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

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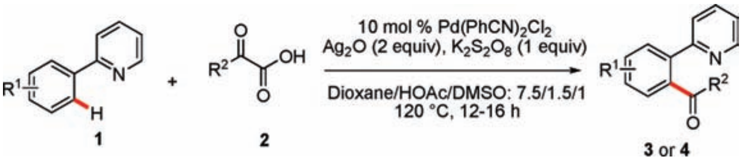
ABSTRACT



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 CO_2 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 Meyers[3] and Forgione,[4] and Cu-catalyzed decarboxylative coupling of potassium polyfluorobenzoates with aryl iodides or bromides by Liu.[5] Recent studies showed that alkenyl[6] or alkynyl[7] carboxylic acids, α-oxocarboxylate[2f,8] and potassium oxalate monoesters[9] 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 sp^2 C−H bonds is rare. Based on the success of

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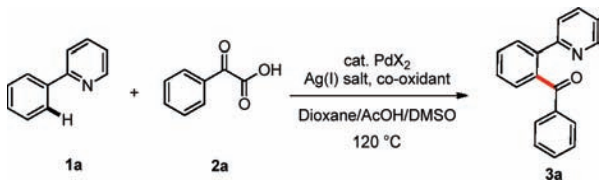
C−H activation on 2-phenylpyridine and other nitrogen-containing substrates,[10f] herein we describe the first palladium-catalyzed decarboxylative acylation of unactived arenes with α-oxocarboxylic acids via C−H activation.

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_2CO_3 (3)		61	88
2[c]		Ag_2CO_3 (3)		0	<1
3[d]	$Pd(TFA)_2$			0	<10
4	$PdCl_2$	Ag_2CO_3 (3)		59	81
5	$Pd(OAc)_2$	Ag_2CO_3 (3)		66	86
6	$Pd(MeCN)_2Cl_2$	Ag_2CO_3 (3)		72	89
7	$Pd(PhCN)_2Cl_2$	Ag_2CO_3 (3)		73	89
8	$Pd(PhCN)_2Cl_2$	AgOAc (3)		69	91
9	$Pd(PhCN)_2Cl_2$	Ag_2O (3)		79	96
10	$Pd(PhCN)_2Cl_2$	Ag_2O (1)	$(NH_4)_2S_2O_8$ (2)	38	54
11	$Pd(PhCN)_2Cl_2$	Ag_2O (1)	$K_2S_2O_8$ (2)	57	97
12	$Pd(PhCN)_2Cl_2$	Ag_2O (1)	Oxone (2)	40	67
13[e]	**$Pd(PhCN)_2Cl_2$**	**Ag_2O (2)**	**$K_2S_2O_8$(1)**	**84(81)**[f]	**98**
14	$Pd(PhCN)_2Cl_2$	Ag_2O (2)		71	87

[a] Reaction conditions: 2 equiv of **2a**, 10 mol % PdX_2, 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 Ag_2CO_3 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 (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 Ag_2CO_3[13] 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 $Pd(MeCN)_2Cl_2$ and $Pd(PhCN)_2Cl_2$ could efficiently catalyze the reaction (entries 6 and 7), whereas $Pd(OAc)_2$ and $PdCl_2$ 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 Ag_2O in the presence of $Pd(PhCN)_2Cl_2$ as a catalyst (entry 9). Next, the amount of Ag_2O was reduced by the addition of a co-oxidant, and a moderate yield of **3a** was obtained with 1 equiv of Ag_2O and 2 equiv of $K_2S_2O_8$ (entry 11). Further optimization demonstrated that the coupling yield could be raised to 84% with 2 equiv of Ag_2O and 1 equiv of $K_2S_2O_8$ in 12 h (entry 13). It should be noted that $K_2S_2O_8$ is required for obtaining a high yield since 2 equiv of Ag_2O 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 CF_3 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*-CF_3, 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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(10) For some recent reviews, see: (a) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (b) Li, B. J.; Yang, S. D.; Shi, Z. J. *Synlett* **2008**, 949. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (d) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

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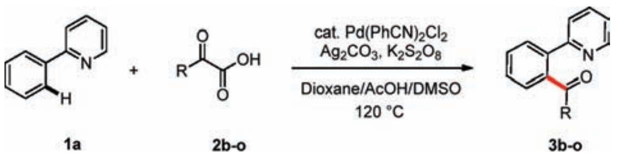
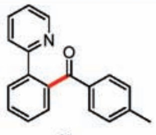
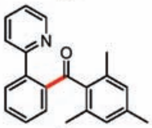
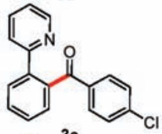
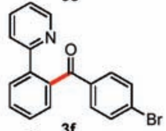
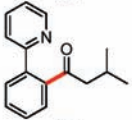
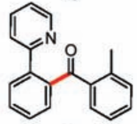
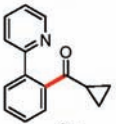
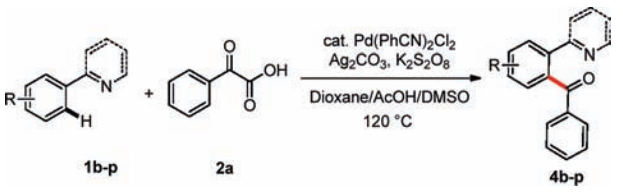
Table 2. Scope of α-Oxocarboxylic Acids[a]

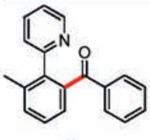
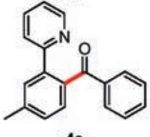
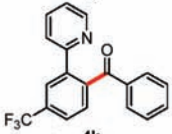
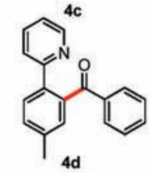
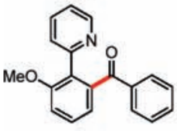
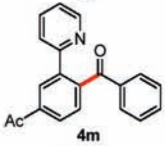
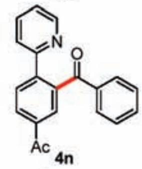
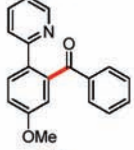
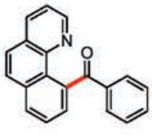
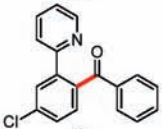
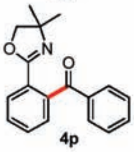
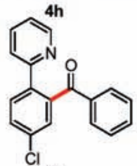


product	yield (%)[b]	product	yield (%)[b]
 **3b**	81	 **3j**	95
 **3c**	72[c]	 **3k**	84
 **3d**	87	 **3l**	37[c, d]
 **3e**	83	 **3m**	61
 **3f**	85	 **3n**	71
 **3g**	59[d]	 **3o**	59[c, d]
 **3h**	74[c]	 **3p**	69[d]
 **3i**	70[d]		

[a] Reaction conditions: 2 equiv of **2b−p**, 10 mol % Pd(PhCN)$_2$Cl$_2$, 2 equiv of Ag$_2$O, 1 equiv of K$_2$S$_2$O$_8$, 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 Ag$_2$O, without K$_2$S$_2$O$_8$. [d] 16 h.

Table 3. Scope of 2-Phenylpyridines[a]



product	yield (%)[b]	product	yield (%)[b]
 **4b**	87	 **4j**	67
 **4c**	72	 **4k**	77
 **4d**	84	 **4l**	56[c]
 **4e**	85	 **4m**	93
 **4f**	95	 **4n**	83
 **4g**	68	 **4o**	95
 **4h**	65	 **4p**	41[c]
 **4i**	90		

[a] Reaction conditions: 2 equiv of **2a**, 10 mol % Pd(PhCN)$_2$Cl$_2$, 2 equiv of Ag$_2$O, 1 equiv of K$_2$S$_2$O$_8$, 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.

phenyl-4,5-dihydrooxazole[14] also gave a modest yield of product **4p**.

In summary, an efficient approach for the direct acylation of the aromatic sp^2 C−H bond based on a Pd/Ag bimetallic system has been developed. This novel method allowed for the decarboxylative cross-coupling of

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(14) (a) Chen, X.; Li, J. J.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (b) Giri, R.; Liang, J.; Lei, J. G.; Li, J. J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C. Y.; Foxman, B. M.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420.

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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