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Palladium-Catalyzed Chemoselective Decarboxylative Ortho Acylation of Benzoic Acids with α-Oxocarboxylic Acids

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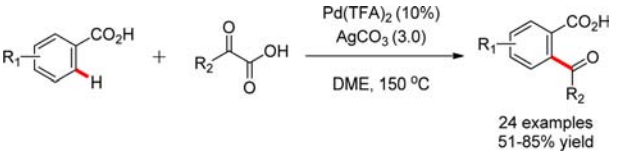
ABSTRACT



Palladium-catalyzed chemoselective decarboxylative cross coupling of benzoic acids with α-oxocarboxylic acids was realized via an arene sp^2 C−H functionalization process. This work represents the first example of transition-metal-catalyzed cross-coupling reactions with two acids acting in different roles. The synthetic utility of this method was confirmed by the synthesis of pitofenone, an antispasmodic used in the combined drug Spasmalgon.

2-Benzoylbenzoic acid derivatives are important intermediates for the synthesis of various bioactive compounds[1] and are often encountered as subunits of many biologically active compounds,[2] including natural products, pharmaceuticals, and agrochemical compounds. For example, balanol, a fungal metabolite produced by the fungus *Verticillium balanoides* and other fungi, is a potent inhibitor of protein kinase C (PKC),[1e,f] narceine, an opium alkaloid produced by the *Papaver somniferum* plant, is a bitter compound with narcotic effects,[1d] and pitofenone, the key ingredient in Spasmalgon (a combined drug), is an antispasmodic (Figure 1).[1c] Additionally, 2-benzoylbenzoic acids are often used as functional groups or substrates in photochemistry,[3] chromatography,[4] and food chemistry.[5]

Despite the demonstrated biological importance of 2-acylbenzoic acids, synthetic methods for these species are far from maturity. The most common routes start from 1,3-isobenzofurandione derivatives and involve either a nucleophilic addition/elimination process by organometallic reagents[6] or a Friedel−Crafts acylation process (Scheme 1).[7] In many cases, these reactions suffer severely from poor regioselectivity on the benzofurandione, and

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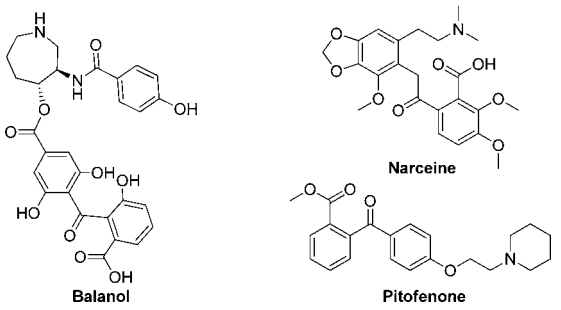
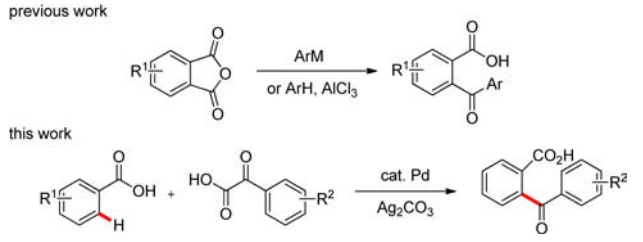


Figure 1. Representative biologically active compounds containing a 2-acylbenzoic acid/ester moiety.

thus substituted 2-acylbenzoic acids are difficult to obtain in a satisfactory yield.[6b,7c] Therefore, the need for complementary, concise, and effective approaches to access these compounds is clear. On the basis of our success on direct ortho acylation of 2-phenylpyridines and acetanilides,[8] we proposed that an efficient approach for the synthesis of 2-acylbenzoic acids could be achieved by decarboxylative cross coupling of benzoic acids with α-oxocarboxylic acids by a Pd(II)-catalyzed C−H functionalization process (Scheme 1).

Scheme 1. Synthesis of 2-Acylbenzoic Acids



Transition-metal-catalyzed cross coupling reactions remain one of the most powerful methods for carbon−carbon (C−C) bond formation.[9] Among these methods, Pd(0)-catalyzed decarboxylative cross coupling has recently attracted considerable attention due to the low cost, ready availability, and environmentally benign properties of carboxylic acids.[10] Along with the well-studied benzoic acids, alkyl, alkenyl and alkynyl acids, α-oxocarboxylates, and oxalates have also been demonstrated as effective substrates, which enable the installation of a variety of functional groups on aromatic rings. Furthermore, since Crabtree first reported a direct decarboxylative cross coupling of arenes with aromatic acids through a Pd(II)-catalyzed C−H functionalization process,[11] the method has attracted considerable attention because the prefunctionalization of reaction substrates is avoided.[12]

As substrates, benzoic acids have been extensively studied in decarboxylative cross-coupling reactions by both Pd(0) and Pd(II) catalysis. It has been demonstrated that either a silver or copper source could effectively mediate the decarboxylation. On the other hand, from Yu's studies, benzoic acid derivatives were fairly stable at high temperature (130 °C) in the presence of a catalytic amount of a Pd(II) source and an excess Ag(I) source.[13] Moreover, α-oxocarboxylic acids, utilized in Goossen's laboratory in Pd(0)-catalyzed decarboxylative cross couplings,[14] have also been demonstrated as effective coupling partners in Pd(II) catalysis in our laboratory with either a silver or persulfate source as an oxidant and the decarboxylation reagent.[8,15] It was also noted that, along with acteanilides and 2-phenylpyridines, cyclic enamides,[16] *O*-methyl oximes,[17] phenylacetamides,[18] *O*-phenyl carbamates,[19] and 1-(pyrimidin-2-yl)-1*H*-indoles[20] were also effective

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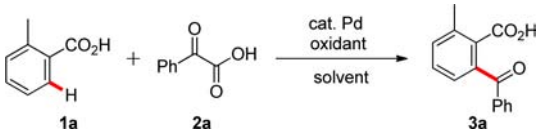
substrates for the direct decarboxylative acylation. These results support the feasibility of chemoselective decarboxylative cross coupling of benzoic acids with α-oxocarboxylic acids through Pd(II) catalysis under well-defined reaction conditions. It is noteworthy that, although the benzoic acid derivatives have been well studied as the substrates in metal-catalyzed C−H bond activation reactions,[9] direct ortho acylation of the benzoic acids remains a challenge. Furthermore, transition-metal-catalyzed cross coupling of two acids with different roles in the reaction has never been reported. As part of our program to develop novel transition-metal-catalyzed cross coupling reactions with diverse substrates,[8,15,21] we have developed and report herein the synthesis of 2-acylbenzoic acid derivatives through chemoselective decarboxylative cross coupling of benzoic acids with α-oxocarboxylic acids via a palladium-catalyzed C−H bond functionalization process.

Table 1. Optimization of Reaction Conditions[a]



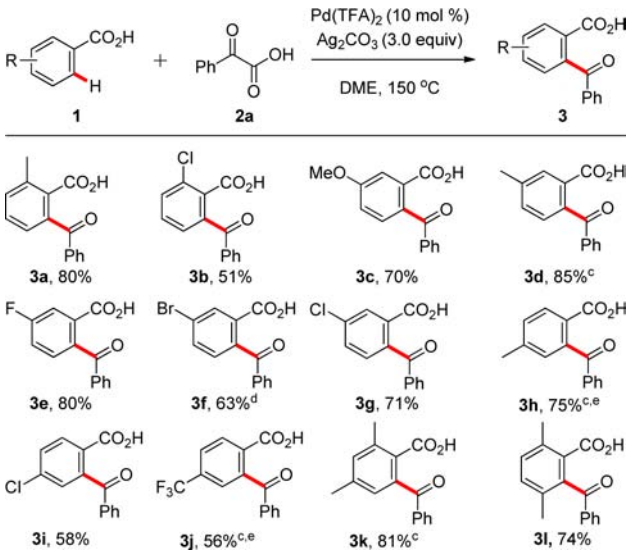
1a 2a 3a

entry	Pd source (amt (mol %))	oxidant (amt (equiv))	solvent	yield (%)[b]
1	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	DMF	trace
2	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	THF	trace
3	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	^{t}BuOH	32
4	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	dioxane	55
5	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	DME	58
6	$PdCl_2(PhCN)_2$ (10)	Ag_2CO_3 (2.0)	DME	trace
7	$PdCl_2(MeCN)_2$ (10)	Ag_2CO_3 (2.0)	DME	41
8	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0)	DME	48
9	$Pd(TFA)_2$ (10)	Ag_2O (2.0)	DME	20
10	$Pd(TFA)_2$ (10)	AgOAc (2.0)	DME	38
11	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (2.0)	DME	0
12[c]	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2.0)	DME	60
13	$Pd(TFA)_2$ (10)	Ag_2CO_3 (3.0)	DME	64
14[d]	**$Pd(TFA)_2$ (10)**	**Ag_2CO_3 (3.0)**	**DME**	**80**
15	$Pd(TFA)_2$ (5)	Ag_2CO_3 (3.0)	DME	56
16[d]	$Pd(TFA)_2$ (10)	Ag_2CO_3 (3.0)	dioxane	67

[a] Conditions: **1a** (0.2 mmol), Pd source, oxidants, **2a** (0.6 mmol), 2 mL of solvent, 120 °C, 24 h unless otherwise noted. [b] Isolated yields. [c] 48 h. [d] 150 °C.

Considering that α-oxocarboxylic acid is a potential source of benzoic acid through decarboxylation and oxidation, *o*-methylbenzoic acid was chosen as the substrate for the decarboxylative cross-coupling reaction with α-oxocarboxylic acid in the presence of a catalytic amount of $Pd(TFA)_2$ and an excess of Ag_2CO_3 as the oxidant and the decarboxylation reagent on the basis of our previous reports.[8,21] After an extensive solvent screening, DME and dioxane were shown to be optimal solvents for this coupling, providing the desired product in moderate yields (Table 1, entries 4 and 5). The following survey of catalysts indicated that although $PdCl_2(MeCN)_2$ and $Pd(OAc)_2$ could also catalyze this reaction, $Pd(TFA)_2$ is more effective (entries 7 and 8). Further screening of oxidants showed that silver carbonate was the best choice. Due to our success in the decarboxylation of α-oxocarboxylic acids with a persulfate salt, replacement of Ag_2CO_3 with $K_2S_2O_8$, $Na_2S_2O_8$, and $(NH_4)_2S_2O_8$ was also examined. However, the addition of these persulfate salts led to the decarboxylation of both acids while no desired product was obtained (entry 11). Further optimization of reaction conditions showed that although increasing the reaction time had no apparent effect on this reaction, the yield was significantly improved by increasing the amount of Ag_2CO_3 and raising the reaction temperature (entries 12−14). It was also noted that the coupling product was obtained either with less Pd catalyst or when dioxane was used as the solvent, albeit in lower yields (entries 15 and 16).

Scheme 2. Substrate Scope of Benzoic Acids[a,b]



[a] Conditions: **1** (0.2 mmol), $Pd(TFA)_2$ (0.02 mmol), **2a** (0.6 mmol), Ag_2CO_3 (0.6 mmol), 2 mL of DME, 150 °C, 24 h unless otherwise noted. [b] Isolated yields. [c] 165 °C. [d] 130 °C. [e] 48 h.

With the optimized reaction conditions in hand, we then carried out the substrate scope study of substituted benzoic acids. As shown in Scheme 2, this transformation is compatible with electron donating and electron withdrawing group substituted benzoic acids (**3a**−**j**), while substrates containing electron-donating groups provided higher yields than their electron-withdrawing counterparts, with the exception of **3e**. As expected, halogens (F, Cl, and Br) were tolerated under the current reaction system, allowing the further manipulation of the initial products. Furthermore, good yields were also observed with disubstituted benzoic acids (**3k**,**l**).

Next, a substrate scope study for the α-oxocarboxylic acids was carried out. As shown in Scheme 3, electron-rich groups (MeO and Me), and halogens (F, Cl, and Br) are compatible with the current reaction conditions (**3m**−**v**).

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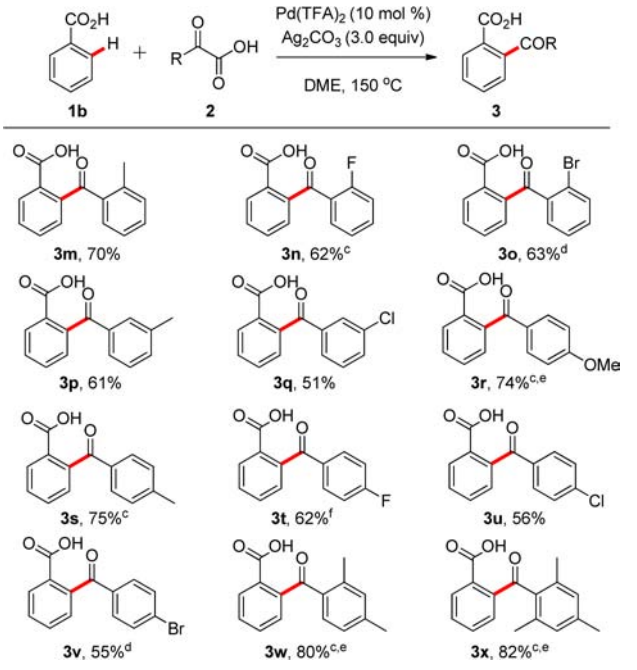
Scheme 3. Substrate Scope of α-Oxocarboxylic Acids[a,b]



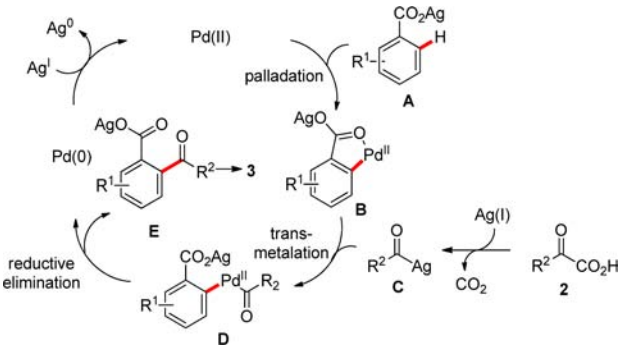
[a] Conditions: **1a** (0.2 mmol), $Pd(TFA)_2$ (0.02 mmol), **2** (0.6 mmol), Ag_2CO_3 (0.6 mmol), 2 mL of DME, 150 °C, 24 h unless otherwise noted. [b] Isolated yields. [c] 165 °C. [d] 130 °C. [e] 48 h. [f] Ag_2CO_3 (0.5 mmol).

Unfortunately, strong electron-withdrawing groups are not well tolerated in the current reaction system. As observed in our previous studies,[8] there is not an apparent steric effect on these substrates (**3n**,**o**). In contrast, there is a clear electronic effect. Furthermore, the sterically hindered substrate 2,4,6-trimethylbenzoylformic acid also provided the desired product **3x** in high yield.

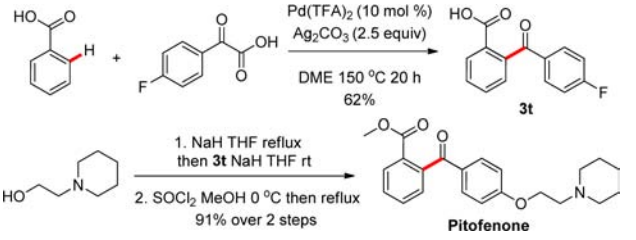
On the basis of the reports from Yu and our laboratory,[8,13,22] a decarboxylative cross-coupling reaction mechanism is proposed (Scheme 4). It is believed that this transformation starts with the palladation of silver benzoate **A** into the Pd(II) intermediate **B**, which then undergoes a transmetalation step with the acylsilver species **C** formed by the silver-mediated decarboxylation of **2**, to generate the Pd(II) intermediate **D**. Reductive elimination of **D** provides the silver salt **E** and Pd(0), which will be reoxidized into Pd(II) by Ag_2CO_3. Protonation of intermediate **E** provides the desired product **3**.

To demonstrate the synthetic utility of this method, it was applied to the synthesis of pitofenone (Scheme 5). Pd(II)-catalyzed direct decarboxylative ortho acylation of benzoic acid with (4-fluorobenzoyl)formic acid provided 2-(4-fluorobenzoyl)benzoic acid (**3t**) in 62% yield. Nucleophilic

Scheme 4. Proposed Reaction Mechanism



Scheme 5. Synthesis of Pitofenone



substitution of **3t** by 1-(2-hydroxyethyl)piperidine, followed by methylation, produced pitofenone in 91% yield over two steps. It is noteworthy that this route also allows the installation of extra substituents on the phenyl rings, which facilitates the medicinal chemistry study of this compound.

In summary, an efficient decarboxylative cross-coupling reaction of benzoic acids with α-oxocarboxylic acids has been developed via a palladium-catalyzed C−H bond functionalization process. This transformation is the first example of direct ortho acylation of benzoic acids. The method provides an efficient access to 2-acylbenzoic acid derivatives. Furthermore, the synthesis of pitofenone was also achieved by employing this transformation as a key step. In comparison with the two reported syntheses,[23] this route provides a more efficient approach to access this compound.

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Supporting Information Available. Text and figures giving experimental details and characterization data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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