

KIO₃-Catalyzed Aerobic Cross-Coupling Reactions of Enaminones and Thiophenols: Synthesis of Polyfunctionalized Alkenes by Metal-Free C–H Sulfenylation

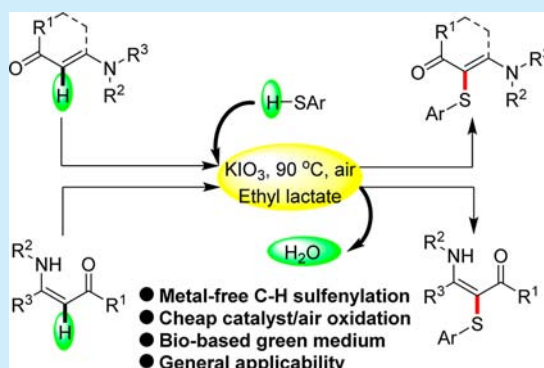
Jie-Ping Wan,^{*,†} Shanshan Zhong,[†] Lili Xie,[†] Xiaoji Cao,[‡] Yunyun Liu,[†] and Li Wei[†]

[†]College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, China

[‡]Research Centre of Analysis and Measurement, Zhejiang University of Technology, 18 Chaowang Road, Hangzhou, Zhejiang 310014, China

S Supporting Information

ABSTRACT: The synthesis of polyfunctionalized aminothioalkenes has been realized via the direct C–H sulfenylation of enaminones and analogous enamines. These cross-coupling reactions have been achieved by simple KIO₃ catalysis under aerobic conditions without employing any transition metal catalyst or additional oxidant. The employment of bio-based green solvent ethyl lactate as the reaction medium constitutes another sustainable feature of the present work.



The functionalization of alkene C–H bonds represents a class of fundamental transformations in contemporary organic synthesis.¹ The transition-metal-catalyzed Heck reaction, for example, has been identified as a highly practical strategy in both laboratory and industrial synthesis because it offers the generally applicable pathway of Pd-catalyzed C–H alkenylation.² Following the booming progress of transition metal catalysis and oxidative coupling chemistry,³ a number of complementary versions, such as radical process-based oxidative alkene C–H alkylation,⁴ arylation,⁵ alkenylation,⁶ and acylation,⁷ have been developed to enable more sophisticated alkenylation-based syntheses. Similar to the advances in C–C bond-forming reactions, the transition-metal-catalyzed direct generation of C–heteroatom bonds, including C–N,⁸ C–S,⁹ and C–P¹⁰ bonds via alkene C–H functionalization, has also achieved splendid progress in recent years.

On the other hand, following the daily increasing concern with the development of sustainable organic synthesis, transition-metal-free catalysis has rapidly evolved as a new trend in the chemistry of C–H functionalization.¹¹ In this context, research on metal-free alkene C–H functionalization has accordingly received dramatic attention.¹² Enaminones are a class of useful functional alkenes showing prevalent application in the synthesis of organic products with enriched structural diversity.¹³ Due to the invaluable utilities of enaminones, developing efficient methodologies to synthesize polyfunctionalized enaminones or heterocycles containing an enaminone backbone by direct C–H functionalization has attracted much interest.¹⁴ As typical examples, Georg and co-workers¹⁵ have reported the Pd(OAc)₂/Cu(OAc)₂

cocatalyzed arylation of a cyclic enaminone C–H bond for the synthesis of α -aryl enaminones (Scheme 1A). Du and Zhao have realized the C–H oxygenation of primary enamines for the facile synthesis of aminoalkenyl esters and oxazoles (Scheme 1B).¹⁶ Recently, the group¹⁷ has again developed an interesting method for the synthesis of diaminoalkenes via TBHP/TBAI-promoted enaminone C–H amination by using phthalimides or azoles as amine sources (Scheme 1C). Amazingly, although the construction of C–C, C–N, and C–O bond formations via the cross-coupling of the enaminone C–H bond have been achieved, corresponding cross-coupling reactions toward C–S bond formation have not been reported despite the known report of enamide C–H sulfenylation.¹⁸ Based on our research interest in both the chemistry of enaminones^{13b–f} and C–H bond functionalization,¹⁹ we report the first example of the C–S bond-formation-based synthesis of polyfunctionalized aminothioalkenes via enaminone C–H sulfenylation under metal-free, aerobic conditions by utilizing only a catalytic amount of KIO₃ in a green medium (Scheme 1D).

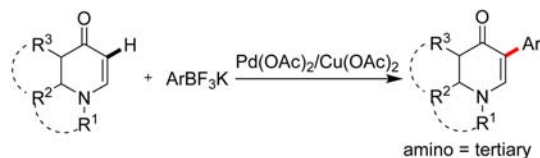
The exploration starts from the coupling reaction between enaminone **1a** and thiophenol **2a**. First, a blank reaction in DMSO without using catalyst did not give any product (entry 1, Table 1). When ionic iodine reagents such as CuI, KI, PhI(OAc)₂, and KIO₃ were employed, the C–H sulfenylation of enaminone **1a** giving product **3a** was observed. The KIO₃ exhibited much higher activity in promoting the formation of **3a**

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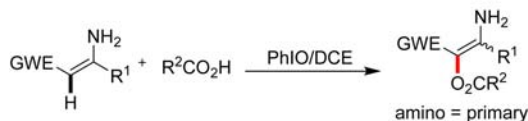
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Scheme 1. Different Catalytic Methods for Enaminone C–H Functionalization

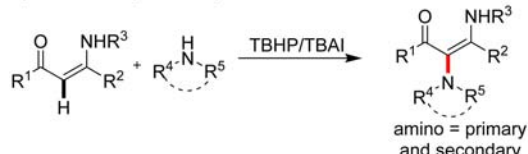
A) Pd/Cu co-catalyzed C–H arylation of enaminones



B) Metal-free, PhIO-mediated C–H arylation of enaminones



C) Metal-free, peroxide promoted C–H amination of enaminones



D) Metal-free, air promoted C–H sulfenylation of enaminones

Table 1. Optimization of the Reaction Conditions^a

entry	catalyst	solvent (mL)	<i>t</i> (°C)	yield (%) ^b
1		DMSO	100	nr
2	CuI	DMSO	100	15
3	KI	DMSO	100	20
4	PhI(OAc) ₂	DMSO	100	45
5	KIO ₃	DMSO	100	60
6	MnO ₂	DMSO	100	trace
7	KIO ₃	DMF	100	70
8	KIO ₃	toluene	100	15
9	KIO ₃	CH ₃ CN	reflux	35
10	KIO ₃	EtOH	reflux	25
11	KIO ₃	1,4-dioxane	100	18
12	KIO ₃	EL	100	75
13 ^c	KIO ₃	EL	100	80
14 ^d	KIO ₃	EL	100	84
15 ^e	KIO ₃	EL	100	80
16 ^d	KIO ₃	EL	110	78
17 ^d	KIO ₃	EL	90	85
18 ^d	KIO ₃	EL	80	80

^aGeneral conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), catalyst (0.3 mmol) in solvent (1.5 mL), stirred for 12 h (nr = no reaction).^bYield of isolated product based on **1a**. ^cCatalyst (0.15 mmol).^dCatalyst (0.09 mmol). ^eCatalyst (0.06 mmol).

(entries 2–5, Table 1) than other reagents. On the other hand, MnO₂ was not able to allow the transformation (entry 6, Table 1). Subsequently, the entries using solvents of different polarity as the

reaction medium suggested that conventional organic solvents could generally mediate the reaction; however, we were delighted to find that ethyl lactate (EL), a biomass-derived, nontoxic, and biodegradable chemical, turned out to be the most favorable medium (entries 7–12, Table 1).²⁰ Additional experiments at reducing the amount of KIO₃ proved that the 30 mol % loading was appropriate (entries 13–15, Table 1). Finally, examination of the effect of reaction temperature implied that 90 °C heating was favored in the reaction (entries 16–18, Table 1).

Investigation of the application scope of this method using different substrates was then conducted under the optimized conditions.²¹ At first, a class of different *N,N*-dimethylamino-functionalized enaminones were subjected with *p*-tolylthiophenol, and the results from the reactions demonstrated general tolerance of enaminones, including both aryl- and alkyl-functionalized ones in the synthesis of corresponding amino-thioalkenes (**3a–3o**, Figure 1). Besides aryl-functionalized

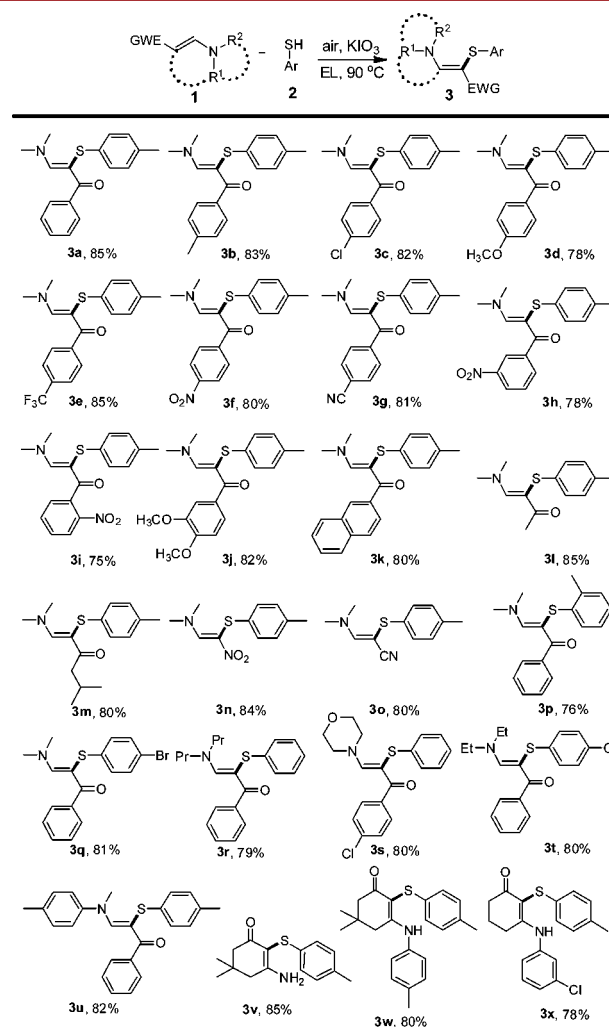


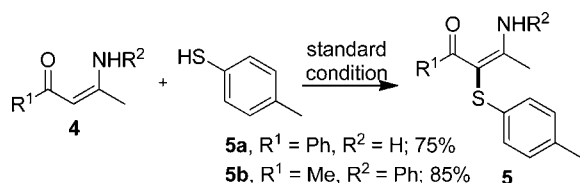
Figure 1. Application scope of *E*-configured enaminones. General conditions: **1** (0.3 mmol), **2** (0.36 mmol), KIO₃ (0.09 mmol) in 1.5 mL of EL, stirred at 90 °C for 12 h (TLC). The yield of isolated product based on **1** was reported.

enaminones, alkyl ketone-based enaminones also showed good compatibility (**3l** and **3m**, Figure 1). In addition, a more notable point was that analogous electron-deficient enamines, including cyano- and nitro-substituted enamines, also displayed smooth

applicability in the synthesis of cyano- and nitro-substituted alkenes via this sulfenylation process (3n and 3o, Figure 1). Afterward, the reactions employing different thiophenols and enaminones bearing different *N*-substitution gave satisfactory results (3p–3u, Figure 1). Finally, the sulfenylation of cyclic enaminones proceeded identically well to provide polyfunctionalized cyclic alkenes 3v–3x (Figure 1).

After examining the general sulfenylation of the enaminones with *E*-configuration, we employed acyclic NH and NH₂-functionalized enaminones 4 with *Z*-configuration. As shown in Scheme 2, the sulfenylation of these enaminones was found to

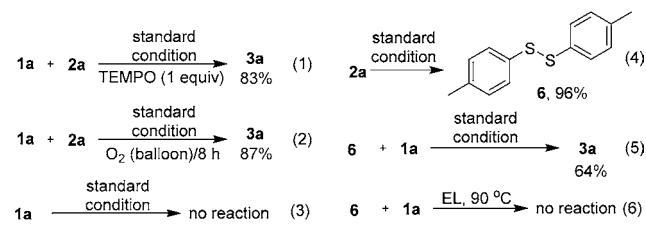
Scheme 2. Sulfenylation of NH and NH₂ Enaminones with *Z*-Configuration



be analogously efficient in this green catalytic system to provide products 5. The results and the aforementioned synthesis of products 3 clearly confirmed the general applicability of this synthetic method toward these new aminothioalkenes.

To acquire insight into the reaction mechanism, control experiments were conducted. First, the reaction in the presence of TEMPO (1 equiv) gave a yield of 3a similar to that of the reaction under standard conditions, excluding the possibility of a radical pathway in the reaction (eq 1, Scheme 3). In addition, the

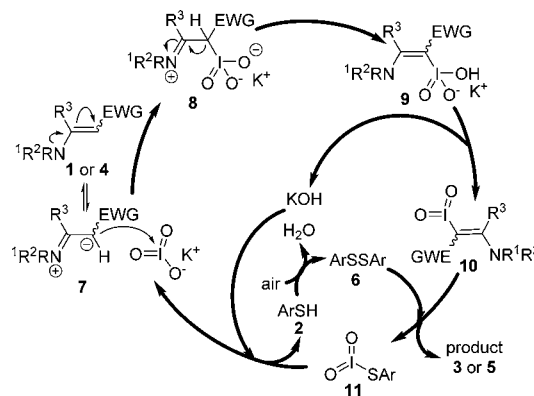
Scheme 3. Control Experiments



entry under O₂ gave target 3a with equally good yield (eq 2, Scheme 3). No reaction took place in the entry using only 1a; on the other hand, the formation of disulfide 6, a transformation known to proceed easily under aerobic conditions,²² was observed with high yield in the entry using only thiophenol 2a (eqs 3 and 4, Scheme 3). The subsequent employment of 6 with enaminone 1a proved that product 3a could be normally obtained in the presence of KIO₃ (eq 5, Scheme 3), and no reaction was observed in the corresponding blank entry (eq 6, Scheme 3).

Based on these results, a possible mechanism was tentatively proposed for the reactions (Scheme 4). Originally, the hypervalent iodate couples the enamine at the α -position via its isomeric version 7 to give intermediate 9 through the zwitterion 8. Further formation of 10 takes place by releasing KOH, and the incorporation of the in situ generated disulfide 6 with 10 produces target products and intermediate 11. The interaction of KOH and 11 allowed the regeneration of thiols 2 and iodate for recycling. The *Z/E*-stereoselectivity can be attributed to the structural stability of the products because the

Scheme 4. Proposed Reaction Mechanism



planar C=N–R³ structure in intermediate 8 displays no impact on the stereoselectivity before the regeneration of the C=C bond in 9. However, it should be noted that an accurate mechanism requires more comprehensive investigation.

In conclusion, we have disclosed a new catalytic method that consists of KIO₃/air for the α -sulfenylation of enaminones and related enamines via direct C–H bond transformation wherein a novel catalytic behavior of KIO₃ as a hypervalent iodate catalyst is proposed. Besides the benign metal-free, aerobic atmosphere conditions, the present method exhibits an additional advantage of sustainability by employing the green bio-based EL as an efficient reaction medium to enable the general application of the aminothioalkene synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03608.

Experimental procedures, characterization data, and ¹H/¹³C NMR spectra of all products (PDF)
Crystallographic data of 3c (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wanjiaping@jxnu.edu.cn.

Notes

The authors declare no competing financial interest.

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