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Highly Selective β-Hydride Elimination in Pd-Catalyzed Decarboxylative Heck-Type Reaction

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ABSTRACT

A variety of β-aryl ketones and aldehydes were facilely synthesized via a Pd(II)/Ag_2CO_3-mediated decarboxylative Heck type reaction between readily available benzoic acid derivatives and allylic alcohols under mild conditions. The control experiments indicated that this transformation may proceed via a hydrogen migration process.

Recently, the oxidative cross-coupling reaction has attracted increasing interest,[1] especially the oxidative Heck-type reaction.[2−5] Due to the instability of traditional carbon nucleophiles (CNs) originating from organometallic reagents,[6] the discovery of new and efficient carbon nucleophiles (CNs) for oxidative cross coupling reactions is of significant importance. Among those, the C−H activation step has been the most direct and atom-economic strategy to form CNs.[7] A variety of aromatic compounds can be employed as arene nucleophiles, and high levels of site selectivity are possible for the substrates containing directing groups.[8] Despite the above illustrated advances, the substrates scope of C−H activation for simple aromatics that do not contain directing groups remains primarily limited to electron-rich derivatives. The electron-deficient

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† L.H. and J.Q. contributed equally to this work.

(1) For selected reviews on oxidative cross-coupling reactions: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (f) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170.

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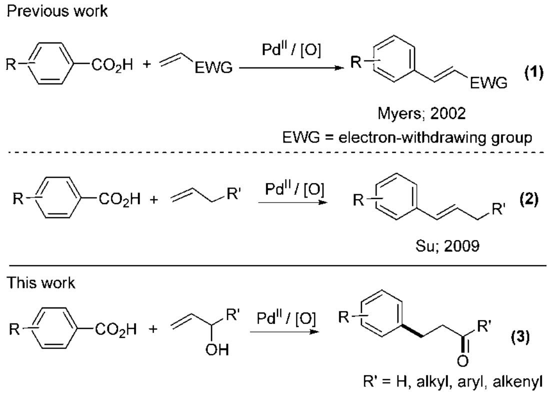
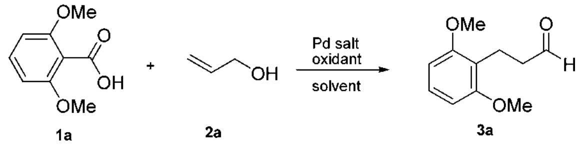
arenes exhibit sluggish reactivity of C−H activation. Decarboxylation provids a complementary approach to obtain carbon nucleophiles (CNs).[9,10] Carboxylates and a series of variants are cheap and easy to obtain substrates for cross-coupling reactions.



In 2002, Myers reported the first example of the decarboxylative Heck-type reaction. However, the alkenes were limited to the active olefins such as α,*β*-unsaturated olefins and styrene (eq 1).[10a] In 2009, Su reported a decarboxylative Heck-type reaction using the electronically nonbiased olefins as the substrates (eq 2).[10d,e] Herein, we directly utilized allylic alcohols as coupling partners with benzoic acids as the carbon nucleophils to obtain *β*-aryl ketones and aldehydes (eq 3).[11]

The inspection of the coupling reaction between 2,6-dimethoxybenzoic acid (**1a**) and allyl alcohol (**2a**) was chosen as a model reaction for the optimization studies (Table 1). Initially, we examined the feasibility of this model reaction using the reaction conditions, which were previously established for the decarboxylative Heck reaction. Gratifyingly, when the reaction of **1a** with 1.2 equiv of **2a** was conducted in a DMSO/toluene (1:20) solvent system at 100 °C in the presence of 5 mol % of Pd(OAc)$_2$ and 1 equiv of Ag$_2$CO$_3$, the yield of the desired product **3a** was 83% (entry 1).[10d,e] Pd(TFA)$_2$ (5 mol %) could slightly increase the yield of the product (entry 2). Further investigation of the oxidants led to the discovery that Ag$_2$CO$_3$ was the best oxidant for this transformation (entries 3−5). In contrast to DMSO/toluene (1:20) solvent system, the use of more polar solvents, such as DMSO/DMF (1:20) and dioxane, resulted in a decreased yield of **3a** with amount of the protodecarboxylation byproduct formed (entries 6 and 7). It might be because decarboxylation was too fast in polar solvent. The reactivity decreased if the reaction temperature was elevated or decreased (see the Supporting Information for details), and the oxidative dehydration of **3a** could be detected when 2 equiv of Ag$_2$CO$_3$ was used or when this reaction went through under air (entries 8 and 9).[12]

Table 1. Impact of Reaction Parameters[a]



entry	catalyst	oxidant	solvent v/v	yield[b] (%)
1	Pd(OAc)$_2$	Ag$_2$CO$_3$	DMSO/toluene =1:20	83
2	Pd(TFA)$_2$	Ag$_2$CO$_3$	DMSO/toluene =1:20	85 (81)
3	Pd(TFA)$_2$	Ag$_2$O	DMSO/toluene =1:20	61
4	Pd(TFA)$_2$	AgOAc	DMSO/toluene =1:20	76
5	Pd(TFA)$_2$	O$_2$ (1 atm)	DMSO/toluene =1:20	NR
6	Pd(TFA)$_2$	Ag$_2$CO$_3$	DMSO/DMF = 1:20	46
7	Pd(TFA)$_2$	Ag$_2$CO$_3$	DMSO/dioxane =1:20	37
8[c]	Pd(TFA)$_2$	Ag$_2$CO$_3$	DMSO/toluene =1:20	59
9[d]	Pd(TFA)$_2$	Ag$_2$CO$_3$	DMSO/toluene =1:20	80(75)

[a] Reactions were carried out under N$_2$, with **1a** (0.5 mmol), **2a** (1.2 equiv), Ag$_2$CO$_3$ (0.5 mmol), Pd(II) (0.025 mmol), solvent (3 mL), 100 °C. [b] Determined by GC using dodecane as the internal standard. The yield of isolated product is shown in parentheses. [c] Ag$_2$CO$_3$ (1 mmol) was used. [d] Under air.

With the optimized conditions in hand, we started employing other substrates to this Pd-catalyzed Heck-type reaction. First, various aryl-substituted allylic alcohols were employed to couple with 2,6-dimethoxybenzoic acid (Scheme 1). A series of *para*-substituted 1-phenylprop-2-en-1-ols, including some with electron-donating groups (R′ = Me, OMe) and some with electron-withdrawing groups (R′ = F, Cl, CF$_3$), were converted into the corresponding *β*-aryl ketones in moderate yields (Scheme 1, **3b−g**). Other substituted 1-phenylprop-2-en-1-ols were also suitable substrates for this transformation to afford the corresponding products **3h−j** in good yields. To our delight, the furan-substituted allyl alcohol was tolerated in

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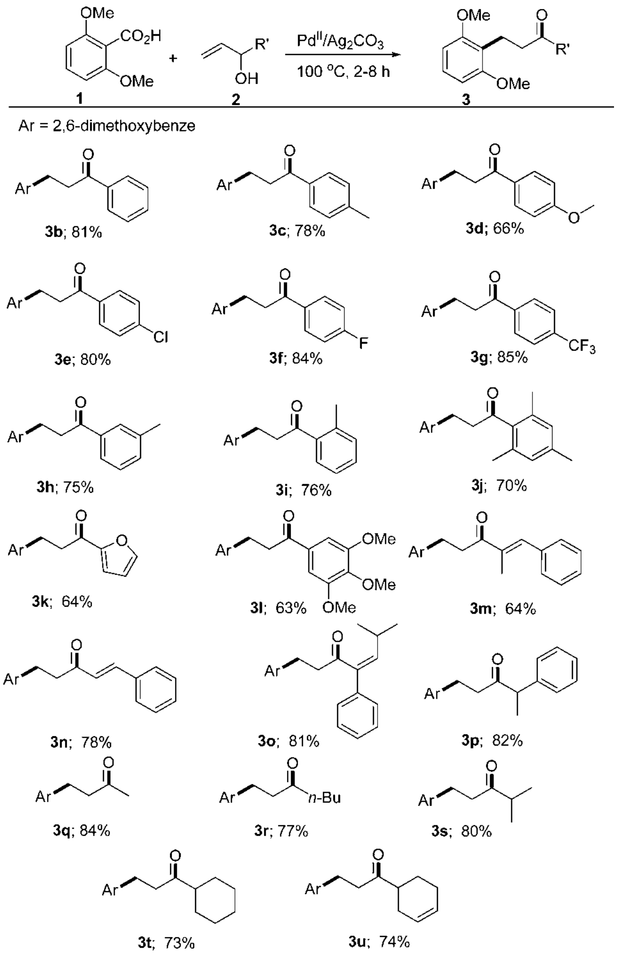
this transformation (Scheme 1, **3k**). And α′-unsaturated β-aryl ketones were facilely obtained when 2,6-dimethoxybenzoic acid coupled with the allyilc alcohols which were synthesized from cinnamaldehyde derivatives (Scheme 1, **3m**–**o**). The alkyl-substituted allyl alcohols were similarly found to be suitable substrates for this transformation and gave the desired products in good yields (Scheme 1, **3p**–**t**). The sole chemical selectivity could be obtained when the substrate containing more than one C–C double bonds (Scheme 1, **3u**).

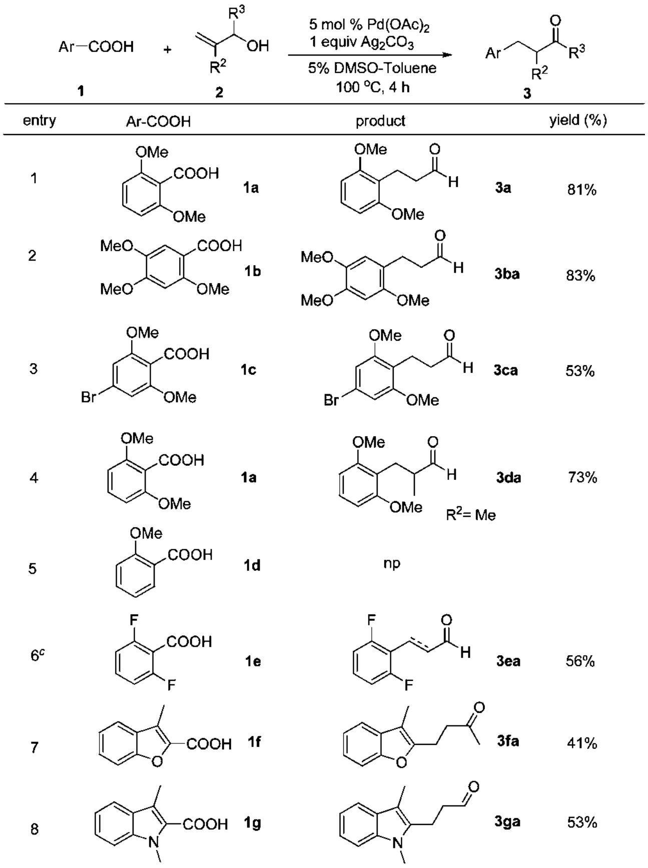
Scheme 1. Scope of Allyl Alcohols[a,b]



[a] Reactions were carried out under N_2 with **1a** (0.5 mmol), **2** (1.2 equiv), Ag_2CO_3 (0.5 mmol), $Pd(TFA)_2$ (0.025 mmol), DMSO/toluene = 1:20 (3 mL), 100 °C. [b] Isolated yield.

Then some other *o*-OMe-substituted benzoic acids proceeded well, coupling with allyl alcohol to give the corresponding β-aryl aldehydes (Scheme 2, **3ba**–**ca**). This transformation was compatible with alkenes that contained Br-substituted aryl rings, which could undergo a Heck-type reaction with themselves under Pd catalysis, but in this case did not (Scheme 2, **3ca**). And 2-methylprop-2-en-1-ol could be also transformed to the desired α-methyl-β-aryl aldehyde (Scheme 2, **3da**) Unfortunately, 2-methoxybenzoic acid was not a suitable substrate for this reaction, possibly because of electronic and steric effects, which was consistent with the significant limitation for decarboxylative coupling reaction.[9,10] In addition, the benzoic acid containing electron-withdrawing group could convert to the corresponding product and dehydrogen product (5:1) in 120 °C (Scheme 2, **3ea**). To our delight, this transformation was also suitable for the heterocyclic acids (Scheme 2, **3fa**–**ga**).

Scheme 2. Scope of Benzoic Acids[a–c]



[a] Reactions were carried out under N_2 with **1** (0.5 mmol), **2** (1.2 equiv), Ag_2CO_3 (0.5 mmol), $Pd(TFA)_2$ (0.025 mmol), DMSO/toluene = 1:20 (3 mL), 100 °C. [b] Isolated yield. [c] 120 °C.

Encouraged by these promising results, we further performed D-labeled experiments. 2, 6-Dimethoxybenzoic acid was employed to couple with D-1-phenylprop-2-en-1-ol under the standard conditions (eq 4). It was as expected that α-D-β-aryl ketone was the sole product and **3b** could not be detected (for details, see the Supporting Information).[11a] Subsequently, no D-labeled product could be detected when 0.2 mL of D_2O was added under

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(13) Examples for quenching the C–Pd^{II} bond by protonolysis: (a) Zhao, L.; Lu, X. *Org. Lett.* **2002**, *4*, 3903. (b) Lin, S.; Lu, X. *Org. Lett.* **2010**, *12*, 2536. (c) Peng, H.; Liu, G. *Org. Lett.* **2011**, *13*, 772. (d) Chen, J.; Lu, X.; Lou, W.; Ye, Y.; Jiang, H.; Zeng, W. *J. Org. Chem.* **2012**, *77*, 8541.

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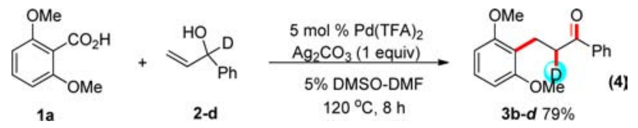
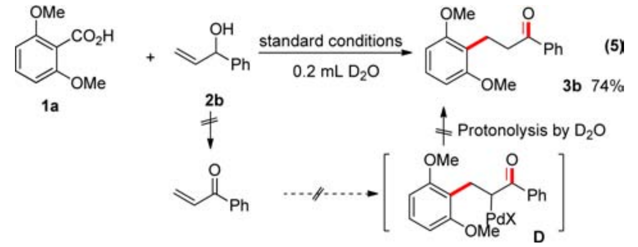
the standard conditions (eq 5). It indicated that **3b** was not formed via the protonolysis of intermediate **D** by D_2O.[13]

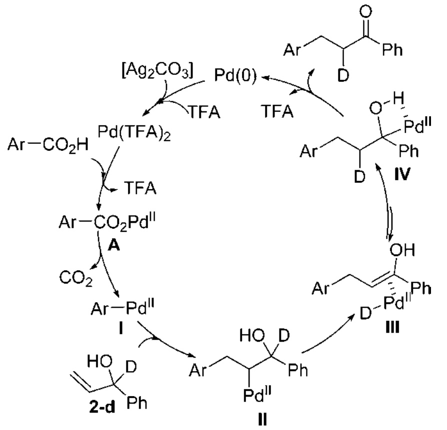




On the basis of the above results, a tentative mechanism for the Pd-cataylzed oxidative Heck-type reaction of benzoic acids with allylic alcohols to synthesize β-aryl ketones and aldehydes was proposed (Scheme 3). When benzoic acids were used as the substrates, the arylpalladium species **I** was formed through the loss of carbon dioxide from intermediate **A**. And then it inserted into the allylic alcohol to afford intermediate **II**. The selective β-H elimination from intermediate **II** generated Pd(II) species **III**, followed by HPdX species inserting into the enol to generate the critical intermediate **IV**. This process realized the hydrogen transfer, just like the oxidative Wacker process.[11a,14,15] And then the desired products would be obtained through two controversial approaches: β-H elimination from α-OH groups or the anion-mediated reductive elimination.[16] Finally, Pd^{II} active species was regenerated by the oxidation of Ag_2CO_3.

In conclusion, we have developed a simple and efficient method for the Pd-catalyzed oxidative Heck reaction of benzoic acids with allylic alcohols to construct β-aryl ketones and aldehydes through hydrogen migration. Several substituted benzoic acids and a series of allylic alcohols were found to be suitable substrates for this transformation. This work opens up a new approach to realize the selective β-H elimination in Pd-catalyzed oxidative Heck reactions. Tentative mechanistic studies indicated that the hydrogen transfer might go through the Wacker oxidative process, and it would be a significant model for the mechanism study of Wacker oxidation. Further studies into the use of aryl−H as the source of aryl nucleophile, as well as more mechanistic investigations, are underway in our laboratory.

Scheme 3. Plausible Reaction Mechanism



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Supporting Information Available. Experimental procedure and characterization of compounds **3a−ga**. This material is available free of charge via the Internet at http://pubs.acs.org

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[16] Another possible mechanism for this transformation can not be excluded completely, that is the isomerization of PhCH=CHCH(OH)R to $PhCH_2CH_2C(=O)R$ in the presence of palladium catalyst. Thanks to one reviewer proposing it for us. And the controlled experiment was conducted in the Supporting Information.

The authors declare no competing financial interest.