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Silacarboxylic Acids as Efficient Carbon Monoxide Releasing Molecules: Synthesis and Application in Palladium-Catalyzed Carbonylation Reactions

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Supporting Information

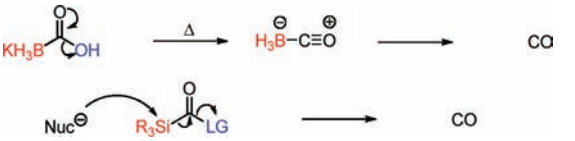
ABSTRACT: Silacarboxylic acids have been demonstrated to be easy to handle, air-stable carbon monoxide precursors. Different silacarboxylic acids were synthesized from the corresponding chlorosilanes and carbon dioxide, and their decarbonylation, upon treatment with an array of activators, was evaluated. The release of CO from crystalline $MePh_2SiCO_2H$ proved to be highly efficient, and it was successfully applied in a selection of palladium-catalyzed carbonylative couplings using near-stoichiometric quantities of carbon monoxide precursor. Finally, the synthesis of $MePh_2Si^{13}CO_2H$ and its application in carbonyl labeling of two bioactive compounds was demonstrated.

Transition-metal-catalyzed carbonylations represents an important class of reactions for the effective preparation of an array of carbonyl-containing compounds. Characteristic of many of these reactions are the mild reaction conditions and the high functional group tolerance. This allows the introduction of a carbonyl group in an advanced intermediate, and hence, much effort has been initiated to improve existing reactions and identify new carbonylation transformations.[1−3]

There is nevertheless a major drawback in the use of transition-metal-catalyzed carbonylations that is related to the nature of the reagents chosen. In most cases, the highly toxic, tasteless, odorless, and colorless gas carbon monoxide is required, and it is often exploited in large excess and in many instances at pressures greater than atmospheric. The need for specially facilitated laboratories equipped with CO detectors and possibly high-pressure reactors limits the use of this small diatomic reagent. Various solids and liquids that are capable of releasing CO upon external stimulation have therefore been developed as alternatives. One example, $Mo(CO)_6$, has been studied and used extensively by Larhed and others, and despite its toxicity, it has proven its worth as a CO surrogate. However, general and mild conditions initiating the decarbonylation steps from these CO precursors are still needed, and most are not feasible for isotopic labeling.[4−7]

We recently reported the use of a two-chamber system that allows several different Pd-catalyzed carbonylation transformations to be conducted in a simple manner.[8,9] The method applies stoichiometric or substoichiometric amounts of a crystalline acid chloride that liberates CO via a Pd-catalyzed decarbonylation process. To simplify this procedure, we have been investigating alternative crystalline CO-releasing molecules (CORMs) that can readily be prepared and activated to release CO upon treatment with a simple non-transition-metal activator. In this communication, we demonstrate the possibility of using silacarboxylic acids as easy-to-handle substrates for this purpose.

Scheme 1. General CO Precursor Motif



Considering earlier work on boranocarbonates as CO-releasing agents, we speculated whether silacarboxylic acids and derivatives thereof could also represent interesting CORMs, as they would potentially be easier to synthesize and handle than the boron-containing analogues (Scheme 1).[10] The limited work previously published demonstrated their CO releasing properties, but only after they were heated at high temperature (>125 °C) or in a nonquantitative manner under basic conditions.[11−13] On the other hand, with the inherent high fluorophilicity of the silicon atom, we were compelled to examine whether decarbonylation could possibly be achieved at ambient temperature with a fluoride source. To this end, several silacarboxylic acids were prepared and their CO-releasing abilities examined.

The silacarboxylic acids were synthesized from their corresponding chlorosilanes via initial reduction using metallic lithium and subsequent reaction with carbon dioxide. With this methodology, three silacarboxylic acids were synthesized in good yields (Table 1). Reduction of the equivalent hydridosilanes with metallic lithium or lithium naphthalide was also examined, but this resulted in less clean conversions and poorer yields.[14,15]

Of the three silacarboxylic acids synthesized, methyldiphenylsilacarboxylic acid (**2**) and *tert*-butyldiphenylsilacarboxylic acid (**3**) proved to be highly crystalline (recrystallization from *n*-heptane), hence facilitating gram-scale synthesis. Attempts to access the triphenylsilacarboxylic acid were also made, resulting in a highly insoluble colorless solid that in the ensuing studies did not release CO upon treatment with a fluoride source.

The decarbonylation of the silacarboxylic acids was evaluated as shown in Table 2. The three precursors were first subjected to

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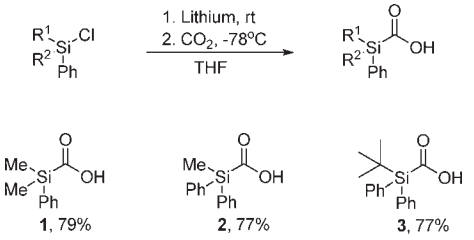
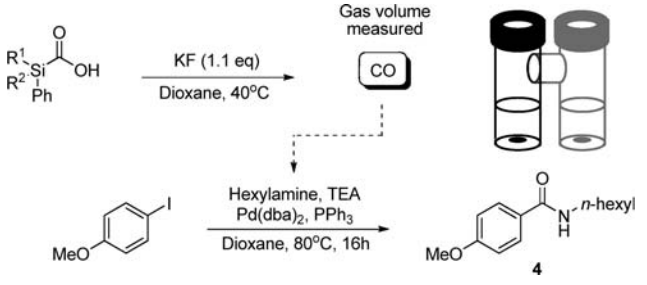
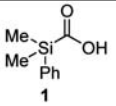
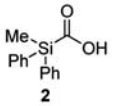
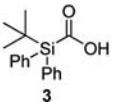
Table 1. Synthesis of Silacarboxylic Acids[a]



[a] Lithium pieces and chlorosilane were stirred in THF for 5 h before the solution was transferred to another flask via cannula, reacted with CO_2 at −78 °C for 20 min, and then allowed to warm to rt.

Table 2. Decarbonylation of Silacarboxylic Acids Using Potassium Fluoride

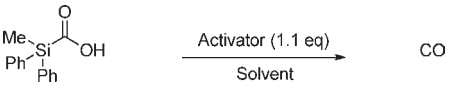


Entry	Precursor	Time [min]	Gas yield [%]	Aminocarbonylation yield [%][a,b]
1	 1	12[c]	90[c]	92
2	 2	10	95	100
3	 3	20	97	96

[a] Chamber A: silacarboxylic acid (0.33 mmol) and KF (0.36 mmol) in dioxane (3 mL). Chamber B: 4-iodoanisole (0.5 mmol), hexylamine (1.0 mmol), TEA (1.0 mmol), $Pd(dba)_2$ (5 mol %), and PPh_3 (10 mol %) in dioxane (3 mL). Both chambers were heated to 80 °C for 16 h [b] Isolated by flash column chromatography. [c] At 60 °C

KF in dioxane, and the gas evolution was monitored over time.[16] To determine the nature and equivalents of the gas released, a substoichiometric amount of each silacarboxylic acid was applied in a Pd-catalyzed aminocarbonylation between *p*-iodoanisole and *n*-hexylamine in a setup involving the two-chamber system as described previously.[8] Both **2** and **3** exhibited near-quantitative CO release at ambient temperature, and excellent yields were obtained for the synthesis of amide **4** (entries 2 and 3). Nevertheless, as silacarboxylic acid **2** was easier to purify by recrystallization and the decarbonylation proved to be the fastest, it was chosen for the subsequent studies.

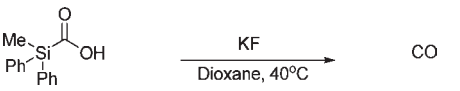
Table 3. Decarbonylation of $MePh_2SiCO_2H$ (2) Employing Different Activators and Solvents



entry	solvent[a]	activator	temp [°C]	time [min]	gas yield [%]
1	DMF	KF	rt	1	94
2	THF	KF	40	5	96
3	dioxane	KF	40	10	95
4[b]	PEG5000	KF	70	20	94
5	water	KF	70	1200	41
6[c]	dioxane	TBAF	rt	1	100
7	dioxane	CsF	rt	7	94
8	dioxane	MeOK	40	7	97
9	dioxane	*t*-BuOK	40	5	86
10	dioxane	$MePh_2SiOK$	40	10	99

[a] Concentration 0.25 M. [b] 0.50 mmol in 1.0 g poly(ethylene glycol) methyl ether. [c] 1 M in THF, concentration 0.20 M.

Table 4. Decarbonylation of $MePh_2SiCO_2H$ (2) Using Substoichiometric Potassium Fluoride[a]



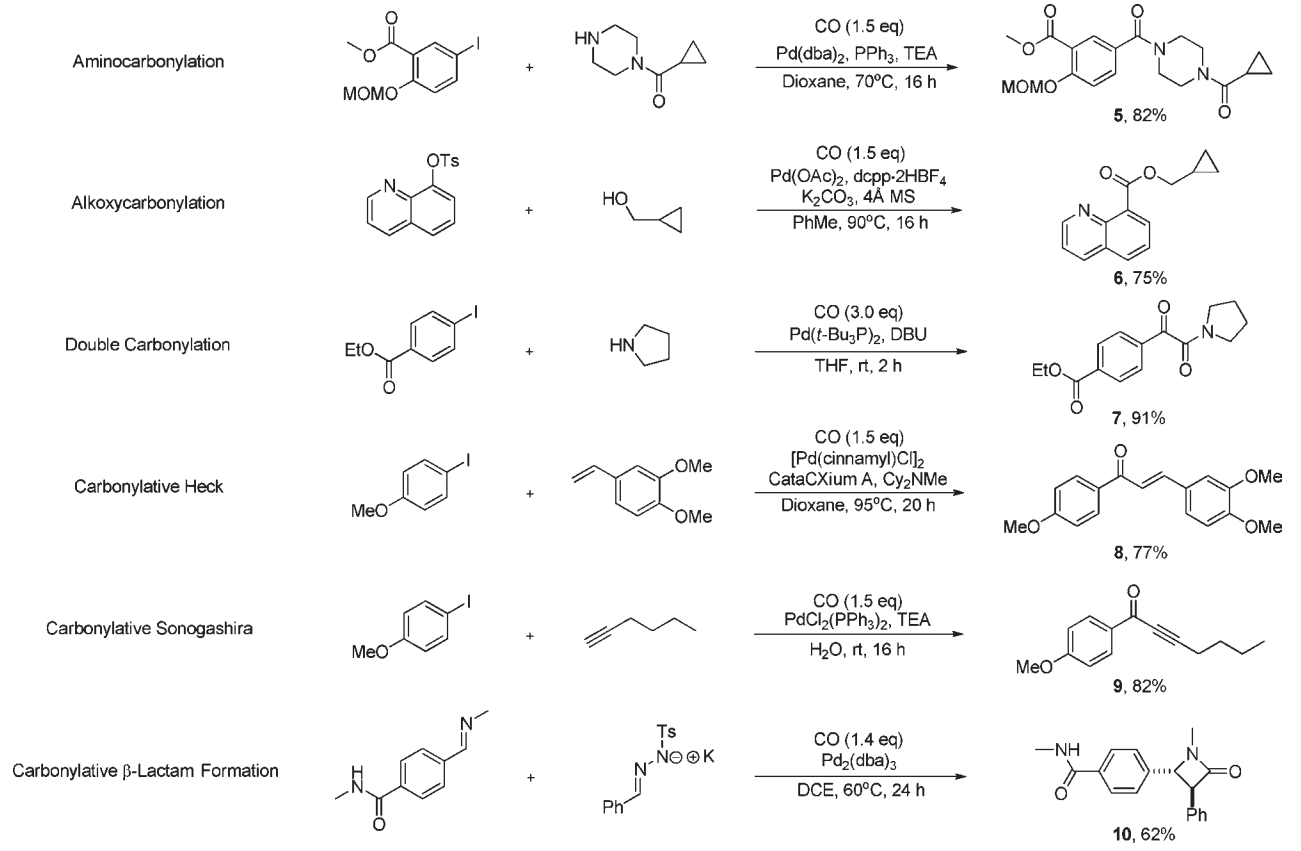
entry	equiv of KF	time [h]	gas yield [%]
1	0.5	0.33	94
2	0.25	0.5	94
3[b]	0.1	2	92
4	0.05	48	78

[a] Concentration 0.25 M. [b] 95% was isolated from an aminocarbonylation producing **4** using 0.67 equiv of $MePh_2SiCO_2H$ and 0.07 equiv of KF.

The results of an evaluation of different solvents and activators for the decarbonylation of **2** are revealed in Table 3. After addition of a slight excess of the given activator and then the solvent, the gas evolution was monitored over time until completion.[16] The decarbonylation of **2** proceeded smoothly in a range of solvents with KF (entries 1−4), with only water giving poor gas evolution (entry 5), which may be explained by the hydration of the fluoride anion and hence modulation of its nucleophilicity. A number of other fluoride activators (entries 6 and 7) and oxygen nucleophiles/bases were also evaluated (entries 8−10).[17] The bulky oxygen-based activators possibly promote decarbonylation through a 1,2-Brook rearrangement rather than nucleophilic addition to silicon by operating as a base with formation of the potassium carboxylate.[18] Whether this is also the operating mechanism in the fluoride-promoted decarbonylation is a matter of ongoing investigations in our group.

The limited solubility of KF in dioxane is in sharp contrast to the fast CO release observed. Additionally, the hydroxide ion leaving the silacarboxylic acid after decarbonylation should be an activator equivalent to potassium methoxide. These considerations indicate that only a substoichiometric quantity of the activator is required. Excellent gas yields were observed even with a loading

Scheme 2. Carbonylative Couplings Using $MePh_2SiCO_2H$ as the CO Source[a]



[a] See Supporting Information for exact reaction conditions.

of 0.1 equiv of KF with only a moderate increase in reaction time (Table 4). This slower CO release could be desirable in a number of cases, as shown by Leadbeater and others.[19−21]

Six different Pd-catalyzed carbonylative couplings were performed with silacarboxylic acid **2** in a two-chamber system (Scheme 2). All of the products were synthesized by applying only a slight excess of the CO precursor at ambient pressure. In general, the CO precursor **2** was dissolved in the same solvent used for the carbonylative coupling, and 1.1 equiv of KF was used as the activator.

In the first example, amide **5** was synthesized using the same conditions as for **4** (Table 2) with a slightly lower temperature, which provided the amide product in 82% yield. Alkoxycarbonylation of 8-tosylquinoline with cyclopropylmethanol afforded the desired ester **6** in 75% isolated yield using slightly modified literature conditions, with only 1.5 equiv of **2** in contrast to the large excess of CO supplied by a balloon.[22]

Double carbonylations of aryl iodides can be conducted at room temperature, as shown by Kondo.[23] Only a few CO precursors, however, have the ability to release quantitative amounts of CO quickly at this temperature.[4−7] As illustrated in the synthesis of compound **7**, silacarboxylic acid **2** proved to be very effective for these types of transformations. When a 3:1 ratio of **2** to aryl iodide was employed, the desired product **7** was isolated in 91% yield after a reaction time of only 2 h.

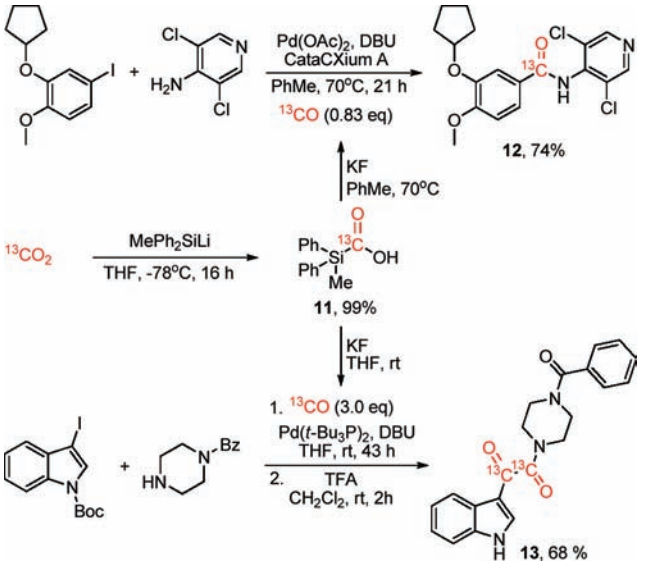
Our group recently published carbonylative Heck reaction conditions using near- and substoichiometric CO generated from a precursor that generally exhibits slower CO release than **2**.[24,25] To reduce the speed of decarbonylation, 0.1 equiv of KF was used for this reaction, resulting in the formation of **8** in 77% yield. Subjecting the same aryl iodide to slightly modified carbonylative Sonogashira reaction conditions with 1-hexyne provided product **9** in 82% isolated yield employing water as solvent.[26] CO release from **2** is, however, very slow in water, and the precursor was therefore dissolved in dioxane using CsF as the activator to ensure prompt decarbonylation.

As a last example, β-lactam **10** was synthesized according to a literature procedure, thereby displaying the mildness and versatility of the carbonylative conditions using silacarboxylic acids. **10** was isolated in a satisfactory 62% yield.[27]

Finally, we examined the potential of this methodology for ^{13}C labeling experiments (Scheme 3). The reaction of a slight excess of methyldiphenylsilyllithium with $^{13}CO_2$ furnished [^{13}C]methyldiphenylsilacarboxylic acid (**11**) in an excellent yield of 99% after recrystallization. Next, **11** was used to provide a substoichiometric quantity of ^{13}CO in the synthesis of piclamilast (**12**).[28] This potent cyclic AMP phosphodiesterase inhibitor was isolated in 74% yield. Compound **13** belongs to a group of HIV-1 inhibitors targeting the glycoprotein gp120 situated in the viral envelope.[29] It was synthesized in a doubly labeled version using a minor excess of ^{13}CO generated from **11** at room temperature and then isolated in 68% yield after deprotection.

In summary, silacarboxylic acids have been presented as versatile, benchtop-stable, easy-to-handle, metal-free CO-releasing molecules.[30] The two-step synthesis of three silacarboxylic acids was demonstrated, and conditions for near-quantitative CO release

Scheme 3. Preparation and Utilization of ^{13}C-Labeled Silacarboxylic Acid[a]



[a] See the Supporting Information for the exact reaction conditions.

from these derivatives were identified. Lastly, near-stoichiometric quantities of $MePh_2SiCO_2H$ were utilized in a number of Pd-catalyzed carbonylative couplings that resulted in good to excellent yields. An application in ^{13}C-isotope labeling was also successfully demonstrated via the synthesis of two labeled bioactive compounds. Efforts to examine the application of these CO-releasing molecules for other carbon-isotope-labeling studies and the challenge of in situ CO generation are now underway.

■ ASSOCIATED CONTENT

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

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