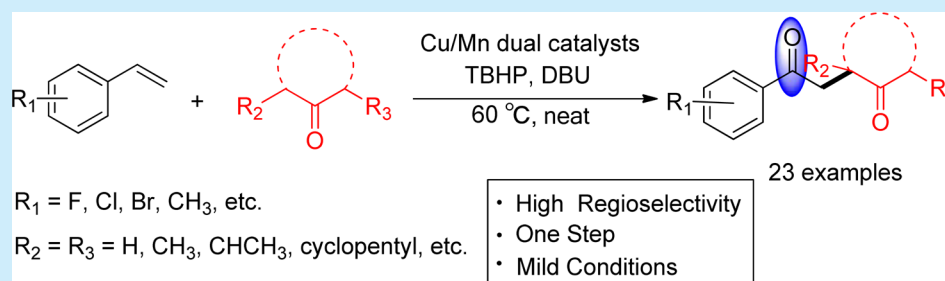


Copper/Manganese Cocatalyzed Oxidative Coupling of Vinylarenes with Ketones

Xing-Wang Lan,[†] Nai-Xing Wang,^{*,†} Wei Zhang,[†] Jia-Long Wen,[†] Cui-Bing Bai,[†] Yalan Xing,^{*,‡} and Yi-He Li[†][†]Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, China[‡]Department of Chemistry, William Paterson University of New Jersey, 300 Pompton Road, Wayne, New Jersey 07470, United States

S Supporting Information



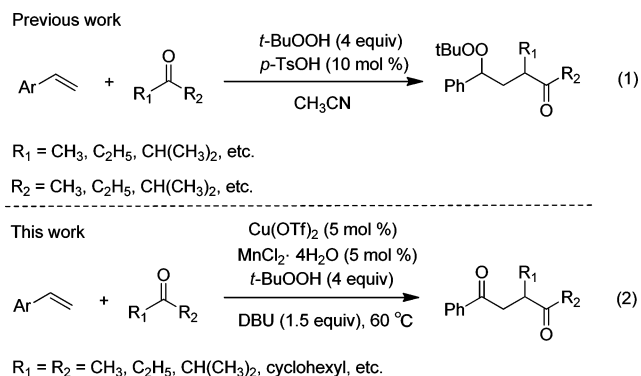
ABSTRACT: A novel copper/manganese cocatalyzed direct oxidative coupling of terminal vinylarenes with ketones via C(sp³)–H bond functionalization following C–C bond formation has been developed using *tert*-butyl hydroperoxide as the radical initiator. Various ketones underwent a free-radical addition of terminal vinylarenes to give the corresponding 1,4-dicarbonyl products with excellent regioselectivity and efficiency through one step. A possible reaction mechanism has been proposed.

Direct difunctionalization of alkenes¹ is an important strategy for the synthesis of complex molecules. In particular, transition-metal-catalyzed direct oxidative coupling of alkenes² has been developed as a fascinating and powerful approach for preparing carbonyl compounds. In this context, the direct difunctionalization of alkenes to introduce both a carbonyl group and another functional group such as ethers,³ alcohols,⁴ amides,⁵ and phosphonates⁶ has been extensively studied recently. Direct C(sp³)–H bond functionalization is highly attractive, but it has been scarcely developed.⁷ Therefore, it is still a challenge to develop the direct and regioselective difunctionalization of alkenes via C(sp³)–H bond functionalization for the efficient synthesis of compounds containing multifunctional groups.^{2a,8}

1,4-Dicarbonyl compounds are versatile scaffolds for the synthesis of carbocyclic and heterocyclic compounds, and significant efforts have been devoted to the development of the synthesis of this valuable synthon.⁹ Recently, Huang and Xie^{9d} reported a cascade carbo-carbonylation reaction of alkenes with ketones to generate 1,4-dicarbonyl compounds using organo-catalyst and transition-metal catalyst via a SOMO enamine. Wan and co-workers^{9f} reported a different method for the formation of 1,4-dicarbonyls which involves a radical process; in particular, a Co-catalyzed alkene addition/trapping/Kornblum–DeLaMare rearrangement was employed. Very recently, Klussmann and co-workers¹⁰ discovered a multicomponent radical addition of unactivated ketones and *tert*-butyl hydroperoxide to vinylarenes via Brønsted acid catalyzed formation of ketone radicals for the synthesis of alkenyl peroxides (Scheme

1, (1)). However, the alkenyl peroxides are labile so that these compounds are difficult to use directly for the synthesis of

Scheme 1. Direct Difunctionalization of Terminal Vinylarenes with Unactivated Ketones



complex molecules or pharmaceuticals. We envisioned that the direct and regioselective difunctionalization of alkenes to provide dual carbonyl groups could be realized in a single procedure via a free-radical pathway. Herein, we present the copper/manganese-cocatalyzed direct oxidative coupling of vinylarenes with ketones via C(sp³)–H bond functionalization

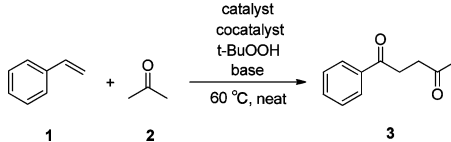
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to generate 1,4-dicarbonyls (Scheme 1, (2)). Compared to Klusmann's work, this work avoided the use of environmentally unfriendly strong acid and used a one-pot reaction to give 1,4-dicarbonyls. To the best of our knowledge, this is first report of the direct oxidative coupling of simple vinylarenes with ketones via C(sp³)–H bond functionalization to assemble the synthetically versatile 1,4-dicarbonyls in one pot.

We began our investigations by exploiting styrene **1** and acetone **2** as model substrates under various reaction conditions (Table 1). After screening a series of transition-metal catalysts

Table 1. Selected Results for Screening the Optimal Reaction Conditions^a



entry	catalyst	cocatalyst	base	yield ^b (%)
1	FeCl ₃ ·6H ₂ O		Et ₃ N	22
2	NiCl ₂ ·6H ₂ O		Et ₃ N	18
3	MnCl ₂ ·4H ₂ O		Et ₃ N	8
4	CuCl ₂		Et ₃ N	0
5	CuBr ₂		Et ₃ N	15
6	CuI		Et ₃ N	10
7	CuSO ₄ ·5H ₂ O		Et ₃ N	18
8	Cu(OTf) ₂		Et ₃ N	24
9	Cu(ClO ₄) ₂		Et ₃ N	11
10	Cu(OAc) ₂		Et ₃ N	17
11	Cu(OTf) ₂		DBU	46
12	Cu(OTf) ₂		<i>t</i> -BuOK	<5
13	Cu(OTf) ₂		K ₂ CO ₃	trace
14	Cu(OTf) ₂		pyridine	trace
15 ^c	Cu(OTf) ₂		DBU	43
16	Cu(OTf) ₂	NiCl ₂ ·6H ₂ O	DBU	45
17	Cu(OTf) ₂	FeCl ₃ ·6H ₂ O	DBU	47
18	Cu(OTf) ₂	MnCl ₂ ·4H ₂ O	DBU	54
19	Cu(OTf) ₂	CuBr ₂	DBU	50
20 ^d	Cu(OTf) ₂	MnCl ₂ ·4H ₂ O	DBU	71
21 ^e	Cu(OTf) ₂		DBU	44
22	Cu(OTf) ₂		DBU	15
23 ^f	Cu(OTf) ₂		DBU	<10
24			DBU	0
25 ^g	Cu(OTf) ₂	MnCl ₂ ·4H ₂ O	DBU	53

^aReaction conditions: styrene **1** (0.5 mmol, 1 equiv), acetone **2** (3 mL), catalyst (5 mol %), cocatalyst (5 mol %), base (1.5 equiv), aqueous TBHP (4 equiv, 70% in water) in seal tube at 60 °C for 24 h.

^bIsolated yields. ^c10 mol % of 1,10-phenanthroline was employed.

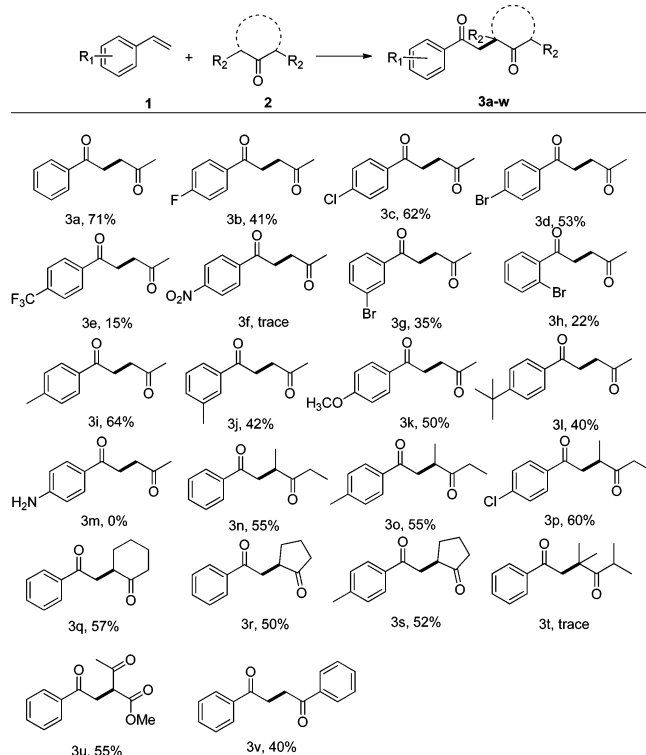
^dReaction within 72 h. ^e20 mol % of Cu(OTf)₂. ^fWithout aqueous TBHP (70% in water). ^gOpen flask (in air).

(Table 1, entries 1–10, and Supporting Information), a 24% yield of the desired 1,4-dicarbonyl product **3** was achieved in the presence of 1.5 equiv of Et₃N and 4 equiv of TBHP (70% in water) using Cu(OTf)₂ as catalyst (Table 1, entry 8). To improve the yield, several other bases, including DBU, *t*-BuOK, K₂CO₃, and pyridine, were examined (Table 1, entries 11–14). Gratifyingly, switching the base to DBU enhanced the reaction efficiency to furnish 46% yield of the product under the same conditions, while other bases were less effective. However, when 10 mol % of 1,10-phenanthroline as additive was added to the reaction, the reaction yield was not improved (Table 1,

entry 15). Interestingly, further exploration showed that a decent yield was obtained when MnCl₂·4H₂O was employed as a cocatalyst (Table 1, entry 18), but other additives cannot provide more excellent results (Table 1, entries 16, 17, and 19, and Supporting Information). To our delight, a 71% yield was achieved when the reaction time was prolonged to 72 h under the optimal conditions (Table 1, entry 20). Finally, by comparison of several control experiments (Table 1, entries 21–25), we further defined the optimal conditions for this transformation, indicating that catalysts, base, and radical initiator are crucial in this reaction, although the α -C–H of ketone possesses some reactivity, and the reaction is not sensitive to air. Several other common radical initiators, such as DTBP, BPO, and DDQ, gave low or no activity, and TBHP (5.5 M solution in decane) as radical initiator gave a 50% yield (see the Supporting Information).

With the optimal conditions in hand, the substrate scope of this reaction was investigated by testing various terminal vinylarenes **1** and ketones **2** (Scheme 2). First, a series of

Scheme 2. Substrate Scope for the Reaction of Alkenes with Ketones^a



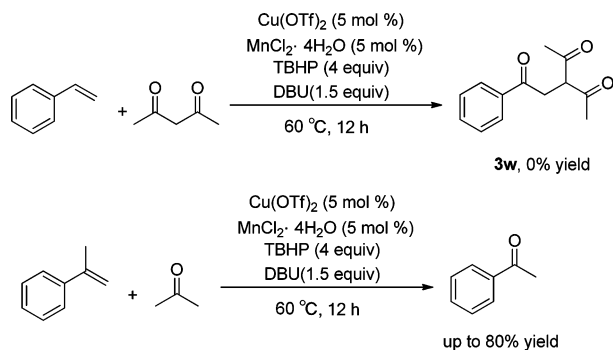
^aReaction conditions: alkenes **1** (0.5 mmol, 1 equiv), ketones **2** (3 mL), Cu(OTf)₂ (5 mol %), MnCl₂·4H₂O (5 mol %), DBU (1.5 equiv), aqueous TBHP (4 equiv, 70% in water) at 60 °C.

substituted terminal vinylarenes was explored for reaction with acetone in sealed tubes as shown in Scheme 2. Styrenes having electron-withdrawing substituents such as halogen substituents (F-, Cl-, and Br-) at the *para*-position afforded the desired products in moderate yields (41%, 63%, and 53%, respectively). Unexpectedly, when the CF₃- or NO₂-substituted styrene was used as a substrate in the reaction, the yield was dramatically reduced to low or even trace. In addition, the *m*- and *o*-bromo-substituted styrenes were also examined, and the order of their reactivity was as follows: *para* > *meta* > *ortho*. Obviously, the

position of substituents impacted the yield of the reaction. Styrenes having electron-donating substituents such as CH_3 -, CH_3O - and $t\text{-Bu}$ - also smoothly generated the corresponding products. Unfortunately, no product was formed when the NH_2 -substituted styrene was employed as a substrate. We believed strong electron-donating and electron-withdrawing groups such as amino and nitro groups on the aromatic ring inhibit the reaction. Similarly, we also found that most previous works rarely involved strong electron-withdrawing and electron-donating groups.^{10,11} Finally, we speculated that this transformation was affected by both electronic and steric factors. Afterward, several ketones were also studied for reaction with typical vinylarenes in an open flask (in air), and most substrates were suitable for this protocol. From primary acetone to secondary diethyl ketone, moderate yields were obtained (3n–p). In addition, cyclohexanone and cyclopentanone were also smoothly converted to the corresponding products, giving moderate yields of products (3q–s). However, the tertiary diisopropyl ketone led to only trace amounts of product 3t, and we speculated the lack of reactivity could be due to steric effects. Then the methyl acetoacetate was also tested, and we found that it selectively gave the desired product 3u in a 55% yield. Moreover, 3v was generated in 40% yield from acetophenone and styrene.

However, in the process of investigation of substrate scope, we found an unexpected result that when acetyl acetone was used as a substrate under the same conditions, no desired product was obtained. In addition, α -methylstyrene and acetone under the same conditions only gave 80% yield of the alkene cleavage product acetophenone (Scheme 3).

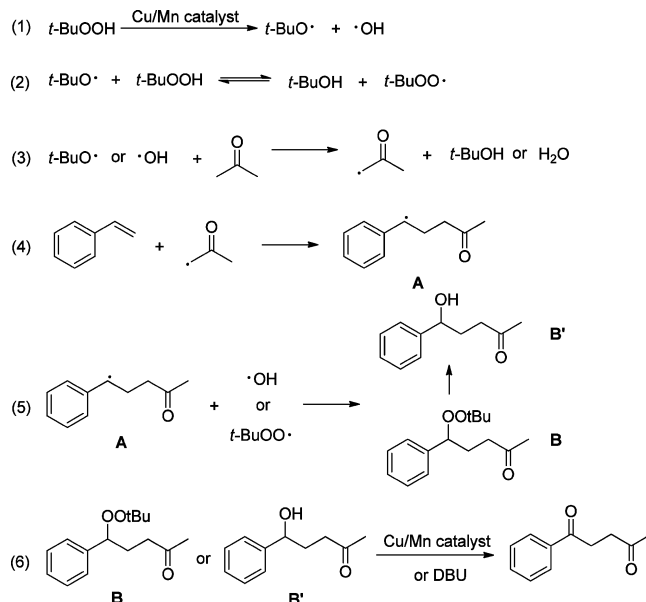
Scheme 3. Two Unexpected Results



To confirm the radical mechanism, two radical inhibitors, tetramethylpiperidin-1-oxyl (TEMPO) and 2,6-di-*tert*-butylphenol (BHT), were introduced to the reaction: 2.0 equiv of radical inhibitors resulted in a very low yield, and no reaction occurred when 4.0 equiv of radical inhibitor was used, which provided good evidence to support a radical pathway for the reaction (see the Supporting Information). To verify the mechanism, we have also tried to use the intermediated *tert*-butylperoxide **B** to directly transform to the desired product under the standard conditions, and a 82% yield of the desired product was obtained, implying **B** functions as a major reaction intermediate in this transformation. Meanwhile, a 17% yield of the desired product was achieved when benzyl alcohol **B'** was used as a substrate under the same conditions, indicating **B'** can be partly oxidized to 1,4-dicarbonyl product (see the Supporting Information). On the basis of our experimental results and previous reports,^{3,4,10,12–14} a tentative mechanism

for the copper/manganese cocatalyzed difunctionalization of terminal vinylarenes is outlined in Scheme 4. Initially, *tert*-

Scheme 4. Possible Mechanistic Pathways



butyloxy radical and hydroxyl radical (eq 1) are generated with the assistance of copper/manganese catalysts.¹² A fast equilibrium exists between *tert*-butyloxy radical and the *tert*-butylperoxyl radical (eq 2),¹³ and then *tert*-butyloxy radical and/or hydroxyl radical abstract a hydrogen radical from ketones to generate the α -ketone radicals (eq 3). Subsequently, addition of the α -ketone radicals to the styrene double bond leads to a transient radical **A** (eq 4), which combines with hydroxyl radical or *tert*-butylperoxyl radical to generate intermediate **B**^{3,10} or **B'**^{2,14} (eq 5). Finally, intermediate **B** or **B'** can form the target product in the presence of metal catalysts or DBU (eq 6).

In summary, we have developed a copper/manganese-cocatalyzed direct oxidative coupling of terminal vinylarenes with ketones via $\text{C}(\text{sp}^3)\text{--H}$ bond functionalization to generate 1,4-dicarbonyls. Various ketones and terminal vinylarenes can be smoothly converted into the corresponding products in moderate yields with good functional group tolerance. This strategy offers a new method to synthesize useful functionalized complex molecules directly using simple and inexpensive reactants. A free-radical pathway was involved in this method. Further studies regarding the detailed mechanism are currently 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.5b02116.

Experimental procedures and copies of spectra for all the compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nxwang@mail.ipc.ac.cn. Tel: +86-10-82543575. Fax: +86-10-62554670.

*E-mail: xingy@wpunj.edu

Notes

The authors declare no competing financial interest.

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