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Construction of vicinal quaternary carbons via Cu-catalyzed dearomative radical addition

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Construction of vicinal quaternary carbons via Cu-catalyzed dearomative radical addition

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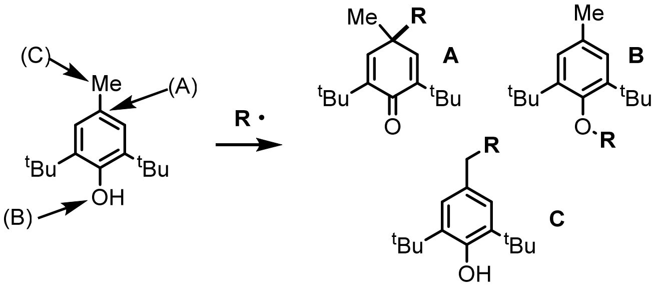
In this paper, we confirmed the dearomative addition of tertiary alkyl radicals onto BHT derivatives to form highly congested vicinal quaternary carbons to produce tert-alkylated styrenes in the presence of copper catalyst. Although there are three-candidate in the reaction of BHT with a radical species, we found that α-radical selectively reacted at ipso position of BHT to produce the corresponding dienone structure. Moreover, heteroatom substituted BHT underwent C-C cleavage coupling reactions with α-radicals.

Keywords: vicinal quaternary carbon, dearomatize, radical, copper

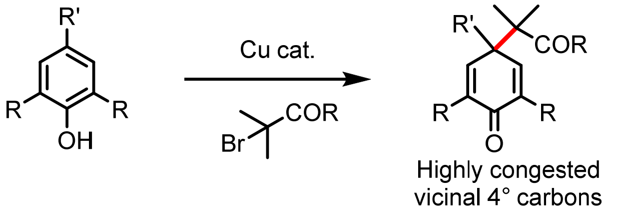
Dearomatization reactions are one of the most difficult reactions in organic synthesis due to the breaking aromaticity[1], can efficiently convert aromatic compounds into aliphatic compounds. Although there are many reports on this topic [2-5], an intermolecular dearomative tert-alkylation reaction to produce vicinal quaternary carbons has not yet been accomplished. One of the problems in this topic is the stability of the dearomative product. The most of the resulting products have a 1,4-cyclohexadiene structure that is easily oxidized to produce the starting aromatic ring. Therefore, the resulting product must be stabilized by bulky substituents in the examination of dearomative addition to aromatic ring. In this context, BHT is very nice reaction partner with a radical species. Because the resulting dearomative adduct has sterically bulky tert-butyl groups to stabilize the structure (Scheme 1 A).

BHT (butylhydroxytoluene) has been used for a radical scavenger reagent[6]. But the resulting products in the reaction of BHT are ambiguous and not fully investigated so far. An oxyl radical species react with the ipso position of BHT[6], whereas BHT generates benzyl radical from a phenoxy radical, and the resulting benzyl radical couples with a carbon radical species[7]. Therefore, there are three candidates including (A) dearomative addition, (B) coupling with OH moiety, and (C) the reaction with benzylic position in a radical reaction or ionic reaction (Scheme 1).



Scheme 1. The reaction modes of BHT with a radical species.

We and other groups have studied tertiary alkyl radical chemistry using α-bromocarbonyl compounds: 1) substitution reaction with terminal alkenes[8], 2) coupling type reaction with nucleophiles[9], 3) addition reaction with alkynes[10], and 4) aromatic C-H bond substitutions[11]. Those tert-alkylations resulted in various quaternary carbon structures via new alkylation methodologies. Our next goal is to synthesize highly congested vicinal quaternary carbon compounds via dearomative addition to produce cyclic dienone derivatives. Herein, we disclose our findings on the reaction of BHT derivatives and α-bromocarbonyl compounds in the presence of a Cu catalyst at room temperature.

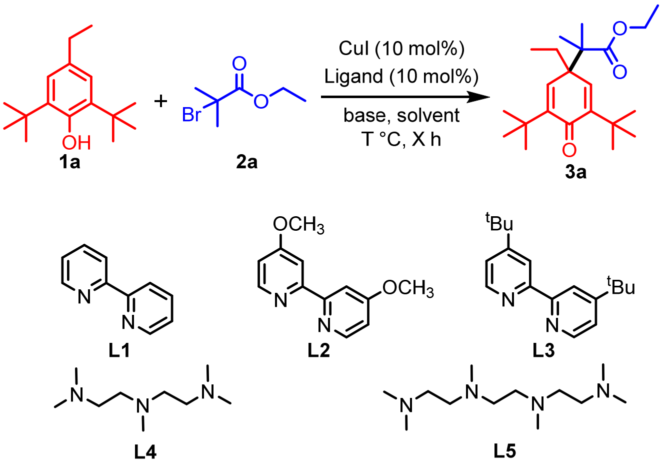


Scheme 2 This work.

Optimization studies employed the combination of **1a** (0.5 mmol), **2a** (0.5 mmol), and a base (2 equiv) in the presence of CuI (10 mol%) and ligand (10 mol%) in a solvent at room temperature. The ligand is very important to obtain the product **3a** in good yield. L1 and L2 were not effective to obtain the product **3a**, but L3 resulted in 76% NMR yield of **3a** (entries 1-3). The structures between L2 and L3 are not big difference but the results were quite different. In the case of L1 and L2, **1a** was recovered completely. The reason of this result is not clear. In previous our study[8a,9a,9b,10c,11c] and ATRP (atom-transfer radical polymerization) chemistry[12], multi-dentate aliphatic amine ligands are effective but L4 and L5 did not gave high yield of the product **3a** (entries 4 and 5). The reaction using L3 for longer reaction time (15 h) gave

93% NMR yield of **3a** (entry 6). We have tested solvents, such as 1,4-dioxane, MeCN, and dichloromethane (DCM) but toluene was the best (entries 7-9). We also tried BHT methyl ether, but no reaction occurred.

Table 1. Optimization[a]



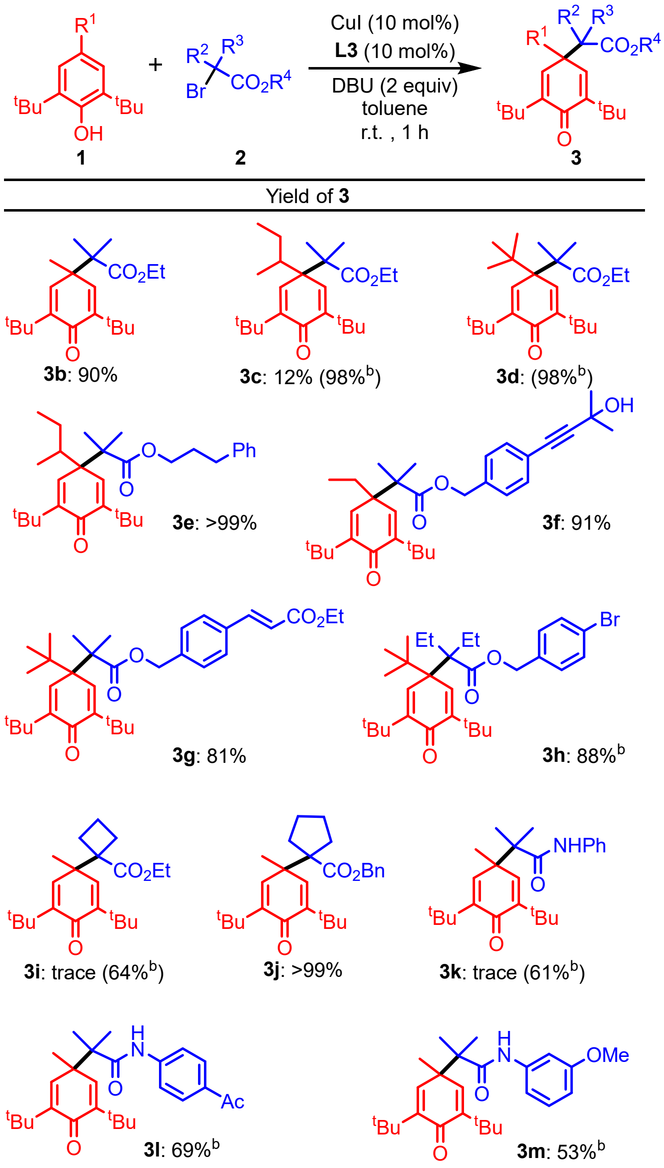
entry	Ligand	base	solvent	T (°C)	X (h)	**3a** yield [b] (%)
1	**L1**	Et$_3$N	toluene	50	10	0
2	**L2**	Et$_3$N	toluene	50	10	0
3	**L3**	Et$_3$N	toluene	50	10	76 (81)[c]
4	**L4**	Et$_3$N	toluene	50	10	43
5	**L5**	Et$_3$N	toluene	50	10	62
6	**L3**	Et$_3$N	toluene	50	15	93 (86)[c]
7	**L3**	Et$_3$N	dioxane	50	15	75
8	**L3**	Et$_3$N	MeCN	50	15	84 (85)[c]
9	**L3**	Et$_3$N	DCM	50	15	79
10	**L3**	DIEA	toluene	50	15	45
11	**L3**	K$_2$CO$_3$	toluene	50	15	23
12	**L3**	DBU	toluene	50	15	>99 (88)[c]
13	**L3**	DBU	toluene	50	3	>99
14	**L3**	DBU	toluene	50	1	99
15	**L3**	DBU	toluene	r.t.	1	95 (85)[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), CuI (0.05 mmol), Ligand (0.05 mmol), base (1.0 mmol) in solvent (1.0 mL). [b] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield.

A base is also important factor to carry out the reaction efficiently (entries 10-12). When DBU (1,8-Diazabicyclo[5.4.0]-7-undecene) was employed for the reaction, >99% NMR yield of **3a** was obtained (entry 12). Ultimately, the reaction at room temperature for 1 h in the presence of CuI and L3 was identified as the most effective at mediating the dearomative addition in excellent yield (entries 13-15).

Under optimal conditions, the dearomative additions proceeded smoothly by using various substrates (Table 2). The reaction of various BHT derivatives **1** and α-bromocarbonyl compounds **2** to give tert-butyl stabilized dienone products (**3b-3m**) achieved the yields of up to 99%. Methyl (**3b**, **3i-3m**), Ethyl (**3f**), 2-butyl (**3c** and **3e**), and tertiary butyl (**3d**, **3g**, and **3h**) groups were able to be used as the substituents (R1) of BHT derivatives **1**. The reactions were partly slow but longer reaction time was effective to obtain

Table 2. Substrate scope[a]

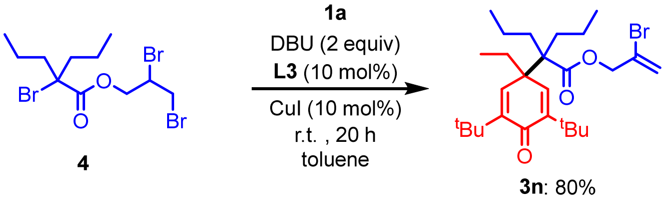


[a]All reactions were carried out in toluene at rt for 1 h with CuI (10 mol%), **L3** (10 mol%), DBU (2 equiv), **1** (1.0 equiv.) and **2** (1.0 equiv.). Yields were isolated. [b]Reaction time was 20 h.

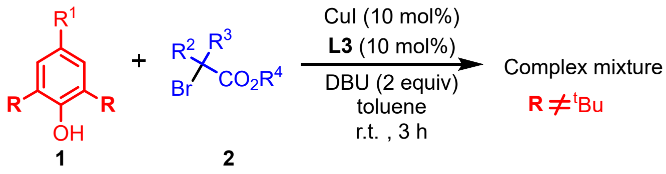
good yields. α-Bromoesters **2** possessing highly congested structure (**3h**), cyclic structure (**3i** and **3j**), propargyl alcohol (**3f**), and conjugated olefin (**3g**) were tested. Sterically bulky products (**3e**, **3f**, **3g**, and **3h**) were obtained within an hour. On the other hand, longer reaction time (20 hrs) was required to obtain the products (**3c**, **3d** and **3h**) in good yields. It was curious that the structures of substrates are very closed but the reactivities were different compared with other combinations. When substrate **2** possessing alkyl−Br bonds was used, elimination of H−Br occurred to produce the corresponding eliminated product **3n** because of the strong basicity of DBU (Scheme 3). Compared with α-bromoesters, the reactivities of α-bromocarboxamides **2** were low probably due to the bonding energy of C−Br. But α-bromocarboxamides **2** also gave good yields (**3k-3m**). The substituent on BHT is very important. For example, p-cresol possessing two ortho-alkyl groups (other than t-Bu) did not give the corresponding dearomative adduct **3** and the reactions were complex mixture (Scheme 4). We also tried the reaction of para-phenyl substituted phenol **5**. The reaction only occurred at para-position of **5** to give **6** in good yield.

Interestingly, substrates **7** possessing carboxylic acid (**7a**), dimethylaminomethyl group (**7b**), and hydroxymethyl group (**7c**) at para-position underwent C−C cleavage couplings to give the corresponding tert-alkyl substituted product **8** (Table 3). Although the mechanistic details are unknown, these reactions could occur through a radical reaction. The reaction of **8d** gave neither dearomative adduct **3** nor C−C cleavage coupling product **8**. We have tried to trap fragmentated substituents but the corresponding products were not obtained. We also tried the reaction with substrates (**7a-7c**) without tert-butyl groups but no reaction occurred.

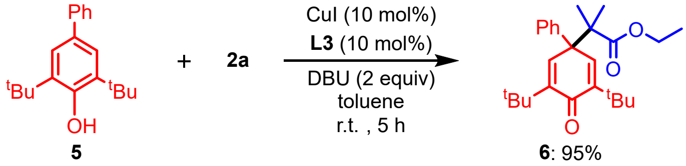
The proposed reaction mechanism is shown in Figure 1. The reaction starts with the generation of tertiary-alkyl radical species **A** from the reaction between Cu^I and **2**. We also detected the homo-coupling products of **2**, but the yields were very low. Next, the reaction of Cu^{II} and the anion of **1** generated from the reaction of **1** and DBU might give the corresponding cyclohexadienyl radical **B**. An evidence of this step is the reaction in the presence of stoichiometric amounts of Cu^{II} and **1a** (Scheme 6). In this case, the corresponding dearomative and C−C cleavage coupling product **9** was obtained. We also tried the reaction of BHT and tempo (2,2,6,6-tetramethylpiperidine 1-oxyl) but the existence of tempo adduct was not clear because the reaction was a complex mixture. This could be through the generation of **B**. Finally, the radical coupling of **A** and **B** could occur to produce **3**.



Scheme 3 Reaction with **4**.

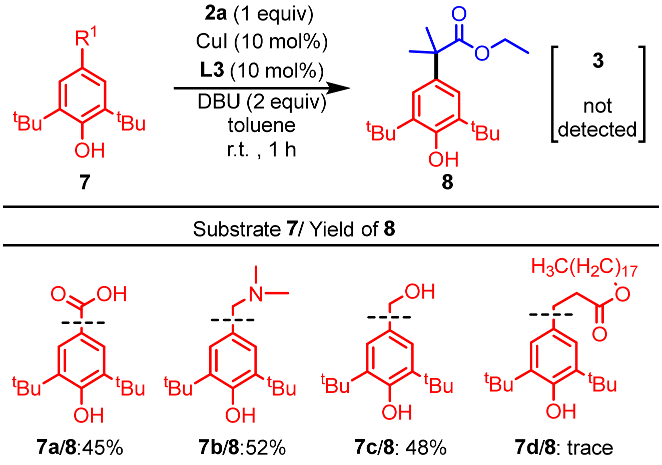


Scheme 4 Reaction with **1** (R≠tBu).



Scheme 5 Reaction with **5**.

Table 3 C-C cleavage reaction[a].



[a] All reactions were carried out in toluene at rt for 1 h with CuI (10 mol%), **L3** (10 mol%), DBU (2 equiv), **7** (1.0 equiv.) and **2a** (1.0 equiv.). Yields were isolated.

In conclusion, we discovered Cu catalyzed dearomative addition reactions of BHT derivatives and α-bromocarbonyl compounds as a tertiary alkyl source to form vicinal quaternary carbons at room temperature. The reaction could occur with the corresponding radical species. Substrates possessing carboxylic acid, dimethylaminomethyl group, and hydroxymethyl group at para-position underwent

C−C cleavage couplings to give the corresponding tert-alkyl substituted product 8. These results will show new aspects of the reactivities of BHT derivatives. Further investigations including synthetic applications using our methodology are currently underway.

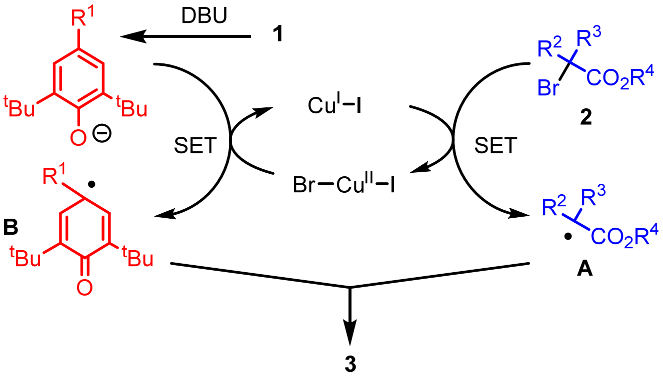
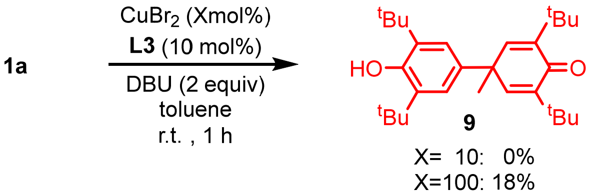


Figure 1 Proposed mechanism.



Scheme 6 Reaction with **1a** with Cu

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