ACS Catalysis

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Copper-Catalyzed α-Benzylation of Enones via Radical-Triggered Oxidative Coupling of Two C−H Bonds

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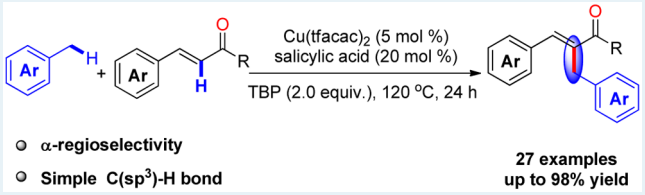
Supporting Information

ABSTRACT: A novel copper(II)-catalyzed, regioselective C−H benzylation of enones with toluenes via radical triggered oxidative coupling has been developed. A series of enones and toluenes with different substituents were successfully incorporated, providing a wide range of α-benzylated enones with TBP as oxidant by cleavage of C(sp^3)−H bond and C(sp^2)−H bond. Preliminary mechanistic study reveals a benzylic carbon radical is generated, and regioselectively reacts with enones to deliver the corresponding products.



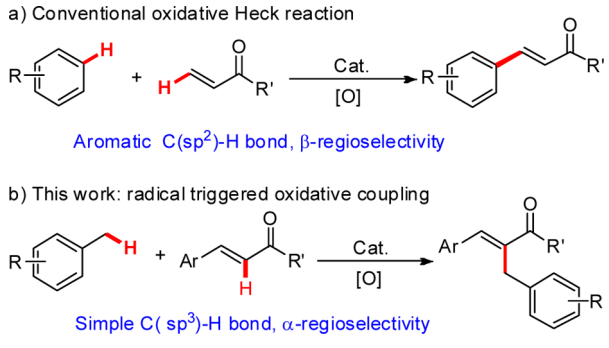
KEYWORDS: *oxidative coupling, C−H activation, radical, copper catalysis, benzylation, enones, regioselectivity*

Enones are not only versatile synthetic building blocks for synthesis of many important compounds,[1] but also a class of important structural motif found in biological active molecules.[2] Consequently, extensive efforts have been devoted to the rapid and direct functionalization of simple enones. Although a variety of catalytic methods now exist for installation of functional groups into the β-position of simple enones,[3] there is still a lack of practical, broadly useful reactions that afford access to α-functionalized enones. Current methods to these molecules have largely relied on the Morita−Baylis−Hillman (MBH) reaction,[4] which suffers from some disadvantages, such as requiring a long reaction time and harsh reaction conditions and being useful only for installing entities with strong electrophilicity. Given the importance of α-alkyl-enones in drug molecules and material science, a general, practical, and selective protocol for direct functionalization of simple and readily available enones at the α-position with simple hydrocarbon molecules is highly desirable.

The direct transformation of hydrocarbon molecules via transition-metal-catalyzed dehydrogenative cross-coupling has emerged as one of the most powerful methods to construct new C−C bonds and has attracted considerable attention.[5] In this regard, the oxidative version of Heck cross-coupling reaction is an interesting approach that provides access to functionalized alkenes directly from two C−H bonds without the need for prefunctionalized partners.[5b,e] However, current oxidative Heck cross-coupling reactions can install aryl groups only into the β-position of alkenes, which significantly has reduced the appeal of metal-catalyzed oxidative coupling and hindered its application. For the past few years, we have concentrated our efforts on the creation of efficient methods for construction of active nucleophilic organometallic species via direct cleavage of C−H and C−N bonds.[6] In this context, we have developed a palladium-catalyzed oxidative carbonylation of benzylic C−H bonds of simple toluene to afford phenylacetic acid derivatives via radical-triggered C−H bond cleavage, in which the benzylic carbon radical is formed and converted to the benzylpalladium species via a single-electron-transfer (SET) process. On the basis of this study, we envisaged that the nucleophilic benzylic carbon radical[7] might be trapped by the electron-deficient carbon−carbon double bond of enones to give the corresponding α-functionalized enones.[8] Herein, we disclose a novel Cu-catalyzed regioselectively oxidative coupling of enones and simple toluenes, which provides an efficient approach to a series of α-alkylation enones (Scheme 1).

At the outset of our studies, we explored the viability of the process with (*E*)-4-phenylbut-3-en-2-one (**1a**) and toluene (**2a**) as substrates. The reaction was performed at 120 °C for 12 h with di-*tert*-butyl peroxide (TBP) as oxidant. Several

Scheme 1. Strategies for the C−H Functionalization of Alkenes

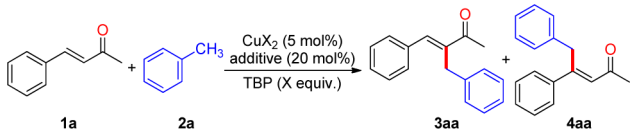


Received: February 13, 2015
Revised: March 24, 2015
Published: March 31, 2015

DOI: 10.1021/acscatal.5b00310
ACS Catal. 2015, 5, 2882−2885

commercially available copper salts, such as $CuCl_2$, $Cu(OAc)_2$, $Cu(acac)_2$, and $Cu(tfacac)_2$ (tfacac = $CF_3COCHCOCH_3$) were screened as catalysts. With $Cu(tfacac)_2$ as the catalyst, the reaction proceeded well to give the desired (*E*)-3-benzyl-4-phenylbut-3-en-2-one (**3aa**) in 31% yield together with a small amount of (*E*)-4,5-diphenylpent-3-en-2-one (**4aa**) as a by-product, whereas other catalysts gave lower yields (Table 1,

Table 1. Optimization of the Reaction Conditions[a]



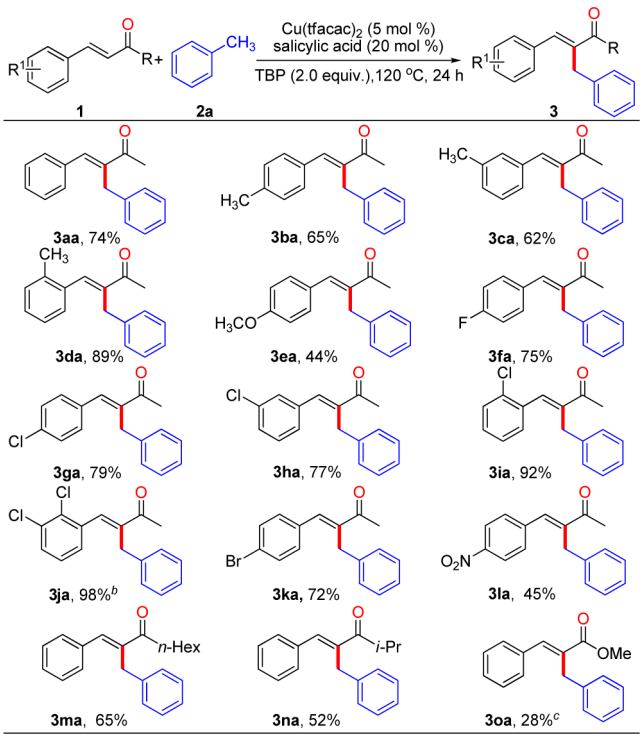
entry	CuX_2	additive	TBP (equiv)	yield (%)[b] 3aa	4aa
1	$CuCl_2$		1.5	NR	NR
2	$Cu(OAc)_2$		1.5	17	trace
3	$Cu(acac)_2$		1.5	trace	trace
4	$Cu(tfacac)_2$		1.5	33	8
5	$Cu(tfacac)_2$		1.5	54	7
6	$Cu(tfacac)_2$	HOAc	1.5	64	22
7	$Cu(tfacac)_2$	$C_6H_5CO_2H$	1.5	67	18
8	$Cu(tfacac)_2$	TsOH	1.5	44	15
9	$Cu(tfacac)_2$	*o*-CH_3–$C_6H_4CO_2H$	1.5	63	18
10	$Cu(tfacac)_2$	*o*-Cl–$C_6H_4CO_2H$	1.5	65	28
11	$Cu(tfacac)_2$	salicylic acid	1.5	70	21
12	$Cu(tfacac)_2$	salicylic acid	1.2	63	16
13	$Cu(tfacac)_2$	salicylic acid	2.0	74	18
14	$Cu(tfacac)_2$	salicylic acid	2.5	72	25
15[c]	$Cu(tfacac)_2$	salicylic acid	2.0	61	26
16[d]	$Cu(tfacac)_2$	salicylic acid	2.0	63	16
17		salicylic acid	2.0	NR	NR

[a]Reaction conditions: **1a** (0.4 mmol), TBP (1.5 equiv), CuX_2 (5 mol %), additive (20 mol %), and toluene **2a** (19.0 mmol) at 120 °C under N_2 for 12 h (entries 1–4) or 24 h (entries 5–17). [b]Isolated yield. [c]The reaction was conducted at 110 °C. [d]The reaction was conducted at 130 °C.

entries 1–4). The solid state structure of **3aa** was unambiguously determined by single-crystal X-ray diffraction analysis.[9] Prolonging the reacting time to 24 h, the yield of **3aa** could be increased to 54% (Table 1, entry 5). To maximize the efficiency of this reaction, a variety of organic acids, such as acetic acid, benzoic acid, salicylic acid, 2-methylbenzoic acid, 2-chlorobenzoic acid, and TsOH, were screened as additives. When salicylic acid served as an additive, the yields of **3aa** and **4aa** were increased to 70% and 21%, respectively (Table 1, entries 6–11). The salicylic acid may act as a ligand to coordinate with copper to tune the redox potential of Cu(I)/Cu(II), which facilitates the corresponding oxidation process.[10] From this result, we further screened other reaction parameters to optimize the reaction conditions. This study led us to find that the highest reactivity and selectivity were obtained when the reaction was performed at 120 °C in the presence of 2.0 equiv of TBP (Table 1, entries 12–16). Finally, control reactions demonstrated that the coupling product **3aa** was not formed in the absence of a copper catalyst.

With the optimized reaction conditions identified, the scope of various aromatic enones **1** were explored at 120 °C under nitrogen using 5 mol % of $Cu(tfacac)_2$ as the catalyst, TBP as the oxidant, and 20 mol % salicylic acid as the additive. As summarized in Table 2, both electron-rich (**1b–1e**) and electron-deficient (**1f–1l**) aromatic enones are suitable

Table 2. Scope of Enones[a]



[a]Reaction conditions: **1** (0.4 mmol), TBP (2.0 equiv), $Cu(tfacac)_2$ (5 mol %), salicylic acid (20 mol %), and toluene **2a** (19.0 mmol) at 120 °C under N_2 for 24 h, isolated yield. [b]The reaction was performed for 36 h. [c]$Cu(tfacac)_2$ (20 mol %) was employed.

substrates for providing oxidative coupling products in moderate to good yields. Functional groups such as fluoride (**1f**), chloride (**1g-1j**), bromide (**1k**), alkyl (**1b-1d**), ether (**1e**), and nitro (**1l**) were well tolerated under the standard reaction conditions. The *β*-benzylated enones were also isolated as byproducts for some enones, but for substrates **1d**, **1e**, **1i**, **1j**, **1l**, and **1n**, only trace amounts of *β*-benzylated products were observed (see Supporting Information). In general, the aromatic enones with electron-deficient substituents displayed higher reactivity than those with electron-donating groups because they are much more electrophilic to be prone to reacting with the benzylic radical.[7] Notably, the substituents at the ortho position exert a positive effect on the reactivity and selectivity of the coupling reaction to give the corresponding products **3da** (89%), **3ia** (92%), and **3ja** (98%) in excellent yields. These results indicated that the steric-demand ortho substituents might prevent the benzyl carbon radical from attacking at the *β*-position of the aromatic enone to increase the regioselectivity.

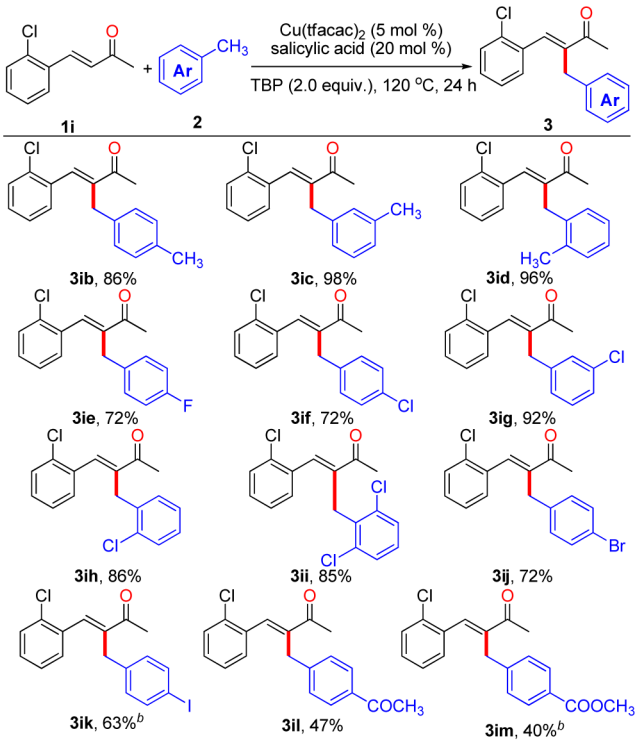
The product regiochemistry observed for the present cross-coupling is consistent with a radical addition pathway instead of metal-mediated typical Heck cross-coupling reaction mechanism because the benzyl carbon radical preferred being added to the *α*-position of the aromatic enone to generate a new benzyl-type carbon radical, which is much more stable than the *α*-carbonyl radical resulting from the addition of the benzylic carbon radical to the *β*-position of the enone.[11] Furthermore, the hexyl-substituted enone (**1m**) and isopropyl-substituted

DOI: 10.1021/acscatal.5b00310
ACS Catal. 2015, 5, 2882–2885

enone (**1n**) were transformed to the corresponding α-benzylated enones **3ma** and **3na** in good yields. Methyl cinnamate (**1o**) could be used as a substrate for this reaction, but a lower yield was obtained (28% yield).

After investigating the generality of this novel oxidative coupling reaction with regard to a series of aromatic enones **1** with toluene **2a**, various substituted toluenes **2** were then studied for the synthesis of diverse α-substituted aromatic enones **3**. The chlorine-containing enone **1i** was chosen as the coupling partner because only trace amount of β-benzylated enones could be formed in the presence of **1i** under the optimized conditions. As summarized in Table 3, electron-donating groups on any position of the phenyl ring favored the reaction, providing the corresponding adducts **3ib** (86%), **3ic** (98%), and **3id** (96%) in good to excellent yields. However, toluenes containing a group at the meta position gave the corresponding products with higher yields than those substituted at the ortho or para position. In general, electron-rich toluene presented higher reactivity than electron-poor substrates because the corresponding benzylic carbon radical is more nucleophilic so as to be prone to reacting with the aromatic enones. Moreover, functional groups, including fluoride, chloride, bromide, iodine, acetyl, and ester, on the aryl ring were well tolerated in this transformation. It is noteworthy that halo-substituted toluene reacted well, thus leading to halo-substituted products, which could be used for further transformations.

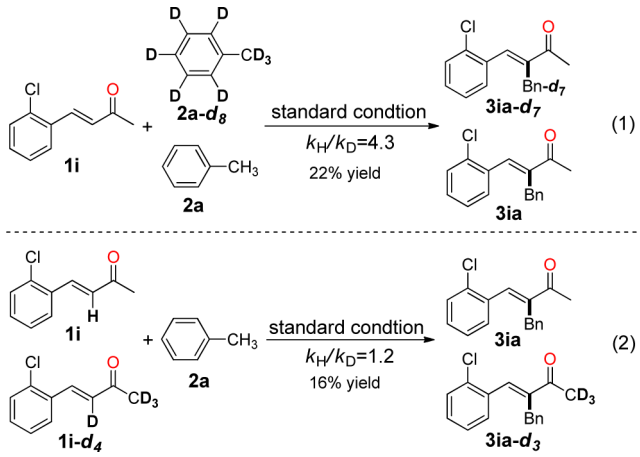
Table 3. Scope of Toluenes[a]



[a]Reaction conditions: **1i** (0.4 mmol), TBP (2.0 equiv), $Cu(tfacac)_2$ (5 mol %), salicylic acid (20 mol %), and toluene **2** (19.0 mmol) at 120 °C under N_2 for 24 h, isolated yield. [b]2.0 mL of benzene was used as solvent.

To gain insight into the mechanism of this novel transformation, control experiments were conducted under the optimized conditions. When radical scavengers, such as TEMPO or 1,1-diphenylethylene, were introduced into the standard reaction, no desired product **3aa** was obtained, which suggested that a free radical process was most likely involved (see Supporting Information). Moreover, the kinetic isotope effect experiments were conducted under the standard reaction conditions (Scheme 2; see also the Supporting Information).

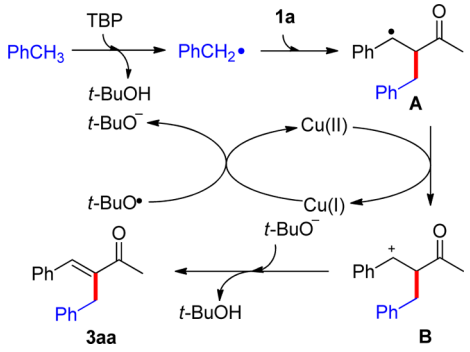
Scheme 2. Kinetic Isotope Effect Experiment



The competition reaction of **2a**-d_8 and **2a** revealed significant isotopic effects (k_H/k_D = 4.3), which indicated that the cleavage of the benzylic C(sp^3)−H bond might be involved in the rate-limiting step of this oxidative coupling. On the other hand, the competition reaction of **1i** and **1i**-d_4 gave little isotopic effects (k_H/k_D = 1.2) and indicated that the cleavage of the α-C−H bond of enones is a fast process.

On the basis of the results we obtained here and previously,[6] a tentative mechanism for this oxidative coupling was proposed, as shown in Scheme 3. First, homolytic cleavage of the TBP generated two alkoxyl radical intermediates, one of which abstracted a benzylic hydrogen atom of the toluene to produce the benzyl carbon radical, which was relatively stable in the reaction system. Next, the benzyl radical added to the substrate **1a**, providing radical intermediate **A**, which was oxidized by Cu(II) to form the cationic intermediate **B**. Finally, the intermediate **B** was deprotonated by the basic *t*-BuO^- to give the desired product **3aa**. The reduced Cu(I) was oxidized by another molecule of alkoxyl radical to regenerate Cu(II) to enter the next catalytic cycle.

Scheme 3. A Proposed Reaction Pathway for the Oxidative Coupling



DOI: 10.1021/acscatal.5b00310
ACS Catal. 2015, 5, 2882−2885

In summary, we have demonstrated a novel Cu-catalyzed direct implanting of a benzyl group into simple enones through nondirected C(sp^3)−H activation of toluene. Various α-substituted enones were efficiently constructed by cleavage of a C(sp^3)−H bond and a C(sp^2)−H bond under mild and neutral reaction conditions. This protocol not only extends the application of toluenes in synthetic organic chemistry but also offers an alternative method to prepare α-substituted enones, which are important structural units in a number of biological active compounds. The practical advantages of this protocol include the use of available starting materials (toluenes and enones) and the avoidance of any preliminary functionalization. Further investigations to apply this C−H bond activation strategy to other reactions are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00310.

Experimental details and full spectroscopic data for all new compounds (PDF)
CIF file for $C_{17}H_{16}O$ (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Chinese Academy of Sciences and the National Natural Science Foundation of China (21222203, 21372231, and 21133011).

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(9) CCDC 1041682 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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DOI: 10.1021/acscatal.5b00310
ACS Catal. 2015, 5, 2882−2885