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An Efficient Generation of a Functionalized Tertiary-Alkyl Radical for Copper-catalyzed Tertiary-Alkylative Mizoroki-Heck type Reaction

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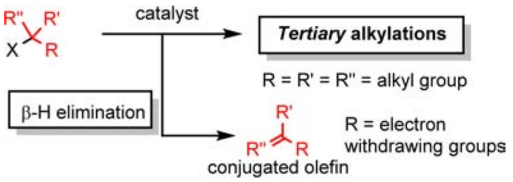
Supporting Information

ABSTRACT: α-Halocarbonyl compounds undergo β-hydrogen elimination to give conjugated olefins in the presence of a transition-metal catalyst. However, a copper/triamine catalyst system can induce the alkylative Mizoroki–Heck reaction of styrenes with tertiary-alkyl halides possessing a withdrawing group under very mild conditions. This reaction provides an efficient synthetic methodology for tertiary-alkylated styrenes.

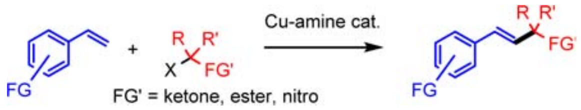
Loading of alkyl groups, including a functionalized tertiary-alkyl group, on an electrophile, such as an olefin, ketone, enone, or other carbonyl compounds, is one of the most difficult reactions in organic synthesis. Although the Mizoroki–Heck (M-H) reaction,[1] cross-coupling reaction,[2,3] and 1,4-addition reaction[4] with nonfunctionalized primary-, secondary-, and tertiary-alkyl halides have been studied, challenges in the field include achieving functionalized tertiary alkylation. Tertiary alkylation with α-halocarbonyl compounds is especially difficult compared to other alkylations because of the strong tendency of the tertiary-alkylmetal intermediate to undergo a β-hydride elimination reaction to give a conjugated olefin (Scheme 1).[5]

Scheme 1. β-Hydride Elimination vs Tertiary Alkylation



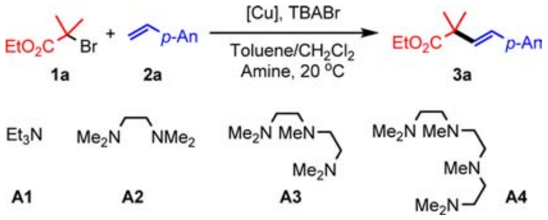
A copper complex is a promising catalyst for tertiary alkylation because "functionalized" tertiary-alkyl radical species are efficiently generated from the reaction of copper salt with a tertiary-alkyl halide. Copper-catalyzed atom-transfer radical addition (ATRA),[6] atom-transfer radical polymerization (ATRP),[7] and their analogue reactions are typical examples of high-efficiency introduction of tertiary-alkyl groups via radical reaction;[8] however, there does not appear to be a general methodology for a copper-catalyzed M-H-type reaction with functionalized tertiary-alkyl groups.[9] Here, we report that a copper-triamine complex is an excellent catalyst for the tertiary alkylation of styrenes under mild conditions with an α-haloalkane containing a ketone, ester, or nitro group (Scheme 2).

Scheme 2. Tertiary-Alkylative M-H Reaction



Optimization studies employed the combination of ethyl 2-bromoisobutyrate (**1a**, 2 equiv) and *p*-methoxystyrene (**2a**, 1 equiv) in the presence of a Cu catalyst (10 mol %), TBABr (tetra-*n*-butylammonium bromide, 0.5 equiv), and amine (**A1–4**, 1 equiv) in toluene/CH_2Cl_2 under nitrogen atmosphere at room temperature (Table 1). Addition of the copper catalyst or amine **A** is crucial to obtain the desired tertiary-alkylated product **3** in good yield. Without the catalyst or amine, no reaction occurred (runs 1 and 2). Although amines **A1** and **A2**

Table 1. Optimization of Tertiary-Alkylation in Heck Reaction[a]



entry	[Cu]	amine	yield (%)
1	CuI	none	nr
2	CuI	A1	nr
3	CuI	A2	nr
4	CuI	A3	90 (90% conv.)
5[b]	CuI	A3	94 (99% conv.)
6	CuI	A4	78 (87% conv.)
7	CuCI	A3	81 (91% conv.)
8	$CuCl_2$	A3	nr
9	CuBr	A3	83 (92% conv.)
10	CuCN	A3	60 (68% conv.)

[a]Conducted at 20 °C for 20 h in toluene/CH_2Cl_2(4/1) with 10 mol % Cu salt, amine **A** (1 equiv), TBABr (50 mol %), **1a** (2 equiv.) and **2a** (1 equiv.). Conversion of **2a** in brackets. [b]Run at 30 °C in toluene.

Received: September 17, 2013
Published: October 21, 2013

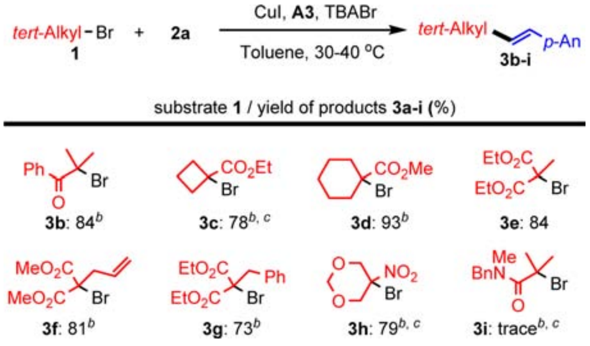
dx.doi.org/10.1021/ja409661n | *J. Am. Chem. Soc.* 2013, 135, 16372–16375

were not effective, amines **A3** and **A4** gave the product in good to excellent yields; 0.5 and 2.0 equiv of **A3** gave lower yields. Amine **A** may behave as both a ligand and a base. It is well-known that a copper complex with an amine ligand containing three or more nitrogen atoms efficiently generates alkyl radical species from an alkyl halide in ATRP or ATRA.[8] Although a generated radical abstract H-atom from the amine in ATRP, a saturated product was not detected in this reaction.

Various copper (I or II) salts were screened (runs 7−10), and CuI gave the highest yield (run 4). Copper(II) did not show any catalytic activities (run 8). Other metals, such as $CoCl_2$, $FeCl_2$, and $PdCl_2$, were not effective as catalysts. The role of TBABr remains unclear, but lack of TBABr loading resulted in a lower yield. Adding CH_2Cl_2 was effective in obtaining good solubility and gave a high yield of the product at room temperature (20 °C). However, increasing the temperature to 30 °C resulted in the highest yield without CH_2Cl_2 (run 5). At this temperature, we examined various solvents, such as MeOH, *i*-PrOH, 1,4-dioxane, *N*,*N*-dimethylformamide (DMF), and hexane, but toluene was the best solvent.

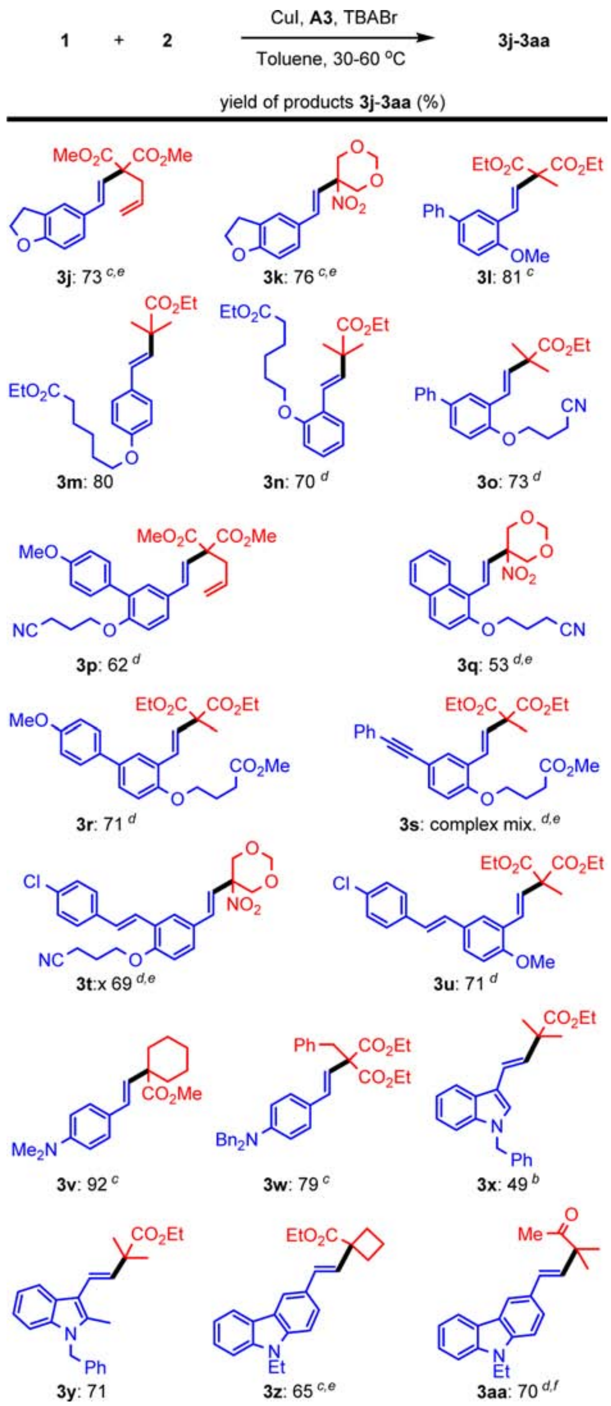
Functionalized tertiary-alkyl fragments via M-H-type alkenylation have previously been challenging reaction partners. Nonetheless, under our conditions, tertiary-alkyl halides with various functional groups can be coupled with **2a** in moderate to excellent yields (Table 2). α-Bromoketone and α-bromocyclic esters smoothly reacted with **2a** and gave the products **3b**−**3d** in good to excellent yields. Especially noteworthy is that the tertiary-alkyl halides with a nitro group and malonate moiety, both of which have a strong tendency to undergo a β-hydride elimination reaction[10] to give the corresponding conjugated olefins, provided the desired products **3e**−**3h** in good yields. In the case of the allylated malonate ester giving **3f**, tertiary alkylation selectively occurred at the vinyl group in **2a**. The reaction with a tertiary-alkyl halide having an amide group was predominated by the β-hydride elimination reaction and provided trace amounts of product **3i**.

Table 2. Reaction of Tertiary-Alkyl Halides with 2a[a]



[a] Conducted at 30 °C for 20 h in toluene with 10 mol % Cu salt, TBABr (50 mol %), amine **A3** (1 equiv), **1** (2 equiv) and **2a** (1 equiv). [b] Run at 40 °C. [c] 3 equiv of **1** was used.

Table 3. Products from the Reactions of 1 and 2[a]

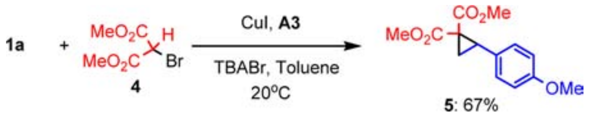


[a] Conducted at 30 °C for 20 h in toluene with 10 mol % Cu salt, TBABr (50 mol %), amine **A3** (1 equiv), **1** (2 equiv) and **2a** (1 equiv). [b] Run at 25 °C. [c] Run at 40 °C. [d] Run at 60 °C. [e] 3 equiv of **1** was used. [f] 4 equiv of **1** was used.

Functionalized styrenes **2** in M-H reactions sometimes led to polymerization[11] or low reactivity because of catalyst poisoning. Nonetheless, under our conditions, substrates with various functional groups, such as ester, nitrile, halogen, amine, and alkene groups, undergo the desired reactions (Table 3). Indications that functional group tolerance is good can be found from the products **3j**−**3aa**, likely reflecting the mildness of the tertiary-alkylation event. Sterically hindered styrenes **2** with ortho-substituents reacted smoothly with **1** to produce the corresponding olefins **3n**, **3o**, **3q**, and **3r** in moderate to good yields. A styrene with an alkyne moiety that produced product **3s** gave us a complex mixture probably because of completing the addition of the tertiary-alkyl moiety to an alkyne group in the substrate. On the other hand, in the case of a styrene having an internal alkene moiety producing the product **3t** or **3u**, the internal alkene moiety remained intact. Generally, amine groups decrease the reactivity of copper species in several catalytic reactions, but the reaction of vinylated heterocycles and anilines resulted in the products **3v**−**3aa**. The tertiary alkylation with *N*-benzyl-2-methylindole giving **3y** occurred smoothly, whereas *N*-benzylindole giving **3x** only produced a moderate yield because of the instability of the starting vinylated indole. Although styrenes with donating groups underwent M-H reaction smoothly, styrenes without donating groups gave both polymer and low yields of the products. But α-methyl styrene derivatives without donating groups reacted smoothly with **1**.[12]

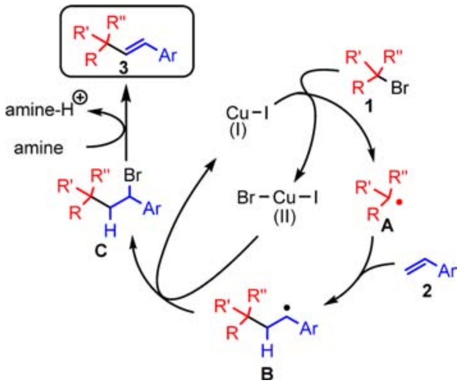
The reaction conditions associated with these reactions can also be used to allow for a cyclopropanation reaction (Scheme 3). Thus, in the presence of secondary alkyl halide **4** instead of tertiary alkyl halide **2**, alkylation afforded cyclopropane **5** exclusively. Generally, haloester derivatives only react with active Michael acceptors to produce the corresponding cyclopropane.[13] Cyclopropanation reaction of **4** with a less active olefin, styrene derivative, is rare.

Scheme 3. Cyclopropanation



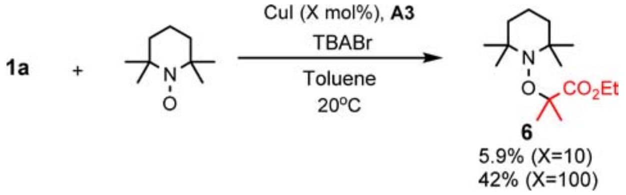
While the exact reaction mechanism is currently unclear, one possibility involves a radical pathway (Scheme 4).[10]

Scheme 4. Proposed Mechanism



The reaction starts with the generation of tertiary-alkyl radical species **A** from the reaction between Cu(I) and **1**. An evidence of this step is the reaction in the presence of TEMPO,[14] shown in Scheme 5. This reaction with TEMPO did not result in the formation of product **3**. Alternatively, tertiary-alkylated TEMPO **6** was obtained, which suggests the existence of radical species **A**.

Scheme 5. TEMPO Capture Reactions



After the generation of **A**, addition of **A** to **2** takes place to give the radical intermediate **B**. Then, intermediate **B** reacts with the Cu(II) species to produce intermediate **C** with concomitant formation of a Cu(I) species to complete the catalytic cycle. The brominated intermediate **C** undergoes elimination with the amine to give the desired product **3**.[15] Although we have no evidence of the existence of the brominated intermediate C,[16] the cyclopropanation shown in Scheme 3 likely supports this step. In the cyclopropanation mechanism, the cyclization step may proceed through intermediate **E** generated from the abstraction of an acidic proton in intermediate **D** with amine (Scheme 6).[17]

Scheme 6. Proposed Cyclopropanation Mechanism

In summary, the first copper-triamine catalyzed tertiary-alkylative M-H reaction of styrenes with functionalized tertiary-alkyl halide under mild conditions is reported. Tertiary-alkyl radical species are a key intermediate to carrying out the reaction smoothly, which was confirmed by adding TEMPO. Further investigations, including other type of addition and mechanistic studies, are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support provided by the Grant-in-Aid for Young Scientists (B) (24750043), Yamaguchi University strategic program for fostering research activities and program to disseminate tenure tracking system, MEXT, Japan is gratefully acknowledgement.

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