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Pd-Catalyzed Cross-Coupling of Aryl Carboxylic Acids with Propiophenones through a Combination of Decarboxylation and Dehydrogenation

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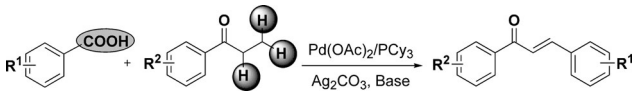
Carboxylic acids are valuable as starting materials in synthetic chemistry, because of their low cost, wide diversity, and ready availability.[1] Under transition-metal catalysis, organometallic intermediates, generated by extrusion of CO_2 from carboxylic acids, undergo cross-coupling reactions with other organic compounds, which represents a promising strategy to form carbon–carbon[2–5] and carbon–heteroatom bonds.[6] The development of new decarboxylative cross-coupling reactions is vital for the realization of the potential of carboxylic acids to serve as versatile starting materials. In this regard, the combination of two newly emerging fields in chemistry, decarboxylative cross-coupling and C–H functionalization, would offer new transformations and expand the application of carboxylic acids in organic synthesis.



Herein, we report a palladium-catalyzed cross-coupling reaction of aryl carboxylic acids with saturated propiophenones through a combination of decarboxylation and dehydrogenation to form Heck-type products [Eq. (1)], and we also present a one-pot procedure involving this reaction that enables the facile synthesis of quinoline derivatives from 2-nitrobenzoic acids. Our findings not only provide a complementary method for the synthesis of chalcones, which are an important class of biologically active compounds[7] (Figure 1, **A**) and synthetically useful intermediates in the formation of complex compounds, including natural products[8] (Figure 1, **B**), but also demonstrate that the in situ dehydrogenation of saturated substrates to the corresponding olefins is a potentially useful strategy to streamline organic synthesis.

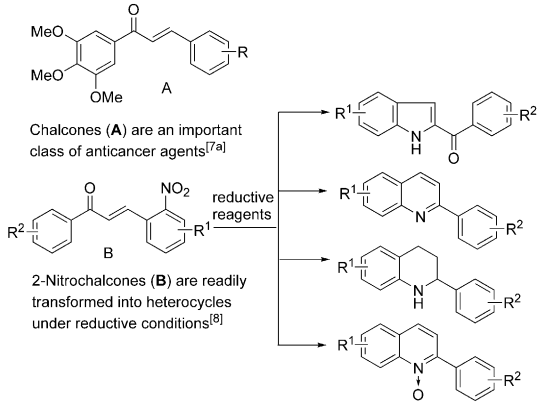


Figure 1. Examples illustrating the importance of chalcones.

Since the decarboxylative Heck-type cross-coupling of benzoic acids with olefins was reported by Myers and coworkers, progress has been made toward improving the efficiency and practicability of this reaction and expanding its substrate scope.[3] Consequently, this decarboxylative Heck-type reaction has been applied to a variety of olefins, including unactivated alkyl-substituted olefins and cyclic α,β-unsaturated ketones. However, no examples of using acyclic aryl vinyl ketones in decarboxylative Heck-type reactions have been reported, in part, because these olefins are not commercially available.[9] Usually, the preparation of α,β-unsaturated carbonyl compounds starts from the corresponding saturated carbonyl compounds and requires two or more synthetic steps, such as a Pd^{II}-mediated dehydrosilylation of silyl enol ethers (Saegusa oxidation)[10] and a halogenation–dehalogenation sequence.[11] The Pd-catalyzed aerobic oxidative dehydrogenation of ketones represents a promising method for the facile synthesis of α,β-unsaturated ketones, but is still limited to cyclic enones or β-arylated enones.[12] Our interest in decarboxylative cross-coupling and C–H functionalization led us to consider whether the in situ dehydrogenation of saturated ketones to enones can be coupled with the decarboxylative cross-coupling process to form the Heck-type product. The realization of such a sequence in a tandem fashion would offer a straightforward and highly efficient synthetic method, because of the avoidance of the troublesome synthesis of enones. Although extremely rare,[13] the coupling of an in situ formed dehydrogenated reactive intermediate with a second reaction process proved

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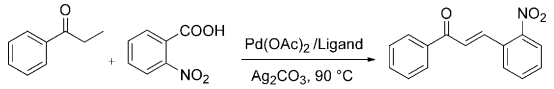
to be a viable approach for the rapid construction of complex molecules from simple starting materials.

We initiated our investigation by studying the reaction of propiophenone (**1a**) with 2-nitrobenzoic acid (**2a**) under a variety of reaction parameters (Table 1). In the presence of Ag_2CO_3, additional bases were observed to have an effect on the reaction outcome depending on the nature of the base (entries 4–10), presumably, because bases play a key role in the formation of the Pd-enolate intermediate that is supposed to be the precursor to enones. Relatively weak bases, such as carboxylate salts, facilitated this reaction and the effect of the bases was a function of their solubility (entries 4–7), while strong bases, such as K_3PO_4 and K_2CO_3, shut down the reaction completely. The simultaneous use of carboxylate salts (2 equiv) and equimolar carboxylic acids significantly improved the yield of **3a** (entry 11 vs. 5 and entry 13 vs. 7), although the use of acetic acid alone was ineffective for the reaction. The complex of tetrabutylammonium acetate and acetic acid gave a similar result (entry 16). The beneficial effect of acetic acid may stem from the acid-promoted separation of the ion pair $[n\mathrm{Bu_4N}]^+[\mathrm{OAc}]^-$[14] and the acid-promoted enolization of ketones. The choice of phosphine ligands was also crucial for achieving this reaction. When phenyl-substituted phosphines, such as PPh_3, Davephos (Davephos = 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl) and Xphos (Xphos = 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl), and sterically bulky $t\mathrm{Bu_3P}$, were used as supporting ligands, no reaction occurred (entries 17–21). Less sterically hindered phosphines, such as $\mathrm{PCp_3{\cdot}HBF_4}$ (Cp = cyclopentyl) and $i\mathrm{Pr_3P{\cdot}HBF_4}$, were observed to be as efficient as PCy_3 (Cy = cyclohexyl; entries 22 and 23).

Table 1. Optimization studies for the decarboxylative olefination reaction.[a,d]



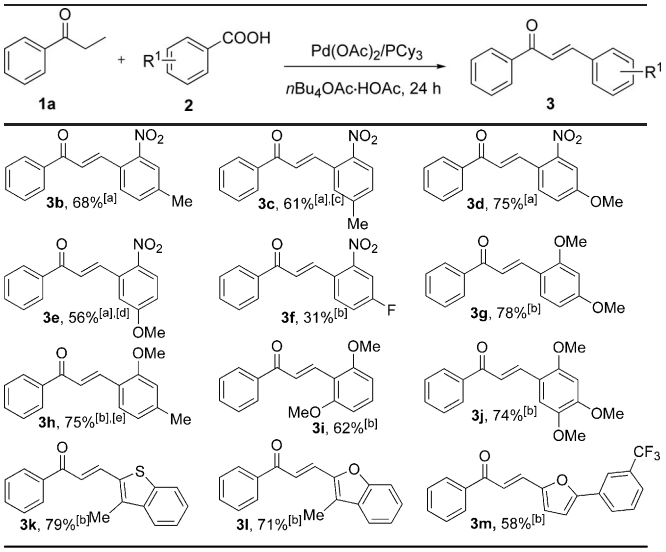
1a 2a 3a

Entry	Ligand	Base ([equiv])	Acid ([equiv])	Yield of **3a** [%] [b]
1	–	–	–	6
2	PCy_3	–	–	10
3	–	KOAc (2)	–	12
4	PCy_3	KOAc (2)	–	31
5	PCy_3	PivOk (2)	–	49
6	PCy_3	Me_4NOAc (2)	–	66
7	PCy_3	$n\mathrm{Bu_4NOAc}$	–	44
8	PCy_3	K_2CO_3 (2)	–	0
9	PCy_3	K_3PO_4 (2)	–	0
10	PCy_3	Ph_3N (2)	–	0
11	PCy_3	PivOk (2)	PivOH (2)	67
12	PCy_3	Me_4NOAc (2)	HOAc (2)	69
13	PCy_3	$n\mathrm{Bu_4NOAc}$ (2)	HOAc (2)	73
14	PCy_3	–	HOAc (2)	12
15	PCy_3	$n\mathrm{Bu_4NOAc}$ (1.7)	HOAc (1.7)	76
16	PCy_3	$n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7)		75[c]
17	PPh_3	$n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7)		0
18	dppe	$n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7)		0
19	Davephos	$n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7)		0
20	Xphos	$n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7)		0
21	$t\mathrm{Bu_3P}$	$n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7)		0
22	$\mathrm{PCp_3{\cdot}HBF_4}$	$n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7)		79
23	$i\mathrm{PrP_3{\cdot}HBF_4}$	$n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7)		76
24	$t\mathrm{Bu_2MeP{\cdot}HBF_4}$	$n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7)		54

[a] Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (3.0 equiv), $Pd(OAc)_2$ (15 mol%), ligand (30 mol%), Ag_2CO_3 (2.5 equiv), DMF (1 mL), 90°C, 24 h. [b] GC yield. [c] 71% isolated yield. [d] The α-arylated product was not detected. dppe = 1,2-Bis(diphenylphosphino)ethane.

After identifying the factors influencing the reaction outcome, we next evaluated the substrate scope of this reaction with respect to aromatic carboxylic acids by using the reaction conditions of entry 16 in Table 1 ($Pd(OAc)_2$ (15 mol%), PCy_3 (30 mol%), Ag_2CO_3 (2.5 equiv), $n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7 equiv), DMF, 90°C, 24 h). Considering that the electronic nature of substituents on the benzene ring have a remarkable influence on the acidity and decarboxylation rate of benzoic acids, we reasoned that the reaction conditions needed to be adjusted for different benzoic acids to achieve efficient transformation. We were pleased to find that slight modifications of the standard reaction conditions enabled the use of a variety of benzoic acids to produce chalcones (Table 2). 2-Nitrobenzoic acids bearing a variety of additional substituents afforded generally good yields. In some cases, $Cu(OAc)_2$ or CuF_2 was found to be more efficient than Ag_2CO_3 for the decarboxylative cross-coupling process, especially, when electron-rich and heterocyclic carboxylic acids were used.

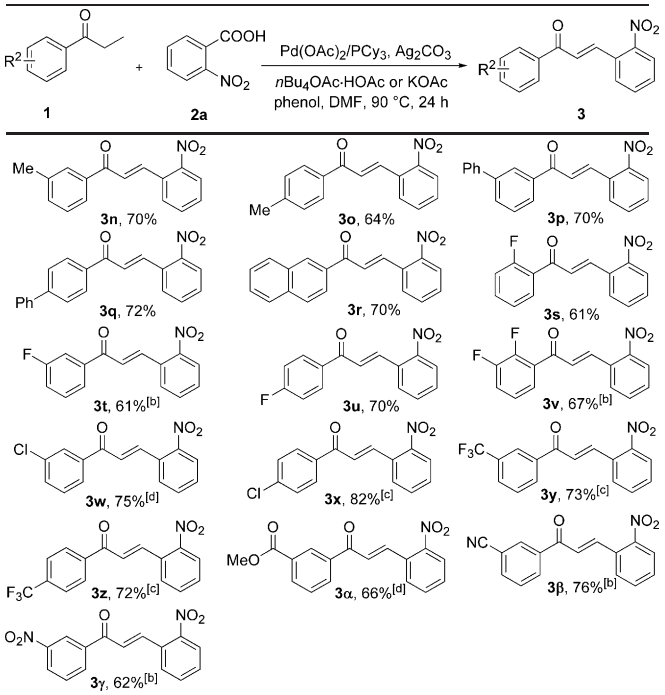
Table 2. Scope of aryl carboxylic acids.[a,f,g]



[a] Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2** (3.0 equiv), $Pd(OAc)_2$ (15 mol%), PCy_3 (30 mol%), Ag_2CO_3 (2.5 equiv), $n\mathrm{Bu_4NOAc{\cdot}HOAc}$ (1.7 equiv), DMF (1 mL), 90°C, 24 h. [b] $Cu(OAc)_2$ (2.5 equiv), DME (DME = dimethyl ether; 1 mL), 90–140°C. [c] 5-Methyl-2-nitrobenzoic acid (4 equiv) was used. [d] 80°C. [e] CuF_2 (2.5 equiv) was used. [f] Isolated yield. [g] When non-*ortho*-substituted benzoic acids were used, the final chalcones were not obtained.

We further investigated the compatibility of functional groups on the propiophenones (Table 3). Under the stan-

Table 3. Scope of propiophenones.[a,e]

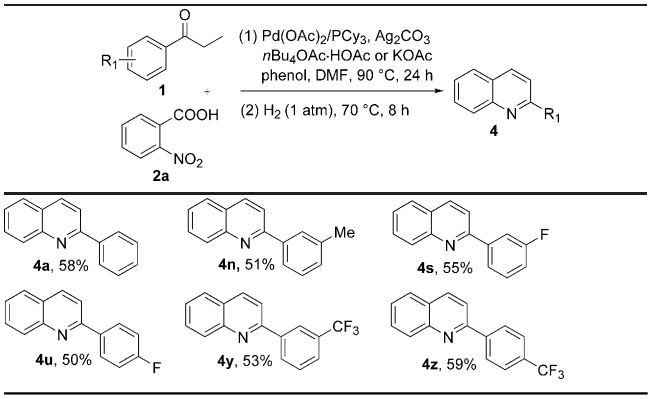


[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), **2a** (3.0 equiv), $Pd(OAc)_2$ (15 mol%), PCy_3 (30 mol%), Ag_2CO_3 (2.5 equiv), $nBu_4OAc{\cdot}HOAc$ (1.7 equiv), phenol (15 mol%), DMF (1 mL), 90°C, 24 h. [b] KOAc (1.5 equiv) was used. [c] KOAc (1.5 equiv) was used in the absence of phenol. [d] KOAc (1.0 equiv) was used in the absence of phenol. [e] Isolated yield.

dard reaction conditions, methylpropiophenone or phenylpropiophenone generated the corresponding products in moderate yields, while only traces of product were detected when 3-nitropropiophenone was used. These observations indicated that the substituents on the benzene ring of propiophenones had a profound effect on the cross-coupling reaction, presumably, because the α-H acidity varies as the substituents change. In regard of this, adequate acids or bases needed to be used to obtain satisfying yields. When adding a catalytic amount of phenol[15] to the reaction system, methylpropiophenone, phenylpropiophenone, ethyl naphthyl ketone, 2′-fluoropropiophenone, and 4′-fluoropropiophenone underwent the dehydrogenative cross-coupling reaction with 2-nitrobenzoic acid to afford the desired products in good yields (**3n–s** and **3u**). Replacing $nBu_4NOAc{\cdot}HOAc$ with less soluble KOAc afforded good yields for the reactions of propiophenones bearing electron-withdrawing groups under otherwise identical conditions (**3t** and **3v–3γ**). As such, this reaction is compatible with ester, cyano, nitro, trifloromethyl, fluoro, chloro, alkenyl, and phenyl substituents.

A one-pot procedure for the synthesis of 2-substituted quinolines from 2-nitrobenzoic acid with propiophenones was also developed (Table 4). At the end of the cross-coupling reaction of carboxylic acids with propiophenones, hydrogen gas (1 atm) was introduced to the reactor vessel. Under the coaction of hydrogen gas and the palladium species from the decarboxylative cross-coupling step, 2-substituted quinolines were obtained as selective hydrogenative cyclization products in synthetically useful yields after 8 h at 70°C. This result differs from the Pd/C, H_2 catalyst system, which affords mainly the 2-substituted 1,2,3,4-tetrahydroquinolines.[8c]

Table 4. One-pot synthesis of 2-substituted quinoline derivatives by decarboxylative cross-coupling and in situ reductive cyclization.[a]



[a] Isolated yield.

In summary, a new Pd-catalyzed cross-coupling reaction of carboxylic acids with saturated propiophenones that proceeds through the combination of decarboxylation and dehydrogenation has been developed. This protocol shows a good functional group tolerance, which can be ascribed to the identification of adequate bases or acids for different substrates. Furthermore, a one-pot procedure for the synthesis of 2-substituted quinolines has been established that involves the cross-coupling reaction of carboxylic acids with saturated propiophenones and a subsequent selective hydrogenative cyclization process.

Experimental Section

General procedure: In a glove box, a 25 mL tube equipped with a stir bar was charged with $Pd(OAc)_2$ (0.0068 g, 0.03 mmol, 15 mol%), PCy_3 (0.0168 g, 0.06 mmol, 30 mol%), propiophenone (0.0268 g, 0.2 mmol, 1 equiv), 2-nitrobenzoic acid (0.1002 g, 0.6 mmol, 3 equiv), Ag_2CO_3 (0.1379 g, 0.5 mmol, 2.5 equiv), and $nBu_4NOAc{\cdot}HOAc$ (0.1226 g, 0.34 mmol, 1.7 equiv). Then, the mixture was heated under nitrogen at 90°C in DMF (1.0 mL) for 24 h. After cooling down, the crude reaction mixture was analyzed by GC with *n*-dodecane as an internal standard to obtain **3a** in 75% GC yield.

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Keywords: aryl carboxylic acids · decarboxylation · dehydrogenation · palladium · propiophenones

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