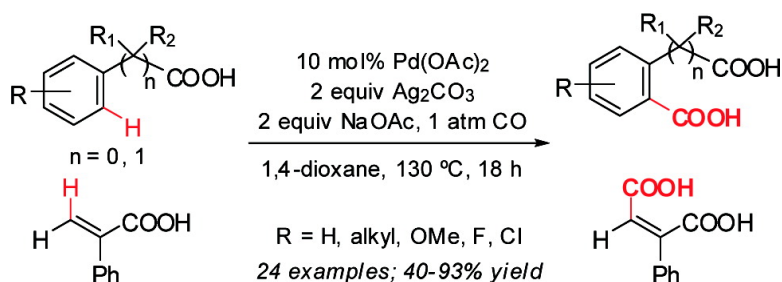


Synthesis of 1,2- and 1,3-Dicarboxylic Acids via Pd(II)-Catalyzed Carboxylation of Aryl and Vinyl C#H Bonds

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J. Am. Chem. Soc., **2008**, 130 (43), 14082-14083 • DOI: 10.1021/ja8063827 • Publication Date (Web): 04 October 2008

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Synthesis of 1,2- and 1,3-Dicarboxylic Acids via Pd(II)-Catalyzed Carboxylation of Aryl and Vinyl C–H Bonds

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Pd(0)-catalyzed Heck carbonylation of aryl halides, triflates, and tosylates is an expedient route to access carboxylic acid derivatives.¹ Direct conversion of aryl and alkyl C–H bonds by Pd(II) catalysts into carboxylic acids using excess arenes and alkanes in trifluoroacetic acid has been reported by Fujiwara.^{2,3} Orito developed an alkylamine-directed regioselective carbonylation of aryl C–H bonds to prepare benzolactams using the substrate as the limiting reagent.⁴ Recently, an intriguing ortho-ethoxycarbonylation of 2-phenylpyridines using diethyl azodicarboxylate as the carboxyl donor was reported.⁵ Herein, we disclose a new carboxylation reaction of broadly useful aryl and vinyl carboxylic acids using a C–H activation/CO insertion sequence. This protocol provides a method for the preparation of dicarboxylic acids which is complementary to the ortho-lithiation/CO₂ insertion process directed by amide groups.⁶ We have also characterized by X-ray crystallography the first C–H insertion intermediate from the cyclometalation of carboxylic acids.

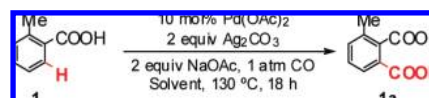
Recently, we found that both inorganic and organic cations drastically accelerate carboxyl-directed C–H activation reactions.^{7,8} We decided to investigate whether this reactivity could be exploited to prepare various dicarboxylic acids via a C–H activation/carboxylation process. Extensive screening of the reaction conditions using *o*-toluic acid as the substrate in the presence of 1 equiv of Pd(OAc)₂ and 1 atm of CO revealed that the use of NaOAc or K₂HPO₄ is crucial for the stoichiometric carboxylation of ortho C–H bonds. Dioxane and *t*-BuOH are suitable solvents for this reaction. Among various oxidants, only Ag₂CO₃ is effective in reoxidizing Pd(0) to Pd(II) to afford catalytic turnovers (Table 1, entries 1–6). Use of other oxidants such as Ag₂O, Cu(OAc)₂, and peroxides gives less than 10% product yields (Table 1, entries 7, 8). Thus, the carboxylation was carried out by stirring a suspension of *o*-toluic acid, 10 mol % Pd(OAc)₂, 2 equiv of NaOAc, and 2 equiv Ag₂CO₃ in dioxane at 130 °C under 1 atm of carbon monoxide to give the product in 80% isolated yield (Table 1, entry 1).

A variety of benzoic acids are carboxylated in good to excellent yields to give phthalic acids (Table 2). While the use of NaOAc as a base is sufficient in most cases, substrates **3**, **4**, and **12** require K₂HPO₄ to give the best yields (Table 2, **3a**, **4a**, **12a**). Interestingly, substrates **5** and **6** require the combination of NaOAc and K₂HPO₄ to achieve good yields (Table 2, **5a**, **6a**).

Significant steric and electronic effects of the substituents on the reactivity are observed. Electron-rich benzoic acids, in general, give better yields and require lower reaction temperature (130 °C) (Table 2, **2a**, **5a–8a**, **10a–14a**). Ortho-substituted benzoic acids are also more efficient substrates than the meta- and para-substituted benzoic acids (Table 2, **2a–8a**). Since the ortho substituents of benzoic acids are known to reduce the electron-withdrawing ability of the carboxyl group as a result of the primary steric effect,⁹ the combined data appear to be consistent with an electrophilic palladation pathway which is favored by electron-rich arenes.¹⁰

Excellent regioselectivity was observed in the carboxylation of meta-substituted benzoic acids. Carboxylation of the more hindered

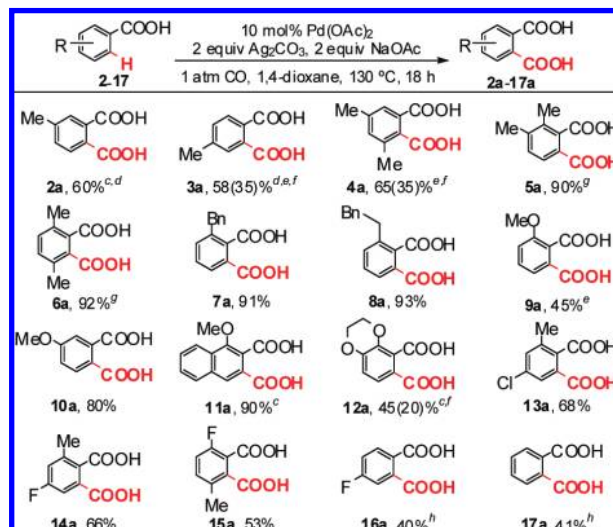
Table 1. Optimization of Reaction Conditions



entry	solvent	yield (%) ^a	entry	solvent	yield (%) ^a
1	1,4-dioxane ^b	80	5	MeCN	50
2	<i>t</i> -BuOH ^b	75	6	toluene	60
3	DMF	33	7	1,4-dioxane	<10 ^c
4	THF	65	8	1,4-dioxane	<10 ^d

^a ¹H NMR yields. ^b Isolated yields. ^c Ag₂O or Cu(OAc)₂ used instead of Ag₂CO₃ as an oxidant. ^d Peroxides or peroxyesters used instead of Ag₂CO₃ as an oxidant.

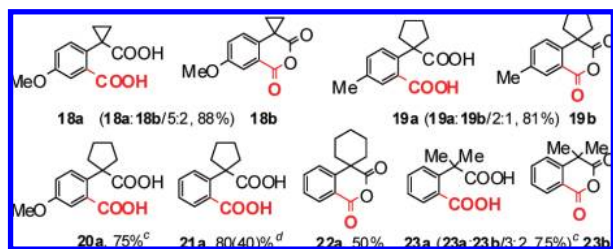
Table 2. Carboxylation of Benzoic Acid and Its Derivatives^{a,b}



^a Run using 10 mol % Pd(OAc)₂, 2 equiv of Ag₂CO₃, 2 equiv of NaOAc, 1 atm of CO, dioxane, 130 °C, 18 h. ^b Isolated yields. ^c Run in 30 h. ^d **2a** and **3a** are the same products obtained from ortho and para toluic acids **2** and **3**, respectively. ^e Run at 150 °C, 30 h. ^f NaOAc was replaced with K₂HPO₄. NMR yields in presence of NaOAc are given in parenthesis. ^g Run with 1 equiv of K₂HPO₄ added. ^h Run at 150 °C, 48 h.

C–H bonds was not observed (Table 2, **2a**, **10a**). The reaction tolerates substrates containing electron-donating groups (methoxy) and moderate electron-withdrawing groups (chloro and fluoro) (Table 2, **9a–16a**). Unfortunately, the presence of strong electron-withdrawing groups such as NO₂ and CO₂Me significantly reduce the yields (<20%), suggesting that the parental carboxyl group and the additional NO₂ or CO₂Me render the aryl ring highly electron-deficient and retard electrophilic palladation.

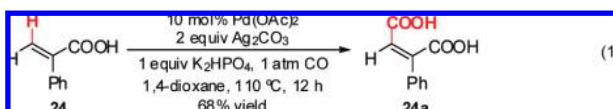
Various α,α -disubstituted phenylacetic acids are carboxylated and/or carbonylated in excellent yields under the current reaction conditions (Table 3).¹¹ Although we have developed *o*-C–H

Table 3. Carboxylation of Phenylacetic Acid Derivatives^{a,b}

^a Run using 10 mol % Pd(OAc)₂, 2 equiv of Ag₂CO₃, 2 equiv of NaOAc, 1 atm of CO, dioxane, 150 °C, 18 h. ^b Isolated yields. ^c Isolated as the corresponding anhydrides. ^d Run with 1 equiv of K₂HPO₄ added. NMR yield in absence of K₂HPO₄ is given in parenthesis.

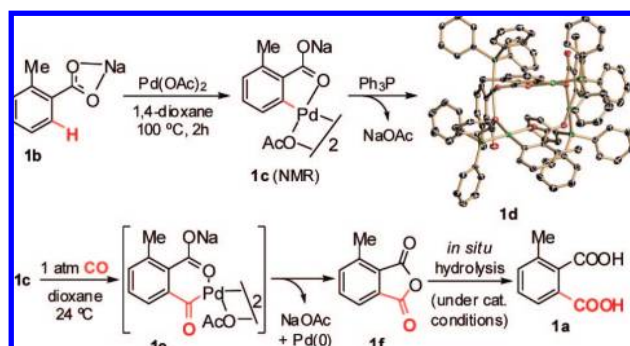
alkylation of phenyl acetic acids using oxazoline as auxiliary,¹² direct functionalization of phenyl acetic acids via six-membered palladacycles has not been achieved to date. This method provides a convenient route for the preparation of 1,3-dicarboxylic acids.

We are pleased to find that the β-vinyl C–H bond in α,β-unsaturated carboxylic acid **24** is also carboxylated selectively to give *cis*-1,2-dicarboxylic acid **24a** in 68% yield.¹³ This reaction protocol could be very useful in the synthesis of natural products containing a succinic acid/anhydride moiety.¹⁴



We have also characterized an intermediate C–H insertion complex in order to gain insight into the catalytic process. Treatment of sodium carboxylate **1b** with Pd(OAc)₂ in CH₂Cl₂ or dioxane at 100 °C gives a cyclopalladated intermediate whose structure is consistent with **1c** by ¹H and ¹³C NMR (Scheme 1).¹⁵ This complex is insoluble in organic solvents other than DMSO. Palladacycle **1c** was also converted into a more soluble tetrameric palladacycle **1d** by stirring it with Ph₃P in CH₂Cl₂ at 24 °C under N₂. The structure of **1d** was then characterized by X-ray crystallography, thus confirming **1c** as the first isolated C–H insertion intermediate from simple carboxylic acids.¹⁶ A suspension of palladacycle **1c** in dioxane or CH₂Cl₂ also reacts stoichiometrically with CO at room temperature to produce the anhydride **1f** quantitatively, possibly via the intermediate **1e**. Under the catalytic conditions, the anhydride **1f** is finally hydrolyzed *in situ* in the presence of base and traces of water to give the dicarboxylic acid **1a**.¹⁷

In summary, we have developed the first Pd(II)-catalyzed reaction protocol for the direct carboxylation of benzoic and phenylacetic acid derivatives to form dicarboxylic acids. The reaction conditions

Scheme 1. Formation and Characterization of Palladacycle **1c**

can be applied to the carboxylation of vinylic C–H bonds. We have also characterized by X-ray crystallography the first cyclo-metalation complex formed from carboxylic acids.

Acknowledgement. We thank The Scripps Research Institute and the U.S. National Science Foundation (NSF CHE-0615716) for financial support, the Camille and Henry Dreyfus Foundation for a New Faculty Award, and A. P. Sloan Foundation for a Fellowship.

Supporting Information Available: Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA8063827