

Palladium-Catalyzed Synthesis of Aromatic Carboxylic Acids with Silacarboxylic Acids

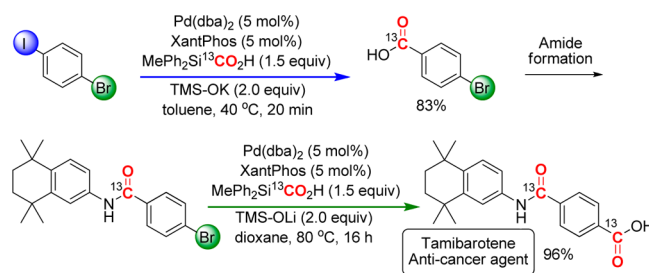
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ABSTRACT



Aryl iodides and bromides were easily converted to their corresponding aromatic carboxylic acids via a Pd-catalyzed carbonylation reaction using silacarboxylic acids as an *in situ* source of carbon monoxide. The reaction conditions were compatible with a wide range of functional groups, and with the aryl iodides, the carbonylation was complete within minutes. The method was adapted to the double and selective isotope labeling of tamibarotene.

Aromatic carboxylic acids and derivatives thereof are important constituents of many bioactive compounds, and hence methods for their synthesis under mild conditions are in continuous demand.¹ The Pd-catalyzed hydroxycarbonylation of aryl halides has emerged as a viable approach to such compounds,² since it overcomes some of the disadvantages of classical methodologies, which often require harsh conditions or reactive intermediates that

may not be tolerant of or compatible with a number of other functional groups.^{1c,3,4} The reaction also requires the manipulation of a highly toxic gas, namely carbon monoxide, and therefore methods that avoid the handling of this gaseous reagent would be of high interest. One possibility is to design reaction conditions that run with substoichiometric CO, generating a reactive intermediate that liberates the product and another molecule of CO.⁵ Another solution is to apply conditions that rely on the *in situ* or *ex situ* generation of CO with carbon monoxide releasing molecules (CORMs) that provide stoichiometric amounts of CO. Such CORMs include $\text{Mo}(\text{CO})_6$,⁶ formates,⁷ acid chlorides,⁸ and others.⁹

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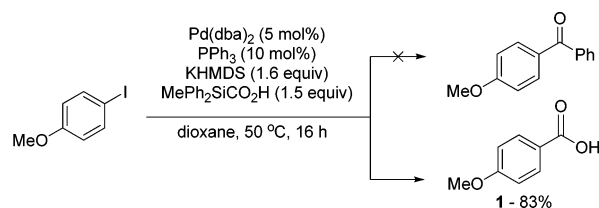
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In this paper, we demonstrate that silacarboxylic acids can operate as an efficient *in situ* CORM for the Pd-catalyzed transformation of aryl iodides and bromides to aromatic carboxylic acids. In particular, some of these reactions are very fast and, in general, a high substrate scope is demonstrated. Furthermore, we show that the methodology can be adapted to the isotope labeling of benzoic acids.

In 2011, we published the application of crystalline silacarboxylic acids as an efficient *ex situ* source of CO in a number of Pd-catalyzed carbonylations with a two-chamber system.¹⁰ In our search for new carbonylative coupling reactions, we recently attempted to utilize the silanoate byproduct, produced via base-induced decarbonylation of a silacarboxylic acid, as a coupling partner in a carbonylative version of the Hiyama–Denmark coupling to generate benzophenone derivatives.¹¹ This transformation was unsuccessful in our hands, leading instead to the rapid generation of the corresponding aryl carboxylic acid **1** (Scheme 1).

Scheme 1. Initial Attempt Results



Nevertheless, with the recognized usefulness of carboxylic acids and short reaction times observed, this result encouraged us to optimize this undesired side reaction. The carboxylation of 4-iodoanisole was found to proceed smoothly in nondried toluene using Pd(dba)₂ and XantPhos¹² in the presence of the weakly alkaline potassium trimethylsilanoate¹³ affording an 85% isolated yield of carboxylic acid **1** after only 15 min at 50 °C (Table 1, entry 3). Changing to other bidentate ligands (DPEphos, BINAP) or PPh₃ only retarded the reaction, and XantPhos was therefore selected for further optimization. Increasing the amount of TMS-OK to 2.0 equiv boosted

the yield to 96% (entry 7),¹⁴ while changing to a Pd(II) precatalyst provided poorer results (entries 8 and 9). Lowering the temperature to 40 °C with a slight increase in the reaction time to 20 min also afforded an excellent yield of the acid (entry 10), whereas a further decrease in the reaction temperature or catalyst loading resulted in the incomplete conversion of 4-iodoanisole to **1** (entries 11 and 12).

Table 1. Optimization Studies for the Pd-Catalyzed Carboxylic Acid Synthesis from Aryl Iodides^a

entry	catalyst	ligand	solvent	time (min)	yield (%) ^b
1	Pd(dba) ₂	XantPhos	THF	120	52
2	Pd(dba) ₂	XantPhos	MeCN	120	64
3	Pd(dba) ₂	XantPhos	toluene	15	85
4	Pd(dba) ₂	DPEphos	toluene	15	59
5	Pd(dba) ₂	BINAP	toluene	15	16
6 ^c	Pd(dba) ₂	PPh ₃	toluene	15	63
7 ^d	Pd(dba) ₂	XantPhos	toluene	15	96
8 ^d	PdCl ₂	XantPhos	toluene	20	0
9 ^d	Pd(OAc) ₂	XantPhos	toluene	20	80
10 ^{d,e}	Pd(dba) ₂	XantPhos	toluene	20	95
11 ^{d,f}	Pd(dba) ₂	XantPhos	toluene	25	85
12 ^{d,g}	Pd(dba) ₂	XantPhos	toluene	20	60

^a Reaction conditions: Under an ambient atmosphere, 4-iodoanisole (0.5 mmol), catalyst (0.025 mmol), ligand (0.025 mmol), MePh₂SiCO₂H (0.75 mmol), TMS-OK (0.75 mmol), and solvent (3.0 mL) were mixed and heated to 50 °C in a closed 8 mL vial. ^b Isolated yield. ^c Ligand (0.05 mmol). ^d TMS-OK (1.0 mmol). ^e 40 °C. ^f 30 °C. ^g Catalyst (0.010 mmol) and ligand (0.010 mmol).

With the catalytic system at hand, operating at low reaction temperatures, we set out to probe the scope and limitations of this rapid carbonylation reaction. Initial investigations were focused on the viability of a range of different *para*-substituted aryl iodides as substrates for the reaction. Gratifyingly, electron-deficient substrates also worked providing compounds **2**, **3**, and **5–7** in excellent yields (Scheme 2). Obtention of product **5** with a free aldehyde demonstrates the mildness of the reactions conditions. 4-Iodothioanisole and the Boc-protected iodoaniline also led to high yields of the acids **8** and **10**. On the other hand, the transformation of 4-iodoaniline and 4-iodophenol failed under these conditions. High selectivity was observed for substrates bearing either a bromide or a boronic ester leading to compounds **9** and **11**, respectively, allowing for further carbon skeleton expansion with for example the Suzuki–Miyaura coupling.¹⁵

3,4-Disubstituted benzoic acid **13** and **16** could be synthesized in good-to-excellent yields, with no observation of demethylated byproducts. The conversion of *ortho*-substituted aryl iodides was more sluggish and required a slight temperature increase to 60 °C, in order to afford **14** and **15**.

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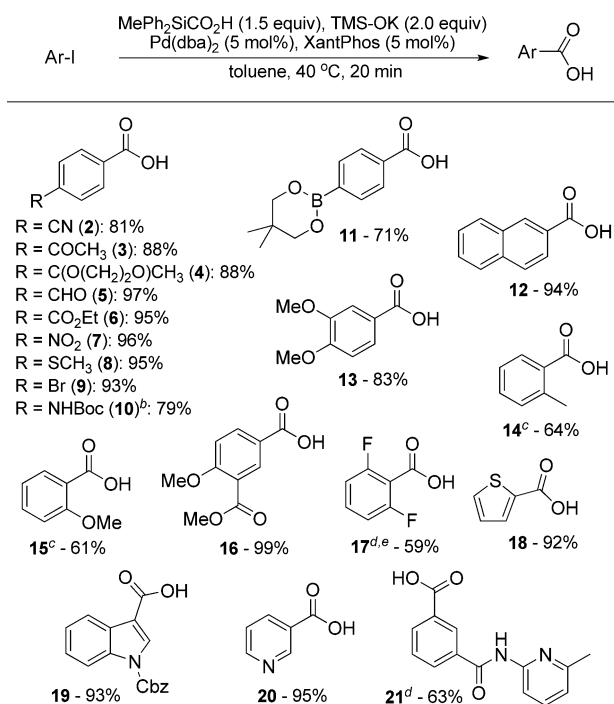
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With the di-*o*-fluoro-substituted aryl iodide, conversion to the corresponding benzoic acid **17** provided a moderate yield of 59%.

Scheme 2. Scope of the Pd-Catalyzed Carboxylic Acid Synthesis from Aryl and Heteroaryl Iodides^a



^a Reaction conditions: Under an ambient atmosphere, aryl/heteroaryl iodide (0.5 mmol), $\text{Pd}(\text{dba})_2$ (0.025 mmol), XantPhos (0.025 mmol), $\text{MePh}_2\text{SiCO}_2\text{H}$ (0.75 mmol), TMS-OK (1.0 mmol), and toluene (3.0 mL) were mixed and heated to 40 °C for 20 min in a closed 8 mL vial; isolated yields given. ^b 0.063 M. ^c 60 °C. ^d 0.13 M. ^e 1 h.

Lastly, a selection of heteroaromatic substrates was examined, providing **18–20** in good yields. Purification of the pyridine-containing compound **21** proved to be somewhat cumbersome, explaining its lower isolated yields and contrasting the full conversion observed by ¹H NMR analysis.¹⁶

We next turned our attention to the suitability of aryl bromides for this transformation. Applying the optimized conditions used in Scheme 2, albeit at 80 °C, provided a 42% yield of acid **1** after 19 h (Table 2, entry 1). Changing the solvent to dioxane produced a comparable yield (entry 3), while exchanging the counterion of the activator to lithium enhanced the yield of benzoic acid **1** to 87% (entry 5). Increasing the amount of silacarboxylic acid and lithium trimethylsilanoate did not furnish a better yield (entry 6), whereas decreasing the reaction temperature to 60 °C almost shut down the reaction (entry 7). Switching to acetonitrile or 2-methyltetrahydrofuran as the solvent led to lower yields of **1** (entries 8 and 9).

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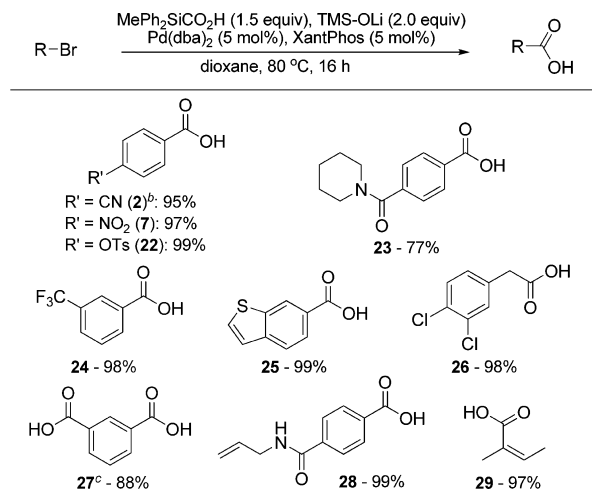
Table 2. Optimization of Reaction Conditions for the Pd-Catalyzed Carboxylic Acid Synthesis from Aryl Bromides^a

entry	solvent	activator	yield (%) ^b
1	toluene	TMS-OK	42
2	toluene	TMS-OLi	18
3	dioxane	TMS-OK	43
4	dioxane	TMS-ONa	37
5	dioxane	TMS-OLi	87
6 ^c	dioxane	TMS-OLi	56
7 ^{c,d}	dioxane	TMS-OLi	5
8	MeCN	TMS-OLi	45
9	2-methyl-THF	TMS-OLi	39

^a Reaction conditions: In a glovebox under an argon atmosphere, 4-bromoanisole (0.5 mmol), $\text{Pd}(\text{dba})_2$ (0.025 mmol), XantPhos (0.025 mmol), $\text{MePh}_2\text{SiCO}_2\text{H}$ (0.75 mmol), activator (1.0 mmol), and solvent (3.0 mL) were mixed and heated to 80 °C for 19 h in a closed 8 mL vial. ^b Isolated yield. ^c $\text{MePh}_2\text{SiCO}_2\text{H}$ (0.85 mmol) and TMS-OLi (1.15 mmol). ^d 60 °C.

With the conditions described in Table 2, entry 5, we proceeded to examine the scope of the transformation of organic bromides into carboxylic acids (Scheme 3). The employment of substrates displaying electron-withdrawing functionalities, including a nitro group in the *para*-position, provided excellent yields of **2** and **7** from the cor-

Scheme 3. Scope of the Pd-Catalyzed Carboxylic Acid Synthesis from Organic Bromides^a



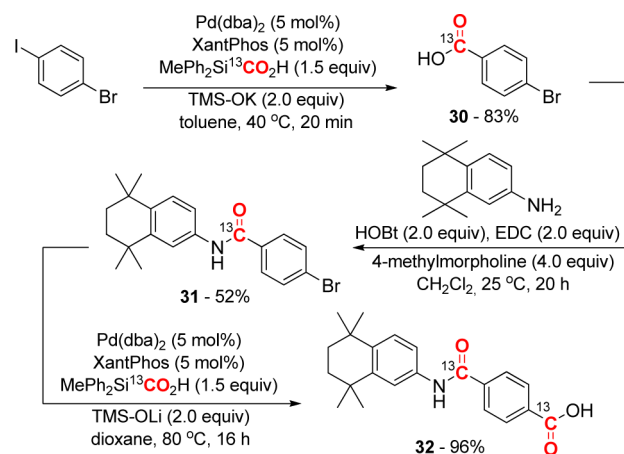
^a Reaction conditions: In a glovebox under an argon atmosphere, organic bromide (0.5 mmol), $\text{Pd}(\text{dba})_2$ (0.025 mmol), XantPhos (0.025 mmol), $\text{MePh}_2\text{SiCO}_2\text{H}$ (0.75 mmol), TMS-OLi (1.0 mmol), and dioxane (3.0 mL) were mixed and heated to 80 °C for 16 h in a closed 8 mL vial; isolated yields given. ^b 97% isolated yield when setup under an ambient atmosphere with subsequent argon flushing. ^c 1,3-Dibromobenzene (0.25 mmol), $\text{Pd}(\text{dba})_2$ (0.013 mmol), XantPhos (0.013 mmol), 7% 3-bromobenzoic acid were observed.

responding bromide.¹⁷ A tosylate and an amide were also well tolerated providing **22** and **23** in yields of 99% and 77%, respectively. On the other hand, ethyl 4-bromobenzoate yielded none of the desired product.

Excellent yields were obtained in the synthesis of *m*-trifluorobenzoic acid **24**, the benzothiophenyl carboxylic acid **25**, and diacid **27**.¹⁸ Compatibility with a terminal double bond was demonstrated by isolating **28** in a 99% yield, with no detectable olefin migration. Finally, we were pleased to observe that alternative substrates such as a benzyl and vinyl bromide were also compatible with these conditions. Hence, phenyl acetic acid **26** was isolated in a 98% yield, whereas, with (*Z*)-2-bromobut-2-ene, 97% of the α,β -unsaturated acid **29** could be isolated with no observable change in stereochemistry.

The applicability of this chemistry was demonstrated in the synthesis of the double ¹³C-labeled version of the potent anticancer agent, tamibarotene.¹⁹ As illustrated in Scheme 4, starting from 1-bromo-4-iodobenzene, the ¹³C-carbonyl labeled benzoic acid **30** was synthesized in an 83% isolated yield using the ¹³C-labeled silacarboxylic acid.¹⁰ After amide formation, the bromide **31** was converted in an excellent yield to double ¹³C-labeled tamibarotene **32**.

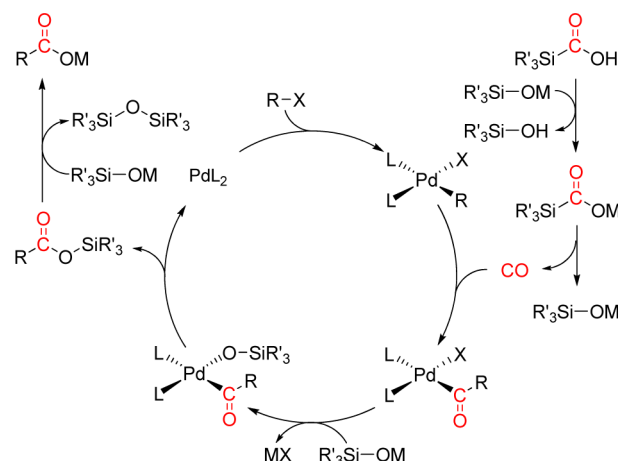
Scheme 4. Double Carbonyl ¹³C-Isotope Labeling of Tamibarotene Employing MePh₂Si¹³CO₂H^a



^a See Supporting Information for experimental details.

A proposed mechanism for the conversion of aryl bromides and iodides to benzoic acids utilizing the described conditions is outlined in Scheme 5.²⁰ Release of carbon monoxide from the silacarboxylic acid can possibly

Scheme 5. Proposed Mechanism



take place by one of two pathways. Deprotonation and subsequent 1,2-Brook rearrangement would generate CO and a silanoate, which can either go on to release another molecule of CO or participate as a nucleophile in the Pd-catalyzed carbonylation.²¹ Alternatively, decarbonylation via S_N2(Si) with TMS-OMe as the nucleophile can also be envisaged,²² leading to CO and hydroxide formation. Equivalent to the silanoate, this hydroxide ion can likely participate at several different stages of the reaction. Subsequent CO insertion into the Pd–C bond formed by oxidative addition, halide–silanoate exchange at the Pd-metal center, and reductive elimination would lead to the silylated benzoic acid. Release of the carboxylate would then be achieved by siloxane formation upon substitution with a silanoate nucleophile.

In summary, we have demonstrated how benzoic acids can be synthesized from aryl and heteroaryl iodides and bromides using palladium catalysis and by applying a silacarboxylic acid as an *in situ* carbon monoxide source. While displaying a wide substrate scope, the methodology also proved to be convenient and high yielding. In particular, reaction times can be as short as a few minutes when using aryl iodides, which suggests the possibility of applying this chemistry for the synthesis of ¹¹C-labeled aromatic carboxylic acids for potential PET investigations. Such studies are ongoing and will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.