

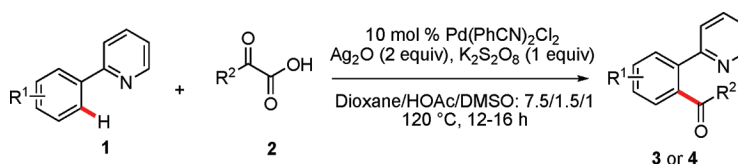
Decarboxylative Acylation of Arenes with α -Oxocarboxylic Acids via Palladium-Catalyzed C–H Activation

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ABSTRACT



An efficient palladium-catalyzed decarboxylative acylation of unactivated arenes with α -oxocarboxylic acids is reported. This method provides a novel access to aryl ketones.

Transition-metal-catalyzed decarboxylative coupling has attracted considerable attention in recent years.¹ This method avoids the preparation and use of stoichiometric organometallic reagents and produces CO₂ as the waste instead of often toxic metal salts. Representative examples include Pd/Cu-catalyzed decarboxylative coupling of benzoic acids with aryl halides or surrogates by Goossen,² palladium-catalyzed decarboxylative Heck-type of olefination and biaryl coupling of aromatic carboxylic acids by Meyers³ and Forgione,⁴ and Cu-catalyzed decarboxyl-

ative coupling of potassium polyfluorobenzoates with aryl iodides or bromides by Liu.⁵ Recent studies showed that alkenyl⁶ or alkynyl⁷ carboxylic acids, α -oxocarboxylate^{2f,8} and potassium oxalate monoesters⁹ could also undergo decarboxylative coupling with aryl halides, and thus product diversity was improved.

Transition-metal-catalyzed cross-coupling directed by either electronic effects or directing groups is also of contemporary interest since this method does not require the prefunctionalization of substrates and is economically advantageous.¹⁰ Inspired by recent studies in this area,¹¹ decarboxylative coupling of aromatic carboxylic acids with unactivated arenes has also been achieved.¹² However, transition-metal-catalyzed decarboxylative acylation on aromatic sp² C–H bonds is rare. Based on the success of

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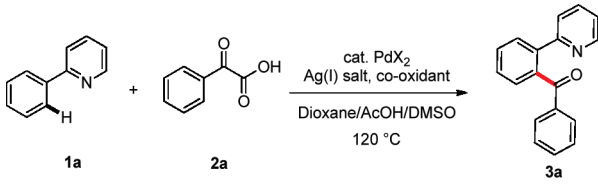
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C–H activation on 2-phenylpyridine and other nitrogen-containing substrates,^{10f} herein we describe the first palladium-catalyzed decarboxylative acylation of unactivated arenes with α -oxocarboxylic acids via C–H activation.

Table 1. Optimization of Reaction Conditions^a



entry	PdX ₂	Ag(I) salt (equiv)	co-oxidant (equiv)	yield (%) ^b	convn (%) ^b
1	Pd(TFA) ₂	Ag ₂ CO ₃ (3)		61	88
2 ^c		Ag ₂ CO ₃ (3)		0	<1
3 ^d	Pd(TFA) ₂			0	<10
4	PdCl ₂	Ag ₂ CO ₃ (3)		59	81
5	Pd(OAc) ₂	Ag ₂ CO ₃ (3)		66	86
6	Pd(MeCN) ₂ Cl ₂	Ag ₂ CO ₃ (3)		72	89
7	Pd(PhCN) ₂ Cl ₂	Ag ₂ CO ₃ (3)		73	89
8	Pd(PhCN) ₂ Cl ₂	AgOAc (3)		69	91
9	Pd(PhCN) ₂ Cl ₂	Ag ₂ O (3)		79	96
10	Pd(PhCN) ₂ Cl ₂	Ag ₂ O (1)	(NH ₄) ₂ S ₂ O ₈ (2)	38	54
11	Pd(PhCN) ₂ Cl ₂	Ag ₂ O (1)	K ₂ S ₂ O ₈ (2)	57	97
12	Pd(PhCN) ₂ Cl ₂	Ag ₂ O (1)	Oxone (2)	40	67
13 ^e	Pd(PhCN)₂Cl₂	Ag₂O (2)	K₂S₂O₈(1)	84(81)^f	98
14	Pd(PhCN) ₂ Cl ₂	Ag ₂ O (2)		71	87

^a Reaction conditions: 2 equiv of **2a**, 10 mol % PdX₂, Ag(I) salt (quantity noted), co-oxidant (quantity noted), 1,4-dioxane/HOAc/DMSO (7.5/1.5/1, v/v/v, c = 0.1 M), 120 °C, 16 h unless otherwise noted. ^b Yields and conversions are based on **1a**, determined by crude ¹H NMR using dibromomethane as the internal standard. ^c Without palladium. ^d Without Ag(I) salt. ^e 12 h. ^f Isolated yield.

Our investigation started with decarboxylative coupling of 2-phenylpyridine (**1a**) with phenylglyoxylic acid (**2a**) in the presence of 10 mol % Pd(TFA)₂ with 3 equiv of Ag₂CO₃ as a decarboxylative reagent and oxidant (Table 1). Solvent screening showed that optimal results could be obtained with a mixture of 1,4-dioxane/AcOH/DMSO

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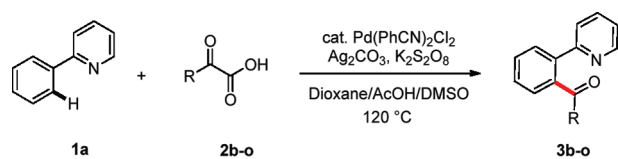
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(7.5/1.5/1, v/v/v), providing the desired product (**3a**) in 61% yield with a high conversion (88%, entry 1). It is important to note that both Pd(TFA)₂ and Ag₂CO₃¹³ are required for this coupling reaction; no desired product could be obtained in the absence of either of these two reagents (entries 2 and 3). Further study showed that both Pd(MeCN)₂Cl₂ and Pd(PhCN)₂Cl₂ could efficiently catalyze the reaction (entries 6 and 7), whereas Pd(OAc)₂ and PdCl₂ gave relatively lower yields (entries 4 and 5). Encouraged by these results, the effect of different silver(I) salts on this reaction was examined, and it turned out that the optimal results could be produced with 3 equiv of Ag₂O in the presence of Pd(PhCN)₂Cl₂ as a catalyst (entry 9). Next, the amount of Ag₂O was reduced by the addition of a co-oxidant, and a moderate yield of **3a** was obtained with 1 equiv of Ag₂O and 2 equiv of K₂S₂O₈ (entry 11). Further optimization demonstrated that the coupling yield could be raised to 84% with 2 equiv of Ag₂O and 1 equiv of K₂S₂O₈ in 12 h (entry 13). It should be noted that K₂S₂O₈ is required for obtaining a high yield since 2 equiv of Ag₂O alone gave 71% yield (entry 14).

The substituent effects of phenylglyoxylic acid on this reaction were then studied (Table 2). It was noticed that *p*-substituted electron-donating groups provided good to high yields (**3b** and **3c**), whereas the strong electron-withdrawing group CF₃ gave a moderate yield (**3g**). Interestingly, high yields were obtained with *p*-fluoro (**3d**), *p*-chloro (**3e**) and *p*-bromo (**3f**) substituted phenylglyoxylic acids, although it is not surprising that halogens were tolerated under the reaction conditions. Further investigation showed that electronic properties do not affect the *o*-substituted phenylglyoxylic acids since both electron-donating groups and electron-withdrawing groups gave good to high yields (70–95%, **3h–k**). With a sterically hindered substrate, a modest yield was obtained (**3l**), and it is noteworthy that Pd/Cu(I)-catalyzed decarboxylative acylation of aryl bromide gave <5% yield with this substrate in a previous report.^{8a} In addition, aliphatic α -oxocarboxylic acids also provide moderate to good yields of desired products (**3o** and **3p**).

The results of substituted 2-phenylpyridines (**1b–p**) compatibility studies are presented in Table 3. As expected, a series of functional groups including methyl, methoxyl, chloro, trifluoromethyl, and acetyl on the phenyl ring were compatible under the optimal reaction conditions, and the desired products were produced in good to high yields (**4b–n**). Interestingly, there does not appear to be an electronic effect on this substrate since both electron-donating groups and electron-withdrawing groups at the *o*-, *m*-, and *p*-positions worked efficiently with the exception of *p*-CF₃, which gave a moderate yield (**4l**). Furthermore, benzo[*h*]quinoline^{10f} worked extremely well to give **4o** in 95% yield. Acylation of 4,4-dimethyl-2-

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Table 2. Scope of α -Oxocarboxylic Acids^a


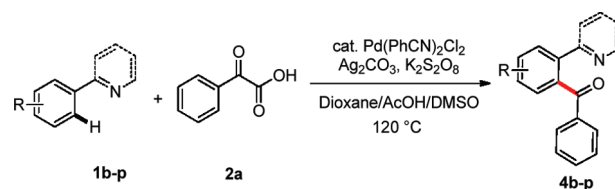
product	yield (%) ^b	product	yield (%) ^b
	81		95
	72 ^c		84
	87		37 ^{c, d}
	83		61
	85		71
	59 ^d		59 ^{c, d}
	74 ^c		69 ^d
	70 ^d		

^a Reaction conditions: 2 equiv of **2b–p**, 10 mol % Pd(PhCN)₂Cl₂, 2 equiv of Ag₂O, 1 equiv of K₂S₂O₈, 1,4-dioxane/HOAc/DMSO (7.5/1.5/1, v/v/v, c = 0.1 M), 120 °C, 12 h unless otherwise noted. ^b Yields isolated based on **1a**. ^c 3 equiv of Ag₂O, without K₂S₂O₈. ^d 16 h.

phenyl-4,5-dihydrooxazole¹⁴ also gave a modest yield of product **4p**.

In summary, an efficient approach for the direct acylation of the aromatic sp² C–H bond based on a Pd/

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Table 3. Scope of 2-Phenylpyridines^a


product	yield (%) ^b	product	yield (%) ^b
	87		67
	72		77
	84		56 ^c
	85		93
	95		83
	68		95
	65		41 ^c
	90		

^a Reaction conditions: 2 equiv of **2a**, 10 mol % Pd(PhCN)₂Cl₂, 2 equiv of Ag₂O, 1 equiv of K₂S₂O₈, 1,4-dioxane/HOAc/DMSO (7.5/1.5/1, v/v/v, c = 0.1 M), 120 °C, 12 h unless otherwise noted. ^b Isolated yields based on **1**. ^c 16 h.

Ag bimetallic system has been developed. This novel method allowed for the decarboxylative cross-coupling of

unactivated arenes with both aromatic and aliphatic α -oxocarboxylic acids.

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Supporting Information Available: Experimental procedures and spectroscopic data (MS, HRMS, NMR) for all newly identified compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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