

Palladium-Catalyzed Decarboxylative Acylation of *O*-Phenyl Carbamates with α -Oxocarboxylic Acids at Room Temperature

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Abstract: A palladium-catalyzed oxidative acylation of *O*-phenyl carbamates with α -oxocarboxylic acids via selective aromatic C–H bond activation is described. This protocol represents the first *ortho*-acylation of phenol derivatives, and a catalytic amount of triflic acid additive is crucial for this transformation.

Keywords: acylation; C–H activation; α -oxocarboxylic acids; palladium; *O*-phenyl carbamates

Transition metal-catalyzed cross-coupling reactions with aryl metal reagents and aryl halides are one of the most reliable tools for the synthesis of natural products and medically relevant molecules.^[1] Recently, transition metal-catalyzed decarboxylative cross-coupling reactions using arylcarboxylic acids or arylcarboxylates as aryl surrogates have emerged as powerful alternatives^[2] since these methods avoid the formation of toxic metal wastes generated from stoichiometric organometallic reagents, thus providing new protocols for Mirozoki–Heck type reactions,^[3] oxidative arylation,^[4] redox-neutral biaryl synthesis,^[5] and allylation.^[6]

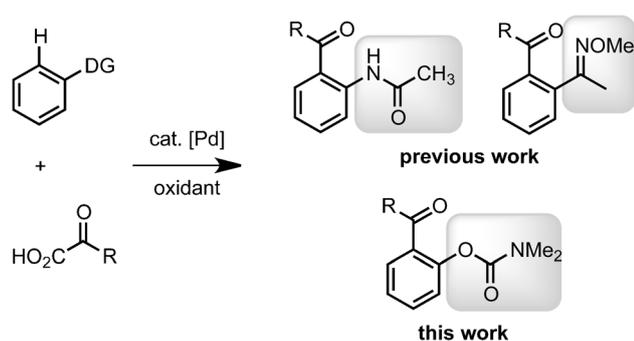
The *ortho*-acylphenols are important structural motifs in natural products,^[7] and are known to be important synthetic intermediates in organic synthesis.^[8] Friedel–Crafts acylation^[9] and anionic Fries rearrangement^[10] are common methods for the preparation of *ortho*-acylphenols. However, these methods present intrinsic drawbacks including the use of hazardous Lewis acids, the deficiency of regioselectivity, and the prefunctionalization of coupling partners. Therefore, the development of truly catalytic alterna-

tives is highly desired to minimize synthetic steps and to avoid waste formation.

Transition metal-catalyzed oxidative acylation of aromatic compounds with various directing groups,^[11] e.g., arylpyridines,^[12] oxime,^[13] acetanilides,^[14] and indole,^[15] with aldehydes or alcohols were described. However, decarboxylative C–H bond acylations using α -oxocarboxylic acids as acyl anion equivalents were relatively unexplored. Gooßen first reported the Pd-catalyzed decarboxylative cross-coupling reaction of aryl bromides with α -oxocarboxylate salts as acyl sources to provide unsymmetrical diaryl ketones.^[16] Later, Ge described elegant studies on Pd-catalyzed decarboxylative *ortho*-acylation of acetanilides and phenylpyridines with α -oxocarboxylic acids via C–H bond activation.^[17] Guo and Duan demonstrated decarboxylative acylation of cyclic enamides with α -oxocarboxylic acids to afford β -acylenamides via a cyclic vinylpalladated intermediate.^[18] Recently, we reported a Pd-catalyzed decarboxylative acylation of *O*-methylketoximes with α -keto acids.^[19]

Catalytic C–H bond functionalization of *O*-phenyl carbamates is a promising synthetic strategy for substituted phenol derivatives.^[20] Inspired by our recent studies on transition metal-catalyzed oxidative acylation of benzamides^[21] with aldehydes, we herein present the palladium-catalyzed oxidative *ortho*-acylation of *O*-phenyl carbamates with α -oxocarboxylic acids via C–H bond activation (Scheme 1).

Our initial study started from the coupling of phenyl dimethylcarbamate (**1a**) with phenylglyoxylic acid (**2a**), according to the reaction conditions used in the coupling of acetanilides with α -oxocarboxylic acids^[17a] (Table 1, entry 1). However, the combination of Pd(TFA)₂ and (NH₄)₂S₂O₈ in diglyme solvent did not promote the coupling of **1a** and **2a**. After extensive examination for optimal reaction conditions, we found the use of a catalytic amount of triflic acid



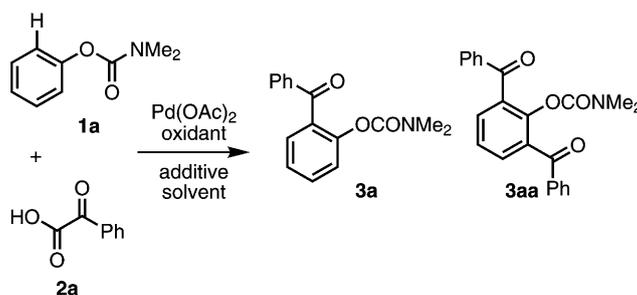
Scheme 1. Pd-catalyzed oxidative acylation of *O*-phenyl carbamates with α -oxocarboxylic acids.

(TfOH) additive in DCE solvent is very crucial for this transformation, producing monoacylated product **3a** and bisacylated product **3aa** in 75% combined yield with a 3:1 ratio, as shown in entries 2 and 3.

Fu and Liu reported the isolation and X-ray analysis of the *O*-phenyl carbamate palladacycle generated

from $\text{Pd}(\text{OAc})_2$ and TfOH.^[20d] In this paper, the triflate anion can tune the electrophilicity of the Pd(II) center and improve the the insertion of Pd(II) into the aromatic C–H bonds of phenol esters. Screening of solvents showed that DCE was the most effective solvent in this coupling reaction (Table 1, entries 4–6). Further study revealed that TfOH is unique in its ability to facilitate high levels of conversion (Table 1, entries 7 and 8). Other oxidants such as $\text{K}_2\text{S}_2\text{O}_8$, Ag_2O and AgCO_3 under otherwise identical conditions were far less effective (Table 1, entries 9–11). Logically, it was thought that the ratio of **3a** and **3aa** can be controlled by the amounts of α -oxocarboxylic acid and oxidant (Table 1, entries 12 and 13). Indeed, upon use of 1.5 equiv. of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ under otherwise identical conditions, the formation of monoacylated product **3a** was found to improve substantially (12:1) in good yield (68%). Also, the combination of 1.5 equiv. of **2a** and 1.2 equiv. of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ provided a significantly increased formation of **3a** (>20:1) in moderate yield (58%). However, a reduction (1.2 equiv.) in the load-

Table 1. Selected optimization of reaction conditions.^[a]



Entry	Oxidant (equiv.)	Additive (mol%)	Solvent	Yield [%] ^[b] (3a : 3aa) ^[c]
1 ^[d]	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)		diglyme	N.R.
2	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)	TfOH (20)	DCE	75 (3:1)
3	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)		DCE	N.R.
4	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)	TfOH (20)	diglyme	N.R.
5	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)	TfOH (20)	THF	trace
6	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)	TfOH (20)	DMF	8
7	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)	AcOH (50)	DCE	N.R.
8	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (2)	TFA (20)	DCE	trace
9	$\text{K}_2\text{S}_2\text{O}_8$ (2)	TfOH (20)	DCE	26 (5:1)
10	Ag_2O (2)	TfOH (20)	DCE	N.R.
11	Ag_2CO_3 (2)	TfOH (20)	DCE	N.R.
12	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (1.5)	TfOH (20)	DCE	68 (12:1)
13 ^[e]	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (1.2)	TfOH (20)	DCE	58 (>20:1)
14 ^[f]	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (1.5)	TfOH (20)	DCE	46 (15:1)
15 ^[g]	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (3)	TfOH (20)	DCE	41 (1:1)

^[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol%), oxidant (quantity noted), additive (quantity noted), solvent (2 mL) at room temperature for 20 h in pressure tubes.

^[b] Combined isolated yields of **3a** and **3aa**.

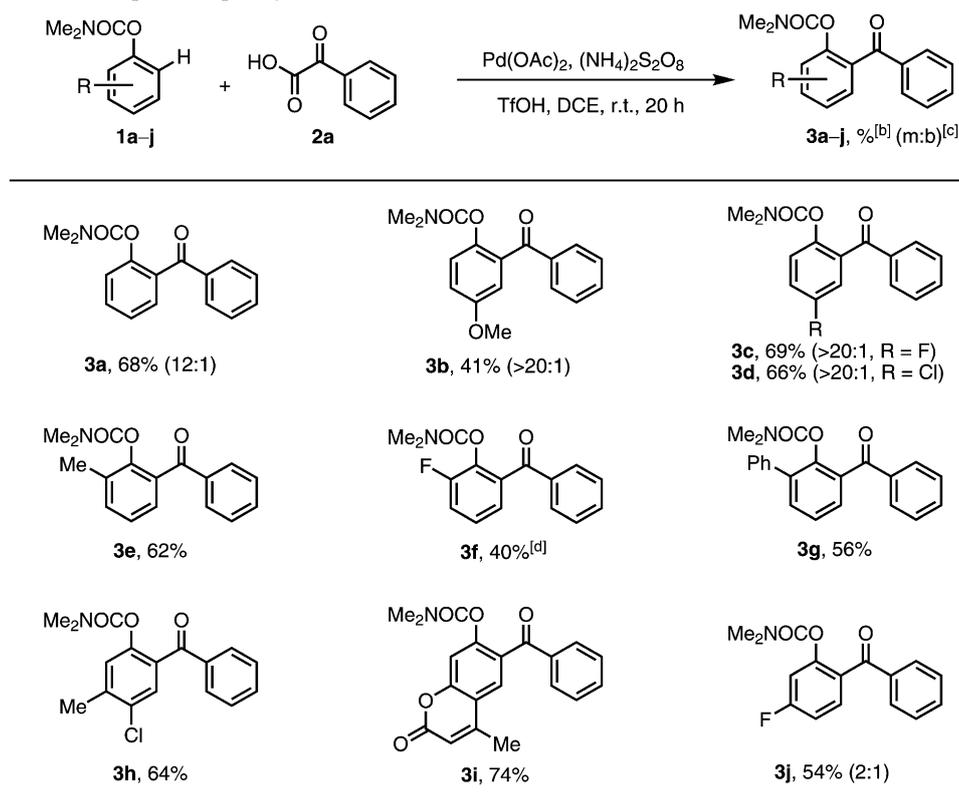
^[c] Ratio of **3a** and **3aa** was determined by crude ^1H NMR analysis.

^[d] $\text{Pd}(\text{TFA})_2$ (5 mol%).

^[e] **2a** (0.45 mmol, 1.5 equiv.).

^[f] **2a** (0.36 mmol, 1.2 equiv.).

^[g] **2a** (0.9 mmol, 3 equiv.).

Table 2. Scope of *O*-phenyl carbamates.^[a]

^[a] Reaction conditions: **1a–j** (0.3 mmol), **2a** (0.6 mmol), Pd(OAc)₂ (5 mol%), (NH₄)₂S₂O₈ (0.45 mmol), TfOH (20 mol%), DCE (2 mL) in pressure tubes.

^[b] Yield isolated by column chromatography.

^[c] Ratio of monoacylated and bisacylated products determined by crude ¹H NMR analysis.

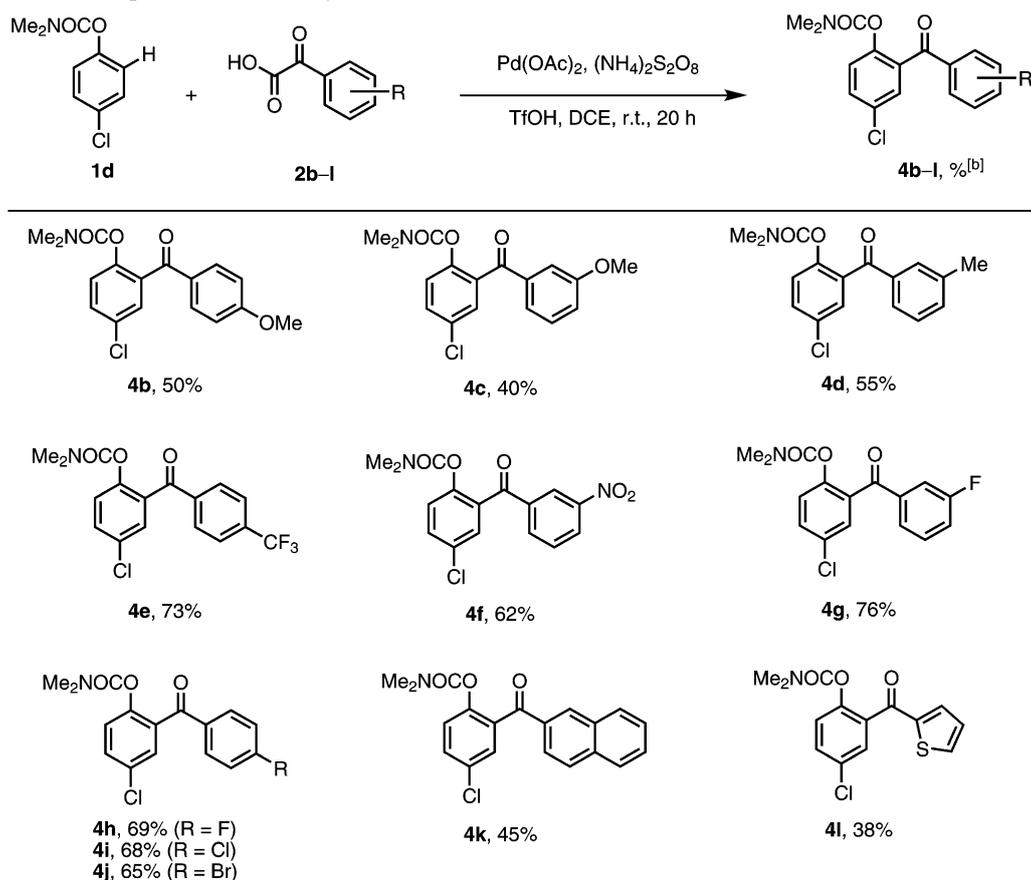
^[d] 40 °C.

ing of **2a** with 1.5 equiv. of (NH₄)₂S₂O₈ was found to decrease the generation of acylated products **3a** and **3aa**, albeit resulting in a high level of monoselectivity (15:1), as shown in entry 14. In contrast, by increasing the amounts of **2a** and (NH₄)₂S₂O₈, the formation of **3a** and **3aa** was significantly decreased (Table 1, entry 15).

To evaluate the substrate scope of this process, a range of *O*-phenyl carbamates was subjected under the optimal reaction conditions (Table 2). The coupling of phenylglyoxylic acid (**2a**) and symmetrical *O*-phenyl carbamates **1b–1d** with an electron-donating group (OMe) and halogen groups (F and Cl) at the *para*-position were found to be favored in the acylation reaction to afford the corresponding products **3b–3d** with excellent levels of monoselectivities (> 20:1), whereas substrates with electron-withdrawing groups (e.g., NO₂ and CO₂Et) at the *para*-position failed to deliver the acylation products under our optimal reaction conditions. The *ortho*-substituted *O*-phenyl carbamates **1e–1g** were also found to be favored in this catalyst system. In addition, the acyla-

tion of *meta*-substituted *O*-phenyl carbamates **1h** and **1i** preferentially occurred at the more sterically accessible position to afford the corresponding product **3h** and **3i** as a single regioisomer. These data suggest that steric effects of the substrate strongly interfere with the formation of the cyclopalladated intermediate or the proximity of α -oxocarboxylic acid **2a** into the cyclopalladated intermediate. However, fluoro-substituted *O*-phenyl carbamate **1j** at the *meta*-position delivered a separable mixture of monoacylated and bisacylated compounds in 54% combined yield with a low level of monoselectivity (2:1) under the current catalyst system.

To further explore the substrate scope and limitations, a range of α -oxocarboxylic acids was screened under optimal reaction conditions, as shown in Table 3. Electron-rich and electron-deficient phenylglyoxylic acids **2b–2f** substituted at either the *para*- or *meta*-positions proved to be good substrates for this transformation, affording the corresponding products **4b–4f**. The halogen moieties on phenylglyoxylic acids **2g–2j** were all tolerated under these reaction condi-

Table 3. Scope of α -oxocarboxylic acids.^[a]

^[a] Reaction conditions: **1d** (0.3 mmol), **2b-I** (0.6 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol%), $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (0.45 mmol), TfOH (20 mol%), DCE (2 mL) in pressure tubes.

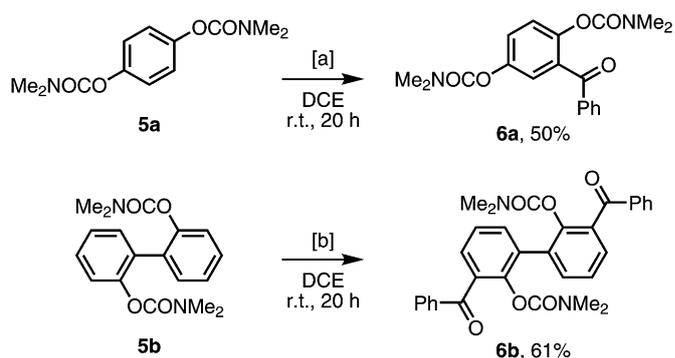
^[b] Yield of product isolated by column chromatography.

tions. Notably, the chloro and bromo groups offer versatile synthetic functionality for further manipulations using other cross-coupling reactions. In addition, 2-(naphthalen-2-yl)-2-oxoacetic acid (**2k**) and 2-oxo-2-(thiophen-2-yl)acetic acid (**2l**) were also found to be favored in the reaction to afford the desired products **4k** and **4l** with a slightly decreased reactivity.

Further investigations for the monoacylation and bisacylation reactions of biscarbamate analogues were conducted (Scheme 2). As expected, biscarbamate **5a** was converted to the monoacylated product **6a** in 50% yield under optimal reaction conditions. Also, biphenyl compound **5b** containing two carbamate directing groups provided exclusively bisacylated product **6b** in 61% yield using two times of the reaction conditions used for monoacylation.

The postulated mechanism is outlined in Scheme 3. First, a coordination of the O atom of **1a** to $\text{Pd}(\text{II})$ and the subsequent directed cyclopalladation provides a 6-membered palladacycle **I**.^[22] At this stage, OTf anion may remarkably improve the electrophilicity of the Pd center, in comparison with acetate anion, en-

hancing the rate of electrophilic metalation.^[23] Thus the palladacycle **I** can react with **2a** to afford the intermediate **II**, which can undergo decarboxylation fol-

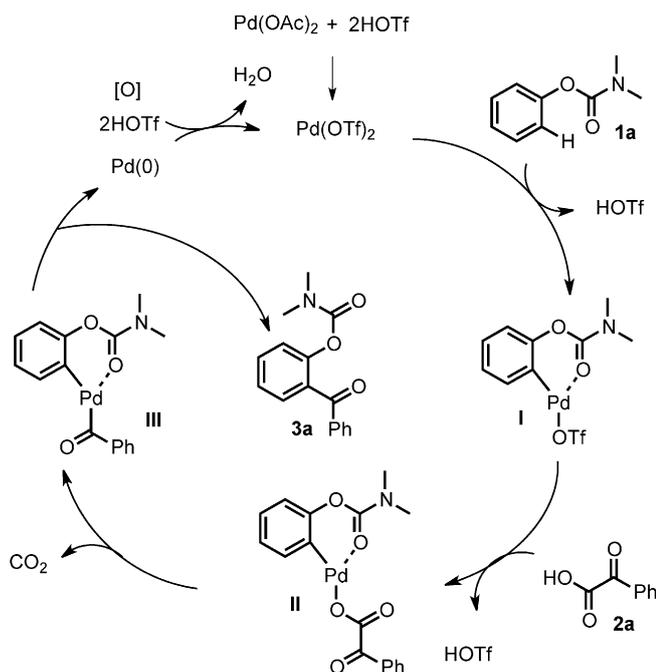


Reaction conditions:

[a] **5a** (0.3 mmol), **2a** (2 equiv.), $\text{Pd}(\text{OAc})_2$ (5 mol%), $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (1.5 equiv.), TfOH (20 mol%).

[b] **5b** (0.3 mmol), **2a** (4 equiv.), $\text{Pd}(\text{OAc})_2$ (10 mol%), $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (3 equiv.), TfOH (40 mol%).

Scheme 2. Monoacylation and bisacylation of biscarbamate analogues.



Scheme 3. Postulated mechanism.

lowed by reductive elimination to give our desired product **3a**, and regenerate Pd(0) catalyst. Finally, Pd(0) can be reoxidized to active Pd(II) catalyst with $(\text{NH}_4)_2\text{S}_2\text{O}_8$. Although the alternative mechanistic pathways involving Pd(II/III)^[24] and/or Pd(II/IV)^[25] catalytic cycles are reasonable to consider, we favor the reaction mechanism based on the Pd(0/II) catalytic cycle.

In conclusion, we have described an efficient method for Pd-catalyzed oxidative *ortho*-acylation of *O*-phenyl carbamates with α -oxocarboxylic acids in the presence of a catalytic amount of triflic acid under ammonium persulfate as a convenient oxidant *via* C–H bond activation. Our ongoing works seek to expand the scope to the acylation of sp^2 C–H bonds without directing groups and unactivated sp^3 C–H bonds.

Experimental Section

Typical Procedure for the Acylation of *O*-Phenyl Carbamates

To an oven-dried sealed tube charged with 4-chlorophenyl dimethylcarbamate (**1d**) (59.9, 0.3 mmol, 1.0 equiv.), Pd(OAc)₂ (3.3 mg, 0.015 mmol, 5 mol%), $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (102.6 mg, 0.45 mmol, 1.5 equiv.), and phenylglyoxylic acid (**2a**) (90.6 mg, 0.6 mmol, 2 equiv.) in DCE (2 mL) was added TfOH (5 μL , 20 mol%). The reaction mixture was allowed to stir at room temperature for 20 h. Then the reaction mixture was diluted with EtOAc (5 mL) and washed with a saturated solution of Na₂CO₃. The aqueous layer was extracted

with EtOAc (10 mL \times 3). The combined organic layer was dried over Mg₂SO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography (*n*-hexanes/EtOAc = 10:1) to afford **3**; yield: 60.2 mg (66%).

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