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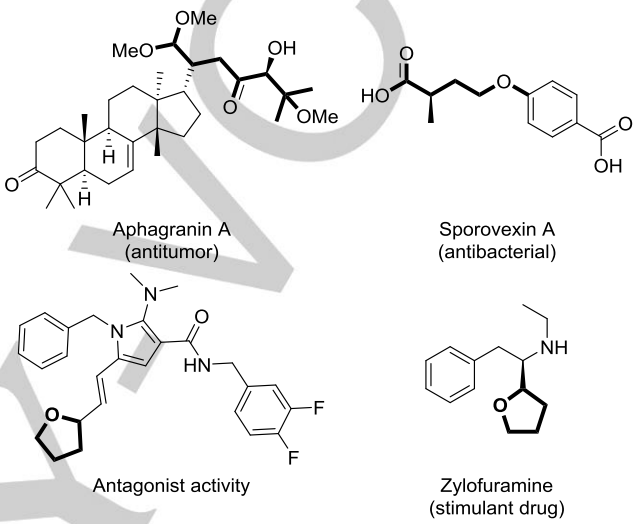
Visible Light Mediated C(sp^3)-H Alkenylation of Cyclic Ethers Enabled by Aryl Ketone

Mengmeng Zhang,[a] Liming Yang,[a] Hui Yang,[a] Guanghui An*[a],[b] and Guangming Li*[a]

Abstract: C-H alkenylation of cyclic ethers (THF, 1,4-dioxane) using the readily available nitroalkenes as the alkenylating reagents has been developed. It allows the rapid access to the *α*-alkenyl ethers with high *E*-selectivity. The previous inaccessible *α*-dienyl ethers are successfully obtained. Acyclic ether can also participate in this alkenylation process. The mechanism study reveals that alkenylation proceeded through a proton coupled electron transfer (PCET) process with a denitration.

The C-H functionalization of ethers has attracted great interest owing to the useful pharmaceutical properties (Scheme 1)[1], ubiquity in the top 200 small-molecule pharmaceuticals and new chemical entities of the generated ether moeities.[1c] Since the pioneering studies of Li and co-workers,[2a] a number of oxidation systems for selective C-H activation of ethers have been developed.[2] These protocols typically require high temperature, strong oxidants, and long reaction times, which normally lead to poor selectivities during the oxidation (Scheme 2A). Therefore, the development of a mild and selective approach for direct C(sp^3)-H functionalization of ethers is highly desired. Recently, visible light photoredox catalysis has become a powerful tool in organic synthesis. It features with mild conditions and low energy consumption, which are cheaper and easier in contrast to UV reactors.[3] Since Macmillan reported the coupling reactions of benzylic ethers with Schiff bases,[4] the development of photoredox catalysis enables *α*-alkoxy alkyl radicals generation under mild reaction conditions in contrary to the previous harsh conditions such as heating or UV light irradiation. However, these photoredox catalysts require expensive heavy metal (Scheme 2B). In 2017, Guin and coworkers disclosed an organocatalytic C(sp^3)-H alkenylation of ethers using vinyl sulfones as coupling partners.[5] Very recently, Martin's group reported C(sp^3)-H alkylation and arylation of ethers enabled by triplet excited ketones and nickel catalysts.[6] Meanwhile, Lei and coworkers developed excellent new-stage C(sp^3)-H functionalization via electrochemical reaction.[3e-3f] Despite the advances, the scope of organocatalytic *α*-alkoxy alkyl radical generation is still limited. Thus, development of readily available coupling partners with C(sp^3)-H of ether remains highly demanding.



Scheme 1. *α*-Substituted Ether Fragments in Bioactive Compounds.

Nitroalkenes recently emerged as a coupling partner in visible light mediated photoredox catalysis. In comparison with vinyl sulfones, most of nitroalkenes are commercially available and readily accessible from diverse aldehydes. Additionally, nitroalkenes are more atomic economic as alkenylation reagent.[7] Thus, *β*-nitrostyrenes have been employed as alkenylation reagents for radical denitrative benzo ylation,[8] carboxylation,[9] trifluoromethylation[10] and arylation.[11] However, to the best of our knowledge, nitroalkenes has never been employed in the C(sp^3)-H alkenylation of ether mediated by visible light. Herein, along our interest in functionalization of nitroalkenes and C(sp^3)-H activation[12], nitroalkenes as alkenylation reagent have been applied in the visible light mediated C(sp^3)-H alkenylation of cyclic ethers catalyzed by 5,7,12,14-pentacenetetrone (PT) (Scheme 2C). The C(sp^3)-H alkenylation of cyclic ethers proceeded in a higher stereoselective manner forming only *E*-isomer in contrast to vinyl sulfones. The mechanism investigation revealed that C(sp^3)-H activation involved a proton coupled electron transfer (PCET) process. Remarkably, the process allowed the rapid the access to *α*-dienyl ethers which are otherwise elusive.

We initiated our investigation by reacting *β*-nitrostyrene **1a** and THF with various photocatalysts (PC) by two blue compact fluorescent lamp (CFL) under Ar at room temperature for 36h (Table 1). Among various catalysts, **PC V** (5,7,12,14-pentacenetetrone, PT)[13] afforded the best efficiency, delivering

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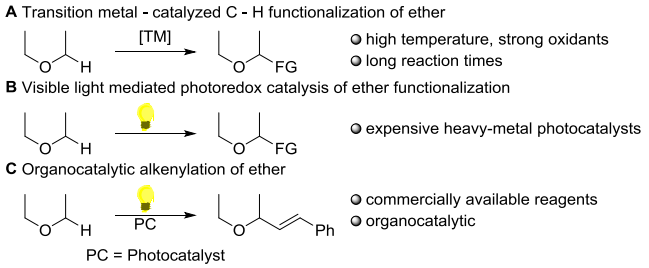


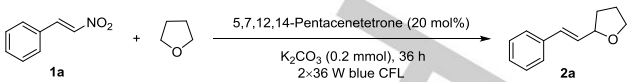
Scheme 2. Evolution of C-H Functionalization in Synthesis of *α*-Substituted Ether.

the desired product **2a** in 38% yield (Table 1, entries 1-9). Introduction of K_2CO_3 into the reaction system significantly boosted the yield of the product **2a** to 92% (Table 1, entry 10). It might be attributed to an appropriate photocatalyst/base combination which would serve to homolyze the adjacent C−H bond in THF *via* an efficient proton coupled electron transfer (PCET) process. Indeed, the replacement of K_2CO_3 with other bases diminshed the reaction efficiency (Table 1, entries 11-16), indicating the **PC V** with K_2CO_3 would be the best combination. Further solvent screening revealed that reducing the amount of THF or using CH_2Cl_2 as solvent significantly decreased the yield of process (See Table S3 in Supporting Information (SI)).

Having established the optimized reaction conditions, we tested a variety of substituted *β*-nitroalkenes to probe the versatility of our catalytic system (Scheme 3). As shown in Scheme 3, substrates bearing mono substituents on the aromatic rings successfully afforded only *E*-products in moderate to good yields (**2b**-**2k**). *Ortho* substituted *β*-nitroalkenes afforded slightly lower yields (**2b** *vs* **2c** and **2d**; **2f** vs **2g**; **2h** vs **2i** and **2j**). Palladium and nickel transformable functional groups, such as fluoro, chloro and bromo, can be tolerated under the standard conditions, overriding the potential decomposition of halo benzenes (**2f**-**2j**). Strong electron-withdrawing group, eg. CN, on the aromatic rings of *β*-nitroalkenes derivatives sharply decreased the reactivity (**2k**). Besides nitroalkenes bearing mono substituents on the aromatic rings, the disubstituted substrates also underwent the alkenylation reaction smoothly (**2l**-**2n**). Naphthalene nitroalkene was also viable substrate for this coupling reaction (**2o**). Notably, heteroaryl nitroalkene could also be used as the alkenylation coupling partner, delivering the desired ether **2p** in 73% yield, which renders the reaction particularly useful for the synthesis of biologically active ether bearing heterocycles. Furthermore, the challenging nitrodiene derivatives can also participate the alkenylation reaction, affording the corresponding products in satisfactory yields (**2r**-**2s**). We next explored the scope of this transformation with respect to ether substrates. 1,4-dioxane could be effectively converted to the vinyl derivatives **2t** in 64% yield. Besides cyclic ethers, acyclic ether, 1,2-dimethoxyethane, underwent the alkenylation smoothly, providing both product **2u1** and **2u2** in 68% yield with 1:1 ratio. However, diethyl ether was incompatible with the standard conditions.

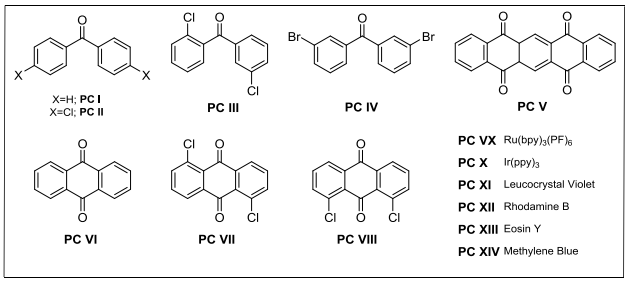
To gain the insights of the mechanism, a series of control experiments were carried out. A single electron tranfer (SET)

Table 1. Optimization of Reaction Conditions.

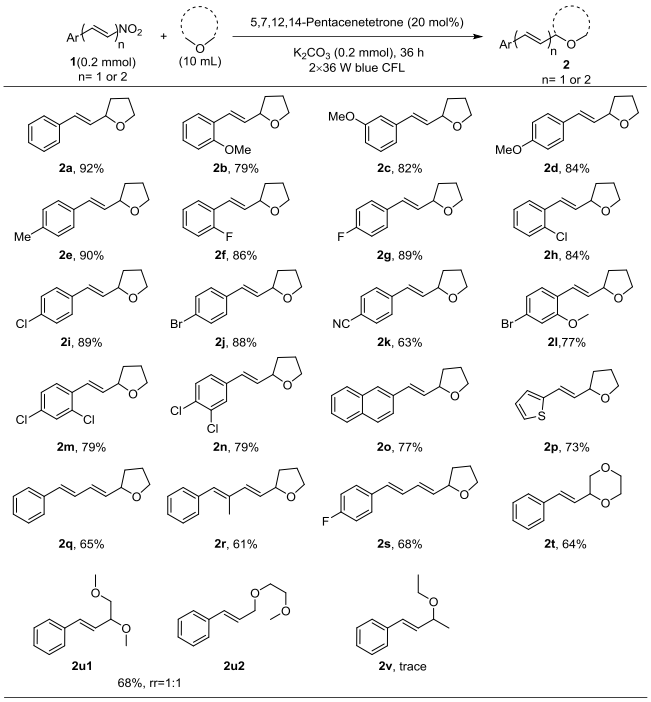


Entry[a]	Catalyst	Base	Yield (%)[b]
1	**PC I**	-	24
2	**PC II**	-	22
3	**PC III**	-	20
4	**PC IV**	-	23
5	**PC V**	-	38
6	**PC VI**	-	18
7	**PC VII**	-	17
8	**PC VIII**	-	19
9	**PC VX-XIV**	-	NR
10	**PC V**	K_2CO_3	92
11	**PC V**	Na_2CO_3	79
12	**PC V**	$NaHCO_3$	72
13	**PC V**	Na_2HPO_4	65
14	**PC V**	NaH_2PO_4	64
15	**PC V**	K_3PO_4	69
16	**PC V**	CsOAc	57

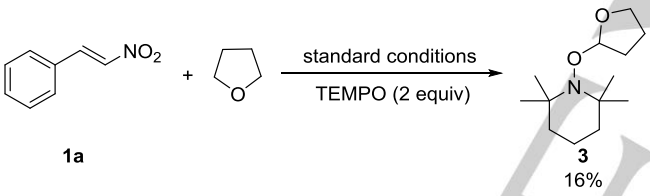
[a]Reaction conditions: *β*-nitrostyrene **1a** (0.2 mmol, 1.0 equiv), photocatalyst (0.04 mmol, 20 mol%), and base (1.0 equiv) in THF (10 mL) under Ar at 25 °C for 36 h. [b]Isolated yields. NR=No reaction.



pathway was suggested by the observed inhibition in the radical inhibition experiments. No alkenylation reaction occurred in the absence of photocatalyst (SI, Scheme S1). Light on/off reaction revealed that the reaction didn't proceed without light, indicating a radical chain reaction is not plausible (SI, Scheme S2). Additionally, TEMPO trapped the alkyl radical to form **3** in 16% yield (Scheme 4). Given these results and previous literatures,[4-7] a plausible mechanism was outlined in Scheme 5. Upon the irradiation, diarylketone catalyst **PC V** can readily oxidize tetrahydrofuran by excited state **4** in the assistance of base, generating alkyl radical **5**. Subsequent addition to nitroalkenes **1**



Scheme 3. Substrate Scope. (Isolated yields)



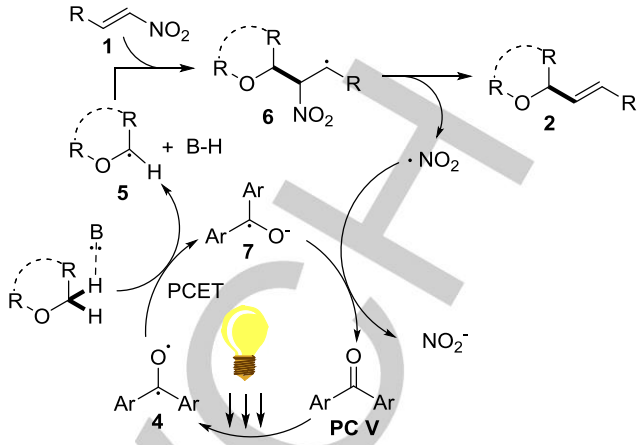
Scheme 4. Radical Inhibition Experiments.

would generate adduct **6**. The **7** promoted denitration of **6**, affording product **2** (Scheme 5).

In summary, we successfully applied the readily available nitroalkenes as the alkenylating reagents for C-H alkenylation of ethers. The protocol allows the rapid access to the *α*-alkenyl ethers with only *E*-isomers. The previous elusive *α*-dienyl ethers are successfully gained as well. The mechanism study revealed that alkenylation proceeded through a PCET process with a denitration, which is responsible for selective C(sp^3)-H activation of cyclic ethers and the good *E*/*Z* ratios. Further application of this protocol to functionalization of ethers with other coupling partners is under investigation in our lab.

Experimental Section

*General experimental procedure (**2a-2v**):* A mixture of nitroalkenes **1** (0.2 mmol, 1.0 equiv), 5,7,12,14-pentacenetetrone (**PC V**) (0.04 mmol, 20 mol%), and K_2CO_3 (0.2 mmol, 1.0 equiv) in ether (10 mL) were irradiated by two blue compact fluorescent lamp under Ar at rt for 36 h. The solution was concentrated and purified by flash chromatography on silica gel to give the pure **2a**-**2s**.



Scheme 5. Proposed Mechanism.

Acknowledgements

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Keywords: PCET • Photoredox catalysis • C(sp^3)-H activation • Alkenylation • Organocatalysis

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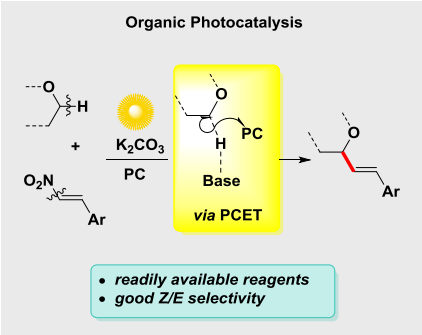

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Visible Light Mediated C(sp^3)-H Alkenylation of Cyclic Ethers Enabled by Aryl Ketone

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