibenzoxyiodo)benzene (PhI(OCOPh)$_2$) promoted the reaction to form **3a** (12-

Table 2 Scope of *α*-oxo ketene dithioacetals **1**[a,b]



[a] Conditions: **1** (0.5 mmol), Cu(O(H)$_2$ (0.1 mmol), PhI(OAc)$_2$ (1.0 mmol), BQ (0.25 mmol), EtOH (5 mL), 50 °C, air, 24 h. [b] Yields refer to the isolated products.

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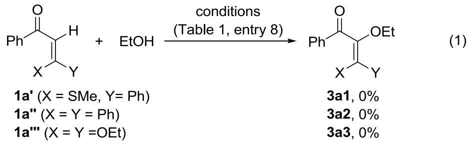
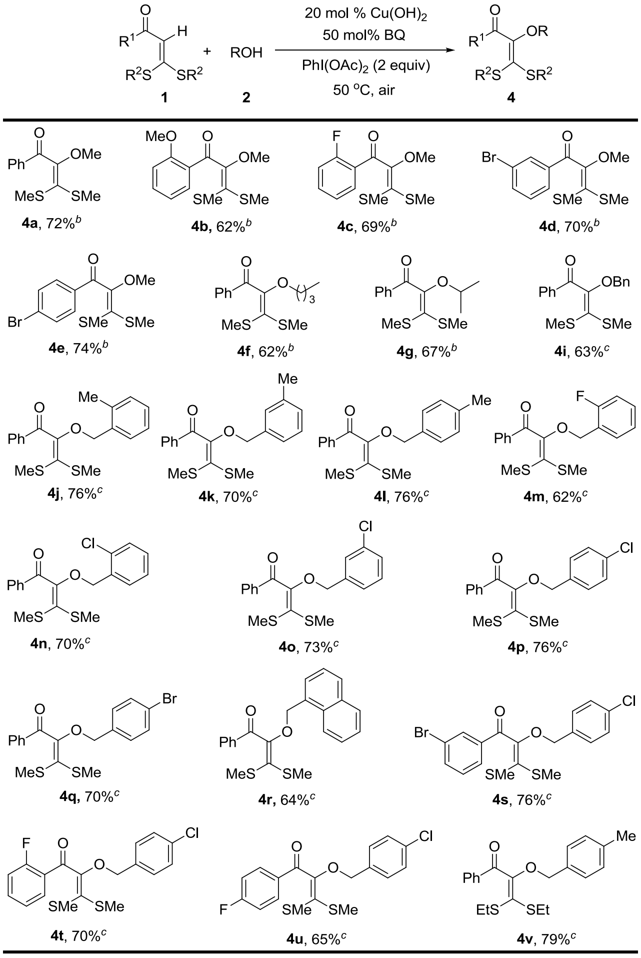


1a' (X = SMe, Y= Ph) **3a1**, 0%
1a'' (X = Y = Ph) **3a2**, 0%
1a''' (X = Y =OEt) **3a3**, 0%

42%) less efficiently than PhI(OAc)$_2$, while both bis(trifluoroacetoxy-)iodobenzene (PhI(OCOCF$_3$)$_2$) and iodosylbenzene (PhIO) rendered the reaction to produce the diethoxylation product **3a′** (10-32%), and 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one could not promote the reaction. It is noteworthy that *α*-oxo ketene monothioacetal **1a′**, 1,3,3-triphenylpropenone (**1a′′**),[16] and acetal **1a′′′** did not react with ethanol under the stated conditions (eqn (1)), suggesting that the dialkylthio functionalities are indispensable in the olefin substrates. Interaction between the two alkylthio functionalities and the olefinic C=C bond *via* p π conjugation thus activates the internal olefinic C–H bond, which makes the *a*-C–H vicinal to the electron-withdrawing carbonyl more reactive towards electrophiles as compared to ethylene.[14a,15]

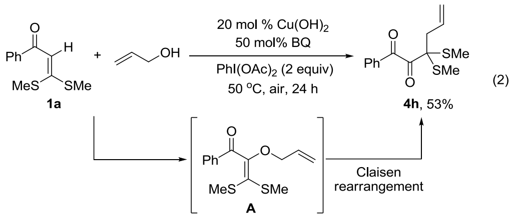
Table 3 Scope of alcohols **2**[a]



4a, 72%[b]
4b, 62%[b]
4c, 69%[b]
4d, 70%[b]
4e, 74%[b]
4f, 62%[b]
4g, 67%[b]
4i, 63%[c]
4j, 76%[c]
4k, 70%[c]
4l, 76%[c]
4m, 62%[c]
4n, 70%[c]
4o, 73%[c]
4p, 76%[c]
4q, 70%[c]
4r, 64%[c]
4s, 76%[c]
4t, 70%[c]
4u, 65%[c]
4v, 79%[c]

[a] Conditions: 1 (0.5 mmol), Cu(O(H)$_2$ (0.1 mmol), PhI(OAc)$_2$ (1.0 mmol), BQ (0.25 mmol), 50 °C, air, 24 h. Yields refer to the isolated products. [b] In ROH (5 mL). [c] Using 10 equiv ROH in toluene (5 mL).

Under the optimal conditions, the scope of *α*-oxo ketene dithioacetals **1** was investigated on a 0.5 mmol scale (Table 2). The reaction of **1a** with EtOH (**2a**) afforded **3a** in 71% isolated yield. Electron-donating methyl group on the *α*-aroyl moiety of **1** had no obvious impact on the product yields of **3b**-**d**. Both 2-methoxyl and 2-fluoro substituents did not exhibit obvious steric and electronic effects, and the corresponding reactions gave **3e** (74%) and **3f** (72%) in good yields. In the cases of using bromo-substituted substrates a steric effect was observed, leading to ***3i***-***k*** in 72-81% yields. The bulkyl *α*-naphthoyl substrate reacted with ethanol less efficiently, yielding **3l** in a moderate yield (64%). *α*-Furoyl and *α*-thienoyl ketene dithioacetals exhibited different reactivities, affording the target products **3m** (71%) and **3n** (60%), respectively, which is presumably attributed to the possible interaction of the thienyl sulfur atom with the catalytically active copper species during the reaction. Unexpectedly, *α*-alkenoyl ketene dithioacetals underwent the reactions to regioselectively form **3o**-**r** in 60-67% yields. *α*-Acetyl ketene dithioacetal and its alkyl analogs also reacted to give ethoxylated products **3s**-**u** (56-63%). Variation of the alkylthio groups from methylthio (MeS) to ethylthio (EtS) did not affect formation of the target products, i. e., **3v**-**x** (70-75%), whereas replacement of the alkylthio by benzylthio resulted in yield decrease of product **3y** (67%). In a similar fashion, cyclic *α*-aroyl ketene dithioacetals reacted with ethanol to form the target product **3z**-**z2** in 53-56% yields, exhibiting an obvious negative steric effect from the cyclic alkylthio functionality. Reactions of the olefin substrates bearing other electron-withdrawing groups such as CN could not form the target products under the stated conditions. The *α*-oxo functionality may help to stabilize species **B** as shown in the mechanism scheme *via* an intramolecular O···H–O hydrogen bond.



Next, the protocol generality was explored by carrying out the reactions of *α*-aroyl ketene dithioacetals with various alcohols (Table 3). *α*-Benzoyl ketene dithioacetal (**1a**) reacted with methanol to afford methoxylated product **4a** in 72% yield. Other substituted *α*-benzoyl ketene dithioacetals also smoothly reacted in methanol to give the corresponding products **4b**-**e** (62-74%), demonstrating diverse substituent effects. Moderate chain alcohol, that is, *n*-butanol, and secondary alcohol 2-propanol, underwent the reactions with **1a** to form **4f** (62%) and **4g** (67%), respectively. However, allyl alcohol reacted with **1a** under the stated conditions to afford diketone **4h** (53%) as the major product (eqn (2)). The process may follow a two-step sequence, that is, C-H alloxylation/ Claisen rearrangement, to generate **4h**. Sterically bulky *tert*-butyl alcohol did not react with **1**. Although benzyl alcohol exhibited a lower reactivity to **1a** to form **4i** in 63% yield, methyl-substituted benzyl alcohols efficiently underwent the reactions with **1a** in toluene, affording the target benzylation products **4j**-**l** (70-76%). A negative electronic effect was observed for 2-flourobenzyl alcohol, while 2-, 3-, and 4-

chlorobenzyl alcohols showed a positive electronic effect to produce **4m-p** in 70-76% yields. 4-Bromobenzyl alcohol also efficiently reacted to give the corresponding product **4q** (70%). However, 2-naphthylmethyl alcohol demonstrated a negative steric effect on the product yield, leading to **4r** in 64% yield. 3-Bromo and 2-fluoro-substituted benzoyl ketene dithioacetals reacted with 4-chlorobenzyl alcohol to form products **4s** (76%) and **4t** (70%), respectively, while the 4-F substituted analog underwent the reaction less efficiently to produce **4u** (65%). The di(ethylthio)acetal substrate also efficiently reacted with 4-methylbenzyl alcohol to generate **4v** (79%). Under the same conditions ketene dithioacetals **1** did not underwent the C–H phenoxylation reactions with phenols. It should be noted that *α*-oxo ketene dithioacetals reacted with benzyl alcohols to form the C–H alkylation products under Lewis acid catalysis.[17] The molecular structures of the C–H alkoxylation products **3** and **4** were further confirmed by the X-ray single crystal structural determination of compound **4i** (Figure 1).

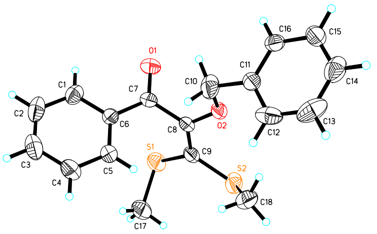
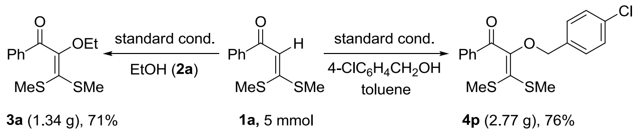
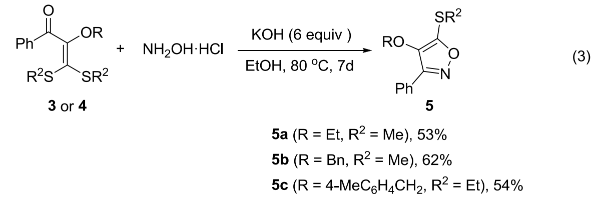


Figure 1 Molecular structure of compound **4i**.

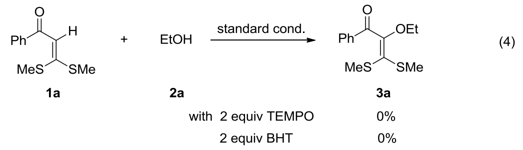


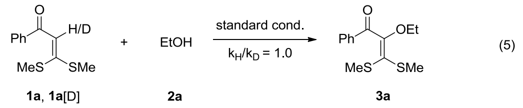
Scheme 3 Scale-up reactions of **1a** with alcohols.

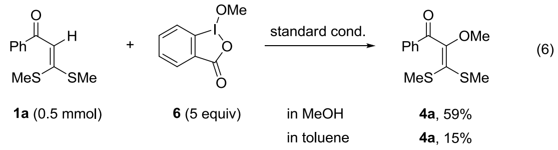
The synthetic protocol was then tested for its applicability in organic synthesis. The scaling-up reactions of *α*-benzoyl ketene dithioacetal (**1a**) with ethanol (**2a**) and 4-chlorobenzyl alcohol on a 5 mmol scale were conducted, affording the corresponding target products **3a** (71%) and **4p** (76%), respectively (Scheme 3).Treatment of the C–H alkoxylation products **3a**, **4i**, and **4v** with hydroxylamine in refluxing ethanol afforded the desulfurative condensation products, that is, fully substituted oxazoles **5a-c** (53-62%) (eqn (3)), illustrating a potential application of the alkoxylated tetrasubstituted olefins.



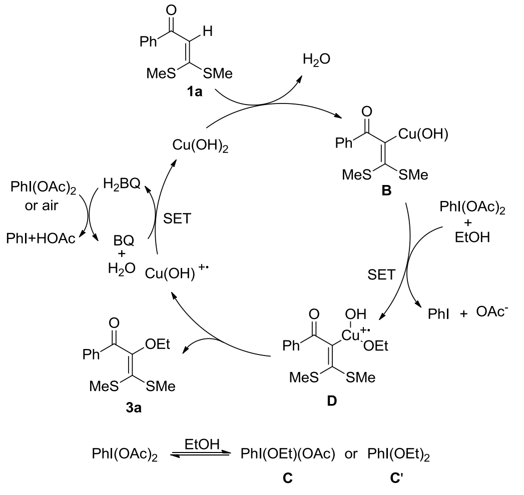
To probe into the reaction mechanism, control experiments were performed. Addition of two equivalents of a radical scavenger such as 2,2,6,6-tetramethyl-1-piperdinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) to the reaction of **1a** and ethanol (**2a**) completely inhibited the reaction under the standard conditions (eqn (4)), revealing a radical reaction mechanism involving a single-electron-transfer (SET) process.[14c] The kinetic isotope effect (KIE) experiments were carried out by means of the reactions of **1a** and its deuterated form **1a**[D] with ethanol (eqn (5)), respectively. A k_H/k_D = 1.0 value was observed, suggesting that cleavage of the internal olefinic C–H bond in *α*-oxo ketene dithioacetals **1** was not involved in the rate-determining step of the overall catalytic cycle.







In order to further verify the reaction mechanism, $PhI(OEt)_2$ and PhI(OEt)(OAc) were tentatively prepared from the reaction of $PhI(OAc)_2$ with EtOH (**2a**) using a literature method.[18] Unfortunately, both $PhI(OEt)_2$ and PhI(OEt)(OAc) could not be successfully obtained due to their high susceptibility to thermal and moisture conditions. Alternatively, stable cyclic methoxyiodo(III) compound, that is, 1-methoxy-1,2-benziodoxol-3-(1*H*)-one (**6**)[19] was prepared and applied to react with **1a** in both methanol and toluene solvents under the standard conditions, forming **4a** in 59% and 15% yields (eqn (6)), respectively. By elevating the temperature to 110 °C in a sealed tube the yield could be improved to 71% and 19%, respectively. These results have implicated the involvement of alkoxyiodo(III) species in the C–H alkoxylation of **1** with alcohols.



Scheme 4 Proposed mechanism.

A plausible mechanism is proposed in Scheme 4. Interaction of $Cu(OH)_2$ with α-oxo ketene dithioacetal **1a** generates Cu(II) species **B** with release of water. A single-electron-transfer (SET) process occurs between species **B** and the ethoxy hypervalent iodine intermediate **C** or **C′** formed *in situ* from the reaction of $PhI(OAc)_2$ and ethanol (**2a**), yielding cationic radical species **D**, which then transforms to the target product **3a** and cationic copper hydroxy radical. A second SET process occurs to regenerate $Cu(OH)_2$. Other in situ formed copper species may also promote the desired C-H alkoxylation reaction. In the overall reaction cycle, benzoquinone (BQ) facilitates the regeneration of catalytically active $Cu(OH)_2$, and both $PhI(OAc)_2$ and air promote oxidation of the reduced form of BQ, that is, hydrobenzoquinone (H_2BQ), to BQ, suggesting a cooperative effect between $PhI(OAc)_2$ and BQ.[20]

Conclusions

In summary, copper(II)-promoted direct α-C–H alkoxylation of *S*,*S*-functionalized α-oxo internal olefins with alcohols was efficiently achieved by means of a combination of $PhI(OAc)_2$ and benzoquinone as the oxidants. Polarization of the olefinic C=C bond is crucial to render the olefinic C–H alkoxylation reactions to undergo under mild conditions. The present protocol provides a concise route to alkoxylated olefins and the related alkoxylated *N*-heterocycles.

Experimental Section

Typical Procedure for the C–H Alkoxylation Reactions of 1 with 2: Synthesis of 3a

A mixture of α-benzoyl ketene di(methylthio)acetal (**1a**) (112 mg, 0.5 mmol), $Cu(OH)_2$ (10 mg, 0.1 mmol), $PhI(OAc)_2$ (322 mg, 1.0 mmol), and BQ (27 mg, 0.25 mmol) in 5 mL EtOH (**2a**) was stirred at 50 °C for 24 h. After cooled to ambient temperature, all the volatiles were evaporated under reduced pressure. The resultant mixture was subject to purification by column chromatography on silica gel (eluent: petroleum ether (60-90 °C)/ethyl acetate = 200:1, v/v), affording **3a** as a yellow liquid (95 mg, 71%).

Acknowledgements

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Notes and references

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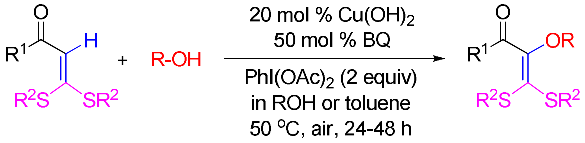

Efficient copper–promoted direct C–H alkoxylation of internal olefins *α*-oxo ketene dithioacetals was achieved with alcohols as the alkoxylating reagents.