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CuBr-Mediated Oxyalkylation of Vinylarenes under Aerobic Conditions via Cleavage of sp^3 C−H Bonds α to Oxygen

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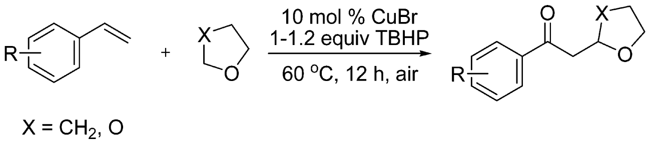
ABSTRACT



A novel difunctionalization reaction of vinylarenes with cyclic ethers has been developed by copper catalysis via direct activation of α-sp^3 C−H bonds of oxygen in the presence of 1−1.2 equiv of TBHP under mild aerobic conditions. The reaction shows excellent regioselectivities and good functional group tolerance to give the oxyalkylated products of vinylarenes.

Transition-metal-catalyzed reactions are versatile methods for C−C bond formations that have found broad applications in organic synthesis and related disciplines.[1] In particular, transition-metal-catalyzed functionalization of C−H bonds has attracted considerable attention because it offers more efficient ways for the construction of complex chemical frameworks.[2] Vinylarenes are common intermediates,[3] and their difunctionalization is an important objective in organic synthesis.[4] In the past decades, remarkable progress has been made in the transition-metal-catalyzed difunctionalization of vinylarenes, including diamination,[5] dihydroxylation,[6] hydroxyacetoxylation,[7] and aminoacetoxylation.[8] Despite the vast structural complexity of the products that these methods for the difunctionalization of vinylarenes offer, they are mainly limited to CX−CX bond-forming reactions. In this regard, manipulation of C−H bonds in the difunctionalization of vinylarenes to form CX−CC bonds should have great synthetic potential.[9] Herein, we report a new type of difunctionalization reaction of vinylarenes where CuBr catalyzes the regioselective oxyalkylation of vinylarenes through the cleavage of an sp^3 C−H bond adjacent to the oxygen atom to give the α-carbonyled *β*-alkylated aryl products in the presence of *tert*-butyl hydroperoxide (TBHP)

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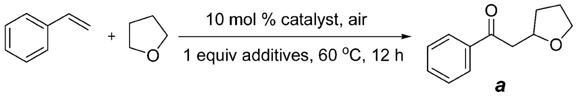
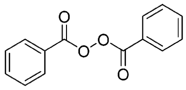
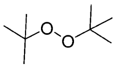
under mild aerobic conditions. This is an unprecedented reactivity mode for vinylarenes, in which the alkylation is spontaneously processed with the Wacker oxidation.[3a]

Copper has been widely studied in organic synthesis because of its promise as a high efficiency catalyst, and Cu-catalyzed C−H activation reactions have been described.[10] The use of this cheap and convenient catalyst in difunctionalization of vinylarenes is still unknown. In the exploration of new metal-catalyzed reactions via C−H bond activation, we evaluated the copper-catalyzed reaction of styrene and tetrahydrofuran in the presence of 1 equiv of TBHP, which showed special effects in the Cu-catalyzed C−H activation processes.[11] It was found that the reaction led to none of the expected adduct of tetrahydrofuran into styrene but instead afforded oxidative oxyalkylation product 2-(tetrahydrofuran-2-yl) phenylethanone in 61% yield (Table 1, entry 1). The presence of both TBHP and CuBr was essential for the oxidative carbonyalkylation. Thus, the reaction without TBHP or CuBr did not afford ***a*** at all (entries 2 and 3). In addition, only a trace of the product was detected under dinitrogen (entry 4), and the reaction could not be improved under pure dioxygen. It is noteworthy that aqueous TBHP was tolerated (entry 5). The use of other generally employed peroxides and additives in C−H bond activation, such as 2,2′-azobisisobutyronitrile (AIBN), *N*-bromosuccinimide (NBS), benzoic peroxide, and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), failed to give the product (entries 6−10).[12] The increase of CuBr loading did not improve the reaction further, and the high loading (>20 mol %) led to decrease of the yield (entries 12−14). The other metal catalysts tested were either less efficient ($AuClPPh_3$) or incompetent ($Pd(OAc)_2$, CuCl, CuI, Cu_2O, $Cu(OAc)_2$, $Cu(OTf)_2$) (entries 15−21). The use of CH_3CN as solvent afforded the desired product, while other solvents such as CH_2Cl_2, toluene, and DME were deleterious to the reaction (entries 22−23 and Supporting Information).

Table 1. Effect of Metals and Additives on the Reaction[a]



a

entry	catalyst	additive	yield (%) [b]
1	CuBr	TBHP	61
2	CuBr	-	0
3	-	TBHP	0
4	CuBr	TBHP	trace [c]
5	CuBr	TBHP	59 [d]
6	CuBr		0
7	CuBr		0
8	CuBr	AIBN	0
9	CuBr	DDQ	0
10	CuBr	NBS	0
11	CuBr	TBHP	58 [e]

[a] Reaction conditions: styrene (52 mg, 0.5 mmol), catalyst (0.05 mmol), additive (1 equiv), 0.10 mL TBHP (1−1.2 equiv), 5−6 M in decane, THF (5 mL), 60 °C, 12 h. [b] Isolated yields. [c] Reaction was carried out under N_2 atmosphere. [d] T-HYDRO, 0.11 g (1 equiv). [e] 5−6 equiv of TBHP was used (5−6 M in decane, 0.50 mL) under N_2 atmosphere.

To test the scope of this copper-catalyzed oxyalkylation reaction, we subjected a variety of vinylarenes to the reaction conditions (Table 2). In general, both electron-rich and electron-deficient vinylarenes are reactive (entries 1−14). Substitution at the 2-position of vinylarenes had only a slight impact on the yields (entries 3, 6, and 13). It should be pointed out that the carbon−halogen bonds tolerated the reaction conditions and the halogen-containing products were afforded smoothly (entries 9−13). The reaction also applicable to 2-vinylnaphthalene. However, efforts to effect the oxidative oxyalkylation of 1,4-dioxane and tetrahydropyran were not so successful (entries 16 and 17). Excellent regioselectivities were observed in this transformation. The

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Table 2. Copper-Catalyzed Oxyalkylation of Vinylarenes[a]

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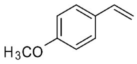
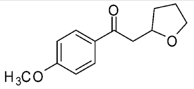
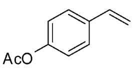
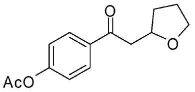
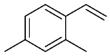
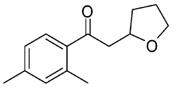
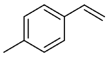
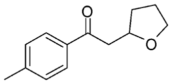
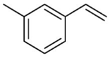
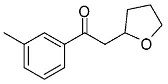
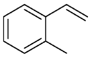
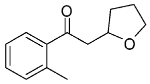
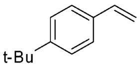
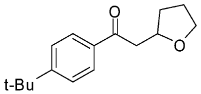
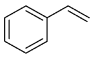
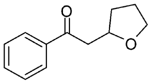
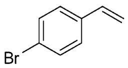
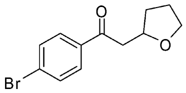
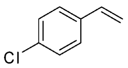
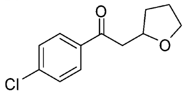
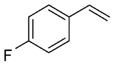
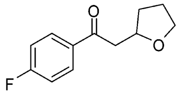
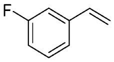
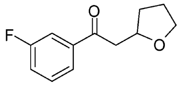
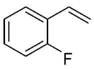
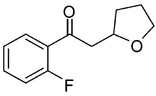
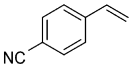
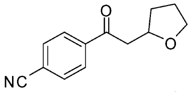
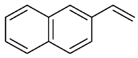
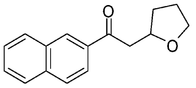
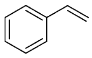
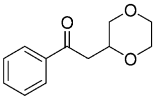
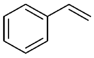
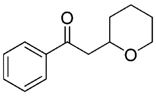
1			50
2			49
3			49
4			47
5			51
6			52
7			51
8			61
9			67
10			56
11			53
12			55
13			50
14			56
15			65
16			12[c]
17			26[d]

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[a] Reaction conditions: vinylarene (0.5 mmol), CuBr (0.05 mmol), THF (5 mL), 0.10 mL TBHP, 5−6 M in decane, 60 °C, 12 h under aerobic condition. [b] Isolated yields. [c] Dioxane (5 mL), 100 °C. [d] Tetrahydro-2*H*-pyran (5 mL), 100 °C.

addition of the α-C−H bond of oxygen to vinylarenes yielded anti-Markovnikov alkylated products, and the oxidative carbonylation occurred at the α-position of vinylarenes.

This reaction can be applied to 1,3-dioxolane, which possesses two types of C−H bonds adjacent to oxygen. The cleavage of the C−H bond at the 2-position of 1,3-dioxolane took place preferentially to give the major products of aryl β-aldehyde protected ketones as shown in Figure 1. The yields in parentheses were obtained under pure dioxygen. In this case, the pure dioxygen atomsphere was more effective and higher yields were afforded. The oxidative products at the 4-position were not identified under the reaction conditions.

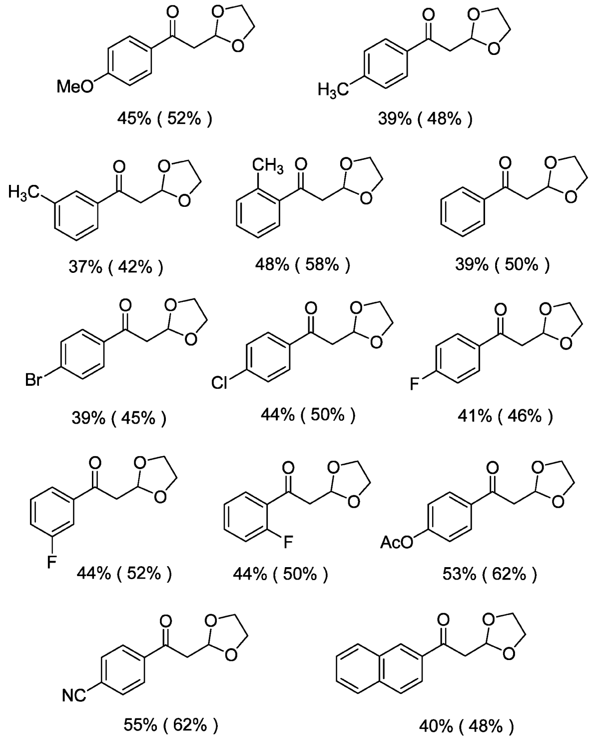
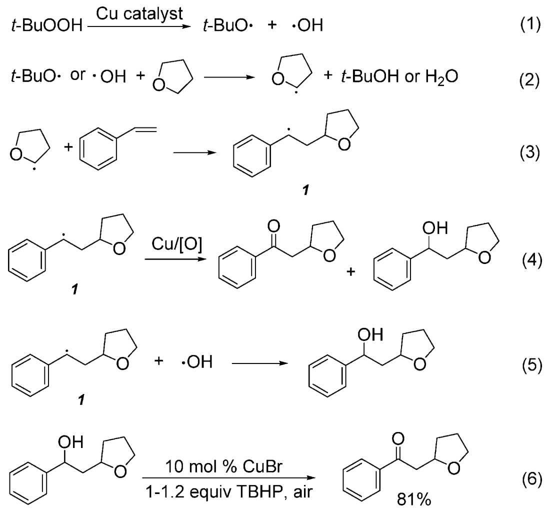


Figure 1. The reaction of vinylarenes with dioxolane. Reaction conditions: vinylarene (0.5 mmol), CuBr (0.05 mmol), dioxolane (5 mL), 0.10 mL TBHP, 5−6 M in decane, 60 °C, 12 h under aerobic condition. Isolated yields.

Although the reaction was not effective under dinitrogen using 1−1.2 equiv of TBHP, product ***a*** was isolated in 58% yield using 5−6 equiv of TBHP under anaerobic conditions (Table 1, entry 11), illustrating that the peroxide is involved in the catalysis. Since peroxides are the most common source of spontaneously induced free radicals and transition metals such as copper(I) usually promote the generation of this kind of free radicals, it was supposed that a free-radical process might be involved in the addition reaction. The preliminary mechanistic studies support our assumption and the addition of 1 equiv of free-radical scavenger 2β-di-*tert*-butyl-4-methylphenol (BHT) suppressed the reaction. In addition, phenyl α-hydroxylalkylated product is detected by GC-MS analysis (see Supporting Information), which is possibly generated from the combination of hydroxyl radical and intermediate **1** (eq 5). We found that phenyl α-hydroxylalkylated product could be oxidized under aerobic conditions in the presence of 10 mol % CuBr and 1−1.2 equiv of TBHP to give the aryl α-oxyalkylated product in 81% isolated yield (eq 6). On the basis of these results, a plausible mechanism is proposed as shown in Scheme 1. The tetrahydrofuran radical is generated by the initiator TBHP, which selectively adds to styrene to produce intermediate **1** (eq 3). The subsquent oxidation (eq 4) or combination of hydroxyl radical and intermediate **1** (eq 5) produce the phenyl α-oxyalkylated product and phenyl α-hydroxylalkylated product. The phenyl α-hydroxylalkylated product can be further converted to phenyl α-oxyalkylated product under the reaction conditions. Wacker oxidation product was not found under the reaction conditions in the absence of THF, and no reaction was observed using acetophenone as the substrate. Therefore, a tandem reaction mechanism is unlikely. However, the mechanistic scenario involving copper-mediated oxidative coupling processes is not able to be excluded at the current stage. Further studies are required for the elucidation of detailed mechanism.

Scheme 1. A Plausible Mechanism



In conclusion, we have developed a novel copper-catalyzed protocol for the difunctionalization of vinylarenes with cyclic ethers to give the oxyalkylation products. The reaction allows the regioselective oxidative insertion of vinylarenes into the α-sp^3 C−H bond of oxygen. Current research is focused on extending this finding to a C−H bond in a wider range of hydrocarbons and gaining more information on the reaction mechanism.

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Supporting Information Available: Experimental procedure and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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