Organic LETTERS

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Iodine-Catalyzed Direct C−H Alkenylation of Azaheterocycle N-Oxides with Alkenes

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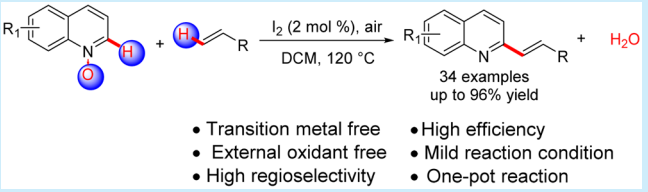
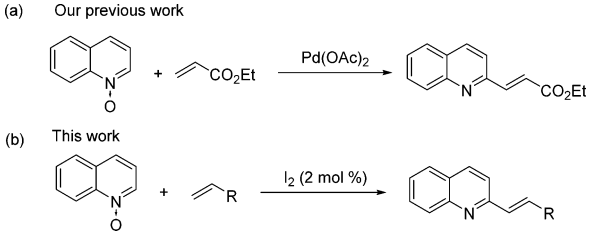
Supporting Information

ABSTRACT: An efficient and regioselective alkenylation of azaheterocycle N-oxides with alkenes catalyzed by iodine under metal- and external oxidant-free reaction conditions has been developed. A variety of (*E*)-2-styrylazaheterocycles have been produced in moderate to excellent yields. The mechanistic exploration indicated that the N-oxide group played dual roles as both the directing group and an internal oxidant in this catalytic cycle.



Direct C−H bond activation has attracted great interest in organic synthesis as the most efficient and straightforward method to build C−C and C-heteroatom bonds.[1] The high bond energy, weak reactivity, and poor regioselectivity of the C−H bond have led to very harsh reaction conditions. Transition metal-catalyzed C−H functionalization through cyclometalation has become an ideal strategy to overcome these substantial challenges.[2] For instance, the transition-metal catalyzed oxidative Heck reaction has been widely used to create functionally diverse and structurally complicated compounds.[3] Generally, an external oxidant is required to regenerate the active catalytic species, which would provide a stoichiometric amount of the reduced external oxidant as waste and reduce the overall "greenness" of the process. Our group has previously developed a novel alkenylation of quinoline N-oxides catalyzed by palladium in which the N-oxides served as an oxidizing directing group (ODG) and additional oxidants were avoided (Scheme 1a).[4] The clear advantages of ODGs, which serve as both directing group and oxidant, thereby simplifying reaction systems and making reactions more concise and efficient, have attracted interest in C−H activation. Further progress has been achieved by the Yu,[5] Ackermman,[6] Hartwig,[7] Li,[8] Shi,[9] Glorius,[10] and other groups.[11] However, the use of transition metals may cause potential contamination of the products, which is particularly significant in the pharmaceutical industry[12] and advanced functional materials.[13] Therefore, C−H activation reactions under metal-free conditions are highly desirable.[14]

Scheme 1. Oxidative Alkenylation Reaction under External Oxidant-Free Conditions



Iodine has concurrently been developed as a newly emerging nonmetal catalyst due to its low toxicity, convenient aftertreatment, and ease of removal, and it has emerged as one of the most active research topics in organic synthesis.[15] Our interest in clean cross-dehydrogenative coupling reactions under external oxidant-free conditions spurred us to test the feasibility of iodine-catalyzed oxidative alkenylation.[14d,16] Herein, we embarked on the development of a highly efficient and selective iodine-catalyzed direct alkenylation of azaheterocycle N-oxides with alkenes as part of our continuing work. In this transformation, the substrate scope was successfully extended to low activity alkenes, and the N−O group served as an oxidizing directing group and avoided the use of a metal catalyst (Scheme 1b).

The condensation of quinoline N-oxide **1a** and styrene **2a** was chosen as an initial model reaction to screen various reaction parameters (Table 1). In an initial attempt, **1a** was treated with **2a** in the presence of I_2 (10 mol %) in toluene at 120 °C under air for 22 h. As a result, the desired dehydrogenative coupling product **3aa** was formed in 57% yield (Table 1, entry 1). The molecular structure of product **3aa** was confirmed by single crystal X-ray diffraction analysis (SI, Figure S1) and NMR spectra. Next, various solvents were screened (entries 2−6). Among them, DCM gave the best results to afford **3aa** in 83% yield. Decreasing the reaction time to 5 h gave the same result (entry 7). Pleasingly, 2 mol % I_2 was sufficient for this transformation, affording the coupling product **3aa** in 83% yield (entries 8−11). No target product was observed in the absence of iodine (entry 12) and in the presence of KI instead of I_2.

Received: November 21, 2016

DOI: 10.1021/acs.orglett.6b03399
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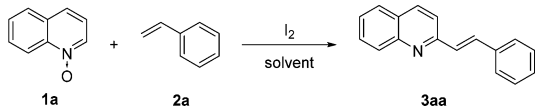
Table 1. Optimization of the Reaction Conditions for Quinoline N-Oxide 1a with Styrene 2a[a]



entry	I_2 (mol %)	solvent	time (h)	yield (%)[b]
1	10	toluene	22	57
2	10	1,4-dioxane	22	71
3	10	MeCN	22	82
4	10	DCE	22	62
5	10	DCM	22	83
6	10		22	75
7	10	DCM	5	83
8	15	DCM	5	82
9	5	DCM	5	85
10	**2**	**DCM**	**5**	**83**
11	1	DCM	5	43
12	0	DCM	5	n.d.[c]
13	2	DCM	24	58[d]
14	2		24	69[e]
15	2	DCM	24	67[e]
16	2	DCM	24	58[f]
17	2	DCM	5	66[g]
18	2	DCM	5	35[h]

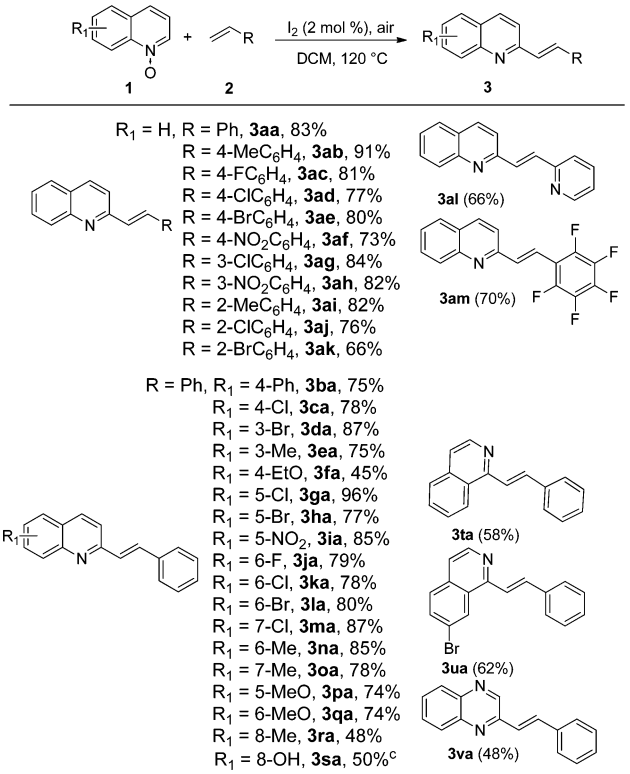
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 mmol), solvent (0.5 mL), under air, 120 °C. [b]Isolated yield. [c]n.d. = not detected. [d]Sealed container. [e]N_2. [f]O_2. [g]**2a** (1.0 mmol). [h]**2a** (0.4 mmol).

The transformation was incomplete after 24 h in a sealed container in air as well as under N_2 and O_2 atmospheres (entries 13−16). Decreasing the loading of **2a** to 1.0 or 0.4 mmol led to lower yield of 66% and 35%, respectively (entries 17 and 18).

With the optimized conditions set, the substrate scope of this transformation was investigated (Scheme 2). A range of alkenes were tested with quinoline N-oxide (**1a**). Styrenes with electron-donating and electron-with drawing substituents (such as Me, F, Cl, Br, and NO_2) at the para-position of the benzene ring gave the desired products in excellent yields (**3aa−af**). Generally, styrenes with electron-donating groups gave higher yields than those with electron-withdrawing groups (**3aa−ab** vs **3ac−af**). The efficiency of the alkenylation was not significantly affected by steric hindrance (**3aa−ah** vs **3ai−ak**). For instance, 4-chlorostyrene (**2d**) gave a similar yield to 2-chlorostyrene (**2j**). Furthermore, 2-vinylpyridine and 2,3,4,5,6-pentafluorostyrene could give the corresponding C2-alkenylated products in 66% and 70%, respectively (**3al** and **3am**). However, aliphatic alkene is not suitable for this reaction system. For example, no desired product was observed when vinylcyclohexane was used as a reactant under the standard reaction conditions.

We next investigated a range of heteroaromatic N-oxides to react with styrene (**2a**) under the optimized conditions (Scheme 2). Electronically and sterically diverse quinoline N-oxides all participated smoothly to provide the targets in good to excellent yields (**3ba−sa**). A strong electron-withdrawing group such as 5-nitroquinoline (**2i**) generated the product **3ia** in 85% yield. C8-substituted quinoline N-oxides (**2r** and **2s**) provided the desired products in 48% (**3ra**) and 50% (**3sa**) yields. Isoquinoline N-oxide (**2t**), 6-bromoisoquinoline N-oxide (**2u**), and quinoxaline N-oxide (**2v**) are also suitable for this catalytic system and generated the desired products in 58%, 62%, and 48% yields (**3ta**, **3ua**, and **3va**). Pyridine oxides instead of quinolone-oxide could not give the desired product.

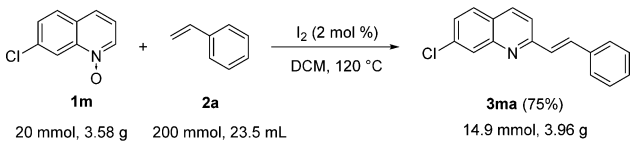
Scheme 2. Substrate Scope of Heteroaromatic N-Oxides with Alkenes[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (2.0 mmol), DCM (0.5 mL), 120 °C, 5 h, air. [b]Isolated yield. [c]Twenty-four hours.

Compounds containing the 7-chloro-2-styrylquinoline moiety are always present in leukotriene receptor antagonists.[17] To demonstrate the synthetic utility of this alkenylation reaction, a gram-scale reaction of 7-chloroquinoline N-oxide (**1m**) and styrene (**2a**) was carried out. As shown in Scheme 3, (*E*)-7-chloro-2-styrylquinoline (**3ma**) was obtained in 75% yield.

Scheme 3. Gram-Scale Reaction of 1m with 2a

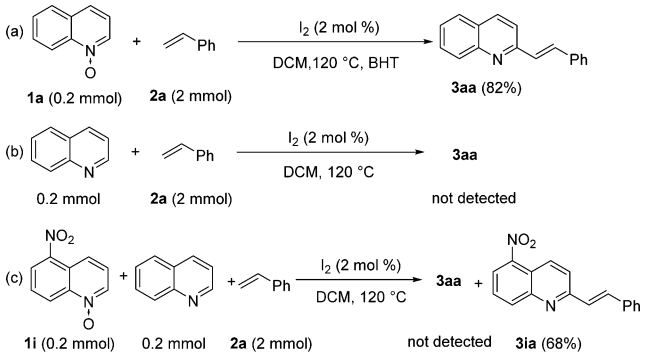


To clarify the reaction mechanism, control experiments were performed (Scheme 4). Addition of the radical scavenger BHT (2,6-di*tert*-butyl-4-methylphenol) to the reaction mixture afforded the target product **3aa** in 82% yield (Scheme 4a), suggesting the impossibility of a radical process. When quinoline was used instead of quinoline N-oxide as the reactant under the standard reaction conditions, no desired **3aa** was found, which indicated that the N−O group played an important role in this transformation (Scheme 4b). Moreover, when a mixture of 5-nitroquinoline 1-oxide **1i** and quinoline (1:1) were added to the reaction system, only **3aa** was detected (Scheme 4c), further indicating the crucial role of N-oxide.

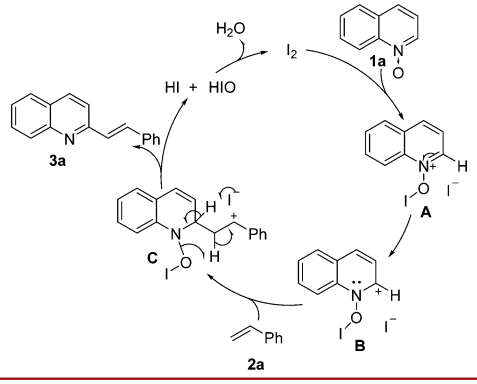
Based on the obtained results and the literature,[18] a plausible reaction mechanism is proposed (Scheme 5). Initially, the oxygen atom in quinoline N-oxide (**1a**) was attacked by the iodine, leading to the formation of quaternary ammonium salt intermediate **A**.

DOI: 10.1021/acs.orglett.6b03399
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Control Experiments



Scheme 5. Plausible Reaction Mechanism



Subsequently, the complex **A** was converted to intermediate **B** through intramolecular rearrangement. Next, the intermediate **B** could convert into intermediate **C** through nucleophilic addition of styrene (**2a**) at C2 of quinoline. Finally, the rearrangement of intermediate **C** gave the product **3aa**, HOI, and HI. Meanwhile, the generated HI was oxidized by HOI to produce iodine for the next catalytic cycle.

In summary, a mild, simple, and efficient protocol for the iodine-catalyzed C2-alkenylation of azaheterocycle N-oxides with alkenes under air atmosphere and metal-free conditions has been developed. In this approach, a broad range of (*E*)-2-styrylazaheterocycles is conveniently obtained in moderate to excellent yield. This protocol is a convergent one-pot cascade sequence, and the N-oxides served as both substrates and internal oxidants. Further exploration of the synthetic potential of the N-oxide-mediated iodine-catalyzed direct C−H bond activation is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03399.

General experimental procedure and characterization data of the products (PDF)
CIF data of **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We greatly acknowledge partial financial support from the NSF of China (21572072), the Science and Technology Innovation Program of the Universities of Henan Province (16HASTIT007), and Zhengzhou University

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DOI: 10.1021/acs.orglett.6b03399
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