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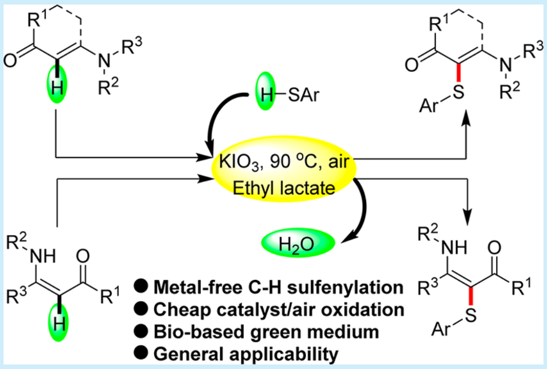
KIO_3-Catalyzed Aerobic Cross-Coupling Reactions of Enaminones and Thiophenols: Synthesis of Polyfunctionalized Alkenes by Metal-Free C−H Sulfenylation

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

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 KIO_3 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−P[10] 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-workers[15] have reported the $Pd(OA)_2/Cu(OA)_2$ 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 group[17] 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 KIO_3 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 KIO_3 were employed, the C−H sulfenylation of enaminone **1a** giving product **3a** was observed. The KIO_3 exhibited much higher activity in promoting the formation of **3a**

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

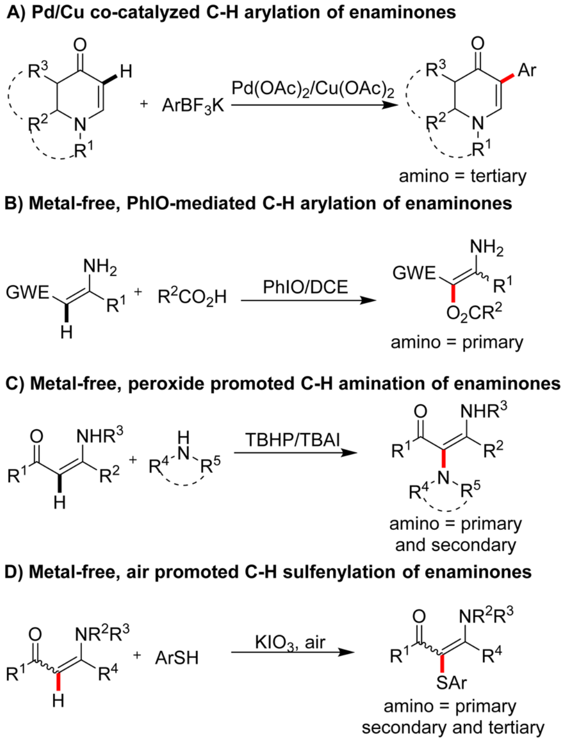
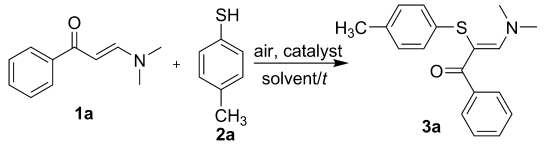


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent (mL)	t (°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_3CN	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

[a] General 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). [b] Yield of isolated product based on **1a**. [c] Catalyst (0.15 mmol). [d] Catalyst (0.09 mmol). [e] Catalyst (0.06 mmol).

(entries 2−5, Table 1) than other reagents. On the other hand, MnO_2 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 KIO_3 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 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

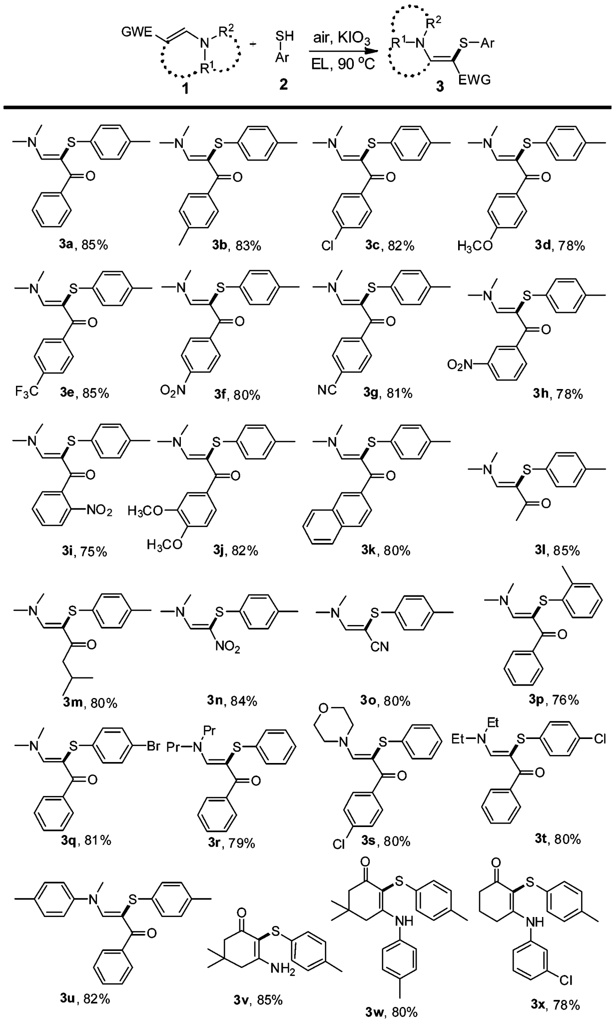
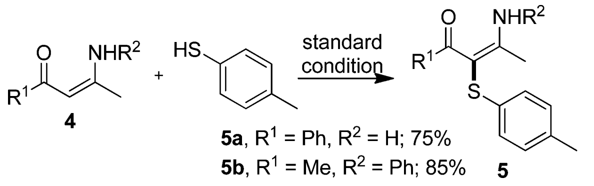


Figure 1. Application scope of *E*-configured enamines. General conditions: **1** (0.3 mmol), **2** (0.36 mmol), KIO_3 (0.09 mmol) in 1.5 mL of EL, stirred at 90 °C for 12 h (TLC). The yield of isolated product based on **1** was reported.

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 NH_2-functionalized enaminones **4** with *Z*-configuration. As shown in Scheme 2, the sulfenylation of these enaminones was found to 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.

Scheme 2. Sulfenylation of NH and NH_2 Enaminones with *Z*-Configuration



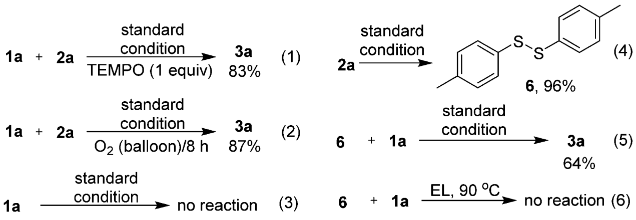
4

5a, R^1 = Ph, R^2 = H; 75%
5b, R^1 = Me, R^2 = Ph; 85%

5

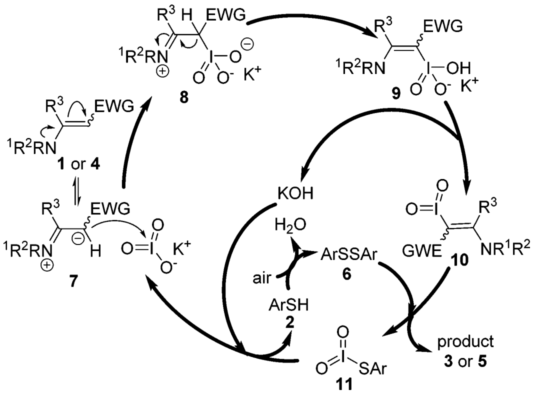
To acquire insight into the reaction mechanism, control experiments were conducted. First, the reaction in the presence of TEMPO (1 equiv) gave a yield of **3a** similar to that of the reaction under standard conditions, excluding the possibility of a radical pathway in the reaction (eq 1, Scheme 3). In addition, the entry under O_2 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 KIO_3 (eq 5, Scheme 3), and no reaction was observed in the corresponding blank entry (eq 6, Scheme 3).

Scheme 3. Control Experiments



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 planar C═N−R^3 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.

Scheme 4. Proposed Reaction Mechanism



In conclusion, we have disclosed a new catalytic method that consists of KIO_3/air for the *α*-sulfenylation of enaminones and related enamines via direct C−H bond transformation wherein a novel catalytic behavior of KIO_3 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 $^1H/^{13}C$ NMR spectra of all products (PDF)
Crystallographic data of **3c** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

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

Notes

The authors declare no competing financial interest.

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(21) CCDC 1434766 (**3c**) 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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