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## COMMUNICATION

## Copper-catalyzed decarboxylative $C(sp^2)-C(sp^3)$ coupling reactions *via* radical mechanism<sup>†</sup>

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We have successfully developed an example of copper-catalyzed decarboxylative  $C(sp^2)$ – $C(sp^3)$  coupling reactions *via* C–H functionalization for the first time. It is noteworthy that our catalytic system is very stable, low-cost, palladium-free, ligand-free, and easily accessible.

In the last few decades, radical reactions have been used as powerful tools for C-C bond formation in synthetic chemistry.<sup>1</sup> In this area, carbon radicals, such as aryl, benzyl, acyl, and carbamoyl radicals, are useful active intermediates. In general, the key step in all of these reactions is the addition (or cyclization) of a radical to a multiple bond. Recently, Shi,<sup>2a</sup> Shirakawa/ Hayashi,<sup>2b</sup> and Kwong/Lei<sup>2c</sup> have reported on the construction of biaryl compounds from unactivated aromatic rings through homolytic radical aromatic substitution (HAS).<sup>2</sup> Many methods for the generation and reaction of acyl radicals have been reported.<sup>3</sup> Formation of acid amides and their derivatives via carbamoyl radicals was proved an effective way.<sup>4</sup> It could be easily found that most free radicals are generated from halides,<sup>1,5a</sup> hydrazines,<sup>5b,c</sup> ozonides,<sup>5d</sup> carboxylic acids<sup>5e</sup> and phosphites,<sup>5f</sup> but examples of the generation of free radicals from alkanes and arenes are somehow limited.5g,h

Recently, another powerful tool for C–C bond formation is the decarboxylative couplings.<sup>6</sup> In 2006, Goossen and co-workers reported an alternative way to prepare biaryls by decarboxylative coupling between aryl halides and carboxylic acids.<sup>7c</sup> Since then, there have been several more reports of decarboxylative couplings of carboxylic acids or their salts.<sup>7</sup> We, in view of this, wish to develop a monometallic catalytic system to achieve decarboxylative C–H functionalization. Here we report a copper-catalyzed decarboxylative C(sp<sup>2</sup>)–C(sp<sup>3</sup>) coupling of cinnamic acids with arenes (Scheme 1).

After screening various catalytic conditions (see ESI<sup>†</sup>), the scope of the reaction with a variety of cinnamic acids **1** bearing electron-withdrawing and donating substituents was investigated (Table 1). Generally, moderate to good yields of the desired



**Scheme 1** Strategy of coupling *via* decarboxylative olefination of sp<sup>3</sup> C–H bonds.

Table 1Copper-catalyzed decarboxylative  $C(sp^2)-C(sp^3)$  coupling ofdifferent cinnamic acids 1 with  $2a^{\prime\prime}$ 







<sup>*a*</sup> Catalytic conditions: Cinnamic acid (1) (0.3 mmol), arene (2a) (2 mL), CuO (10 mol%), DTBP (2 equiv.), 110 °C, 24 h, Ar. <sup>*b*</sup> Isolated yield based on cinnamic acid. <sup>*c*</sup> Determined by <sup>1</sup>H NMR.

products were obtained (entries 1–9). It is noteworthy that the configuration of the double bond could be well retained. We also can see that the electron-releasing methoxyl group (**3d**) at the *para*-position is favorable for the coupling reaction compared with the electron-withdrawing Cl or F group (**3b** and **3c**) (entry 4 *vs*. entries 2–3). For the same substituted cinnamic acids, *ortho*- and *meta*- positions afforded the corresponding products in slightly

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou, 215123, P. R. China. E-mail: jcmao@suda.edu.cn † Electronic supplementary information (ESI) available: Experimental procedures, <sup>1</sup>H, <sup>13</sup>C, HRMS spectral data and analytical data for the products. CCDC 870917. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc33203e





<sup>a</sup> Catalytic conditions: 4-methoxylcinnamic acid (1d) (0.3 mmol), arene (2) (2 mL), CuO (10 mol%), DTBP (2 equiv.), 110 °C, 24 h, Ar.
<sup>b</sup> Isolated yield based on cinnamic acid. <sup>c</sup> Determined by <sup>1</sup>H NMR.

decreased yields (**3e** and **3f**) (entries 5–6). 3-Methylcinnamic acid gave the desired product in 60% yield (entry 7). However, the coupling reaction with 4-nitrocinnamic acid was unsuccessful (**3j**) (entry 10). When more OMe groups were introduced into the aromatic ring of cinnamic acid, the decarboxylative coupling could also be performed efficiently (entries 8–9).

Subsequently, the scope of benzylic hydrocarbons was investigated (Table 2). Moderate to good yields were obtained for several products (entries 1–14). Different xylenes and mesitylene only yielded mono-coupling products (**4b**, **4c**, **4d**, and **4e**) (entries 1–4). The relative configuration of **4b** was confirmed by X-ray diffraction, it showed that our method could retain the original double-bond configuration well (Fig. 1). Direct decarboxylative coupling of **1d** with ethylbenzene was also successful (**4f**) (entry 5). Moreover, cinnamic acid could also react with *tert*-butylbenzene to afford the desired product accompanied by phenyl migration (**4g**) (entry 6). It is important to note that chlorine, bromine and even iodine groups are tolerated in this process (**4h**, **4i**, **4j**, **4k**, **4l**, and **4m**) (entries 7–12).



Fig. 1 X-Ray of 4b



Scheme 2 Copper-catalyzed coupling of 1d with other compounds containing sp<sup>3</sup> C–H bonds.

These valuable functional groups allow for further functionalization. Methyl substituted naphthalenes also showed good activity in this process (4n and 4o) (entries 13–14).

Subsequently, anisole was employed as the substrate in the decarboxylative reaction. The desired product was obtained in 36% yield as shown in Scheme 2. When cyclohexene was investigated, the allylic oxidation product **4q** was acquired in a yield of 66%.

In view of the results above, *n*-propylbenzene, *n*-butylbenzene and methylcyclohexane were employed as the substrates for the couplings with 4-methoxylcinnamic acid as shown in Scheme 3. For *n*-propylbenzene, the two possible desired products were obtained with a total yield of 70%. More involved was the easier activated benzyl carbon. For *n*-butylbenzene which has three methylene groups, three possible products were obtained as expected. Here, a similar regioselectivity was found, since the product from C–H functionalization that is close to the benzene ring was predominantly obtained, with 39% yield. For methylcyclohexane, two possible products were acquired with a total yield of 66%, and the methyl moiety is primarily employed.

To gain more understanding of this reaction, we have preformed some additional experiments in the presence of radical scavengers. The results showed that TEMPO, AIBN or BQ (1 equiv.) completely inhibited the reaction (see ESI<sup>†</sup>), which suggests that the transformation may proceed *via* a radical reassembly.

In addition, we also investigated isotope effect: when toluene was replaced with [D8]-toluene, product [D]-**3d** was achieved in low yield. However, no hydrogen-incorporated product was observed (Scheme 4a). In the absence of cinnamic acid, the self-coupling of toluene was observed (Scheme 4b).<sup>8</sup> Because it has been suggested that reactions involving DTBP usually proceed *via* a *tert*-butyl oxygen intermediate,<sup>8</sup> we replaced **1d** with styrene butyl ether (**5**). However, no **3d** product was observed (Scheme 4c), which suggests that the postulated *tert*-butyl oxygen intermediate does not exist in the present coupling process. Moreover, a KIE of 3.0 was determined, which supports the notion that the C–H bond cleavage is rate limiting (Scheme 4d).

Based on previous observations and literature reports,<sup>9,10</sup> we proposed a plausible catalytic cycle (Scheme 5). The catalytic cycle starts with abstraction of H from toluene by *t*-BuO<sup>•</sup> to give radical **A**. The radical could be further oxidized to a benzyl cation through a single-electron transfer process assisted by a Cu(II) ion. Subsequently, addition of a benzyl cation to the  $\alpha$ -position of the



Scheme 3 Copper-catalyzed oxidative decarboxylative  $C(sp^2)-C(sp^3)$  coupling of 1d with other compounds containing  $sp^3$  C–H bounds.



Scheme 4 Investigation into the reaction mechanism.



Scheme 5 Proposed mechanism for the decarboxylative coupling.



Scheme 6 Further synthetic functionalizations of 6.

double bond in cupric cinnamate **B**, which is generated by the reaction of cinnamic acid with cupricoxide, would give a steady intermediate **C**. **C** then proceeds *via* an elimination of carbon dioxide and Cu(1) to generate the product. Then oxidation of Cu(1) by a *t*-BuO<sup>•</sup> radical in the presence of cinnamic acid would regenerate the cupric cinnamate **B** to complete the catalytic cycle.<sup>11</sup>

We next set out to further functionalize the halogenated product. We obtained a moderate yield of **6** on a 10 mmol scale. Then we investigated the C–C and C–N bond formation of **6** with other coupling partners (Scheme 6). The Suzuki coupling of **6** with phenylboronic acid afforded the corresponding product **7** with good yield, using Pd–Cy JohnPhos system. Furthermore, we were pleased to see that under unoptimized conditions, the amination of **6** with morpholine gave the desired product **8** in 88% yield.<sup>12</sup>

In summary, a novel copper-catalyzed decarboxylative  $C(sp^2)-C(sp^3)$  coupling reaction of cinnamic acids with benzylic molecules was developed using di-*tert*-butyl peroxide as oxidant under neutral conditions.

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