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Silylcarboxylic Acids as Bifunctional Reagents: Application in Palladium-Catalyzed External-CO-Free Carbonylative Cross-Coupling Reactions

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Abstract: A palladium-catalyzed external-CO-free carbonylative Hiyama-Denmark cross-coupling reaction is presented. The introduction of silylcarboxylic acids as bifunctional reagents (CO and nucleophile source) avoids the need for external gaseous CO and a silylarene coupling partner. The transformation features high functional group tolerance and it is successful with electron-rich, -neutral, and -poor aryl iodides. Stoichiometric studies and control experiments provide insight into the reaction mechanism and support the hypothesized dual role of silylcarboxylic acids.

Keywords: Carbonylation; Cross-coupling; Hiyama-Denmark; Palladium-catalysis

Transition-metal-catalyzed carbonylative cross-coupling reactions are considered to be one of the most efficient methods for synthesizing a diverse array of carbonyl compounds. Such carbonylations are widely utilized in pharmaceutical synthesis,^[1] total synthesis of natural products^[2], and valuable chemical manufacturing in industry^[3]. Carbonyl group installation can be realized by employing carbon monoxide (CO), an economical one-carbon building block. However, the toxic nature of CO and the inconvenience of high-pressure storage limit its practical use. In the past decades, CO surrogates such as chloroform,^[4] aldehyde,^[5] transition-metal carbonyl complexes,^[6] N-formylsaccharin,^[7] oxalyl chloride,^[8] and others^[9] have been developed (Scheme 1a). Additionally, our group invented two new CO precursors, Cogen^[10] and SilaCOgen^[11], which combined with a two-chamber reactor, have

been used for various carbonylation reactions.^[12] All the above-mentioned CO sources have their own merits, but they play only one role: providing CO for carbonylation, while the byproducts are treated as waste.

In 2016, we developed a palladium-catalyzed carbonylative Hiyama-Denmark cross-coupling reaction, in which CO₂ is initially reduced by a disilane forming CO and a disiloxane byproduct. Importantly, instead of being discarded as waste, the generated disiloxane takes part in the carbonylative cross-coupling with aryl iodides producing diarylketones (Scheme 1b).^[13] This transformation combines the CO₂ reduction with the carbonylative Hiyama-Denmark coupling reaction efficiently, but the handling is inconvenient due to the requirement of a two-step operation and the need for external gaseous CO₂.

As a continuation of our interest in streamlining carbonylation reactions, we envisioned that it might be possible to combine the CO source and transmetalating agent into one molecule. By using this approach, the addition of a single, bifunctional reagent could facilitate carbonylative cross-coupling reactions and eliminate any need for external gas supply during the reactions. Notably, we have previously developed the silylcarboxylic acid, silaCOgen, as a solid CO precursor, and demonstrated the potential as an *ex-situ* CO source.^[11a] Silylcarboxylic acids are easily prepared on a multigram-scale from CO₂. Subsequent liberation of CO is promoted by fluoride sources leading to a silanol byproduct. However, based on our previous experience and the previous work by others^[14], we hypothesized that, instead of being

wasted, the silanol could serve as an *in-situ* generated nucleophile for carbonylative Hiyama-Denmark cross-coupling reactions. Thus, the silylcarboxylic acid would play a dual role as both CO source and precursor for the nucleophilic cross-coupling partner. Previously, phenyl formate and DMF have been utilized for formal alkoxy- and aminocarbonylations, but these reactions do not involve release of CO (Scheme 1c).^[15,16] To date, our previous report involving external gaseous CO₂ is the only example of catalytic ketone formation employing a dual role CO precursor.

Scheme 1. Overview of Single and Dual Role CO-precursors.

The optimization of this transformation was initiated with 1-iodo-4-methoxybenzene **1a** and methyl diphenylsilanecarboxylic acid **2a**, using Pd(dba)₂ as catalyst, CsF as promotor, and DMF as solvent at 110 °C. After 1 h, the desired product (4-methoxyphenyl)(phenyl)methanone (**3a**) was formed in 12% yield (Table 1, entry 1). A subsequent screening of palladium sources led to identification of PdI₂ as the best-performing palladium source (Table 1, entries 2-7). Interestingly, the addition of phosphine ligands inhibited the reaction (Table 1, entry 8). In contrast, the use of nitrogen ligands generally led to improved yields (Table 1, entry 9). Among them, bipyridine and phenanthroline-based ligands (L5-L10) performed well, especially L6, while bidentate amine ligand (L11-L13) led to lower yields. Addition of copper co-catalysts further improved the yield of **3a** (Table 1, entries 10-12). Among the various solvents tested, NMP showed the best performance (Table 1, entries 13-19). Employing dimethyl(phenyl) silanecarboxylic acid **4** instead of **2a** retarded the transformation (Table 1, entry 20).

Table 1. Optimization of Reaction Conditions for the Carbonylative Hiyama-Denmark Cross-Coupling Reaction with a Silylcarboxylic Acid^[a]

entry	'Pd'	co-cat.	Ligand	Solvent	Yield(3a) ^b
1	Pd(dba) ₂	-	-	DMF	12%
2	Pd(OAc) ₂	-	-	DMF	7%
3	Pd(TFA) ₂	-	-	DMF	15%
4	Pd(acac) ₂	-	-	DMF	20%
5	PdCl ₂	-	-	DMF	20%
6	PdBr ₂	-	-	DMF	22%
7	PdI ₂	-	-	DMF	27%
8	PdI ₂	-	L1-L4	DMF	5%-10% ^[c]
9	PdI ₂	-	L5-L13	DMF	8%-40% ^[c]
10	PdI ₂	CuI	L6	DMF	50%
11	PdI ₂	Cu-1	L6	DMF	62%
12	PdI ₂	Cu-2	L6	DMF	74%
13	PdI ₂	Cu-2	L6	DMA	55%
14	PdI ₂	Cu-2	L6	NMP	91%
15	PdI ₂	Cu-2	L6	DMSO	60%
16	PdI ₂	Cu-2	L6	toluene	trace
17	PdI ₂	Cu-2	L6	dioxane	0%
18	PdI ₂	Cu-2	L6	THF	0%
19	PdI ₂	Cu-2	L6	CH ₃ CN	trace
20 ^[d]	PdI ₂	Cu-2	L6	NMP	75%
21	-	Cu-2	L6	NMP	0%
22 ^[e]	PdI ₂	Cu-2	L6	NMP	0%

^[a]Reactions in this table were performed under an Ar atmosphere at 0.2 mmol scale.

^[b]Yields were determined by GC using dodecane as an internal standard.

^[c]See individual yields by the ligand structures below the table.

^[d]Using **4** instead of **2a**.

^[e]Using PhBr or PhCl instead of **1a**.

A control experiment revealed that the palladium catalyst is essential for the reaction to take place (Table 1, entry 21). Unfortunately, We found that bromobenzene and chlorobenzene failed to proceed this carbonylation. (Table 1, entry 22). Finally, the optimized reaction conditions for this carbonylative

cross-coupling utilizes 5 mol % PdI₂, 10 mol % Cu-2, and 5 mol % L6 as catalyst precursors, 1.8 equiv **2a** as CO source, 2.7 equiv CsF as additive, and NMP as solvent at 110 °C for 1 h (Table 1, entry 14).

Scheme 2. Substrate Scope Investigation for both Aryl Iodides and Silylcarboxylic Acids. Unless Otherwise noted, reactions in this scheme were performed at 0.2 mmol scale. ^[a]Reaction was performed at 5.0 mmol.

With satisfactory reaction conditions established, we next evaluated the scope of this carbonylative Hiyama-Denmark cross-coupling reaction. First, electron-rich aryl iodides were investigated. We found that methyl-substituted iodobenzenes produced the corresponding ketones in excellent yields, even when the methyl group imposes sterical hindrance in the *ortho*-position (**3b–c**). Other electron-donating substituents such as amine (**3d**), pyrrole (**3e**), and dihydrobenzofuran (**3f**) were well-tolerated. The use of electron-neutral aryl iodides also led to high yields of the desired carbonylative cross-coupling products. This is demonstrated with the successful coupling of iodobenzene as well as substrates bearing phenyl, alkenyl, and naphthyl substituents (**3g–k**). Next, the reactivity of electron-deficient aryl iodides was studied. Notably, this methodology proved to be highly efficient in the presence of other aryl halides (**3l–3n**) which can serve as useful handles for further functionalization by other cross-coupling reactions.^[17] Substrates bearing strongly electron-withdrawing

substituents, such as acetyl (**3o**), trifluoromethyl (**3p**), and cyano (**3q**) also successfully underwent the carbonylative cross-coupling reaction. Aryl iodides containing a 3-methoxy group and an ester afforded the diarylketone products in moderate to good yields (**3r–s**). Even a 5-iodo-isatin, which contains a highly reactive carbonyl group, led to a synthetically useful yield of the desired ketone (**3t**). Several heterocyclic aryl iodides were well-tolerated such as indole (**3u**), thiophene (**3v**), 2-, 3-, and 4-pyridine (**3w–y**), pyrazole (**3z**), and quinoline (**3aa**). Finally, different aryl silylcarboxylic acids containing methyl substituents on the benzene ring were examined. Pleasingly, no influence of the positioning of the methyl group was observed as *ortho*-, *meta*-, and *para*-methyl-substituted aryl silylcarboxylic acids all provided comparable yields for the carbonylative Hiyama-Denmark cross-coupling reaction (**3ab–ad**). Moreover, *tert*-butyl-substituted aryl silylcarboxylic acid could react with 4-iodobenzonitrile to give the corresponding ketone (**3ae**) in a moderate yield. Lastly, on a 5.0 mmol scale, ketone **3a** was formed in 61% yield from the corresponding Aryl iodide.

Scheme 3. Investigation of the Reaction Mechanism.

To gain more insight into the reaction mechanism of the transformation, a few experiments were carried out (Scheme 3). By heating a THF solution of 1-iodo-4-methoxybenzene (**1a**) and stoichiometric amounts of Pd(dba)₂ and L6 to 50 °C for 5 h, the oxidative addition complex **I** was isolated in 19% yield.^[18] The structure of **I** was confirmed by X-ray crystallography.^[19] Under a CO atmosphere (THF, 50 °C), palladium complex **I** was cleanly transformed into the CO insertion complex **II**, which was isolated in 90% yield. Under the standard catalytic conditions, the use of palladium complex **I** instead of PdI₂ led to 80% yield of **3a**. Furthermore, the treatment of

palladium complex **II** with methyldiphenylsilanol in the presence of 2.0 equiv Cu-2 and 2.7 equiv CsF in NMP led to the formation of compound **3a** in 50% yield, thus clearly indicating the potential of the silanol byproduct as transmetalating agent.

Based on the results shown above, a plausible mechanism is proposed (Figure 1). First, silylcarboxylic acid (**2a**) is promoted by CsF to release CO and silanolate. Meanwhile, phenanthroline-ligated Pd(0) can undergo oxidative addition into 1-iodo-4-methoxybenzene (**1a**) forming palladium complex **I**. This complex can evolve into palladium complex **II** by addition of the CO released from the silylcarboxylic acid. Next, silanolate **III** enter the cycle via ligand exchange. The formed Cu-silanolate **IV** proceed the transmetalation with complex **II** to furnish a Pd(II) complex **V**,^[13,20] followed by β -Ph elimination to generate complex **VI**. Finally, reductive elimination of product **3a** closes the catalytic cycle.

Figure 1 Mechanistic hypothesis for the carbonylative cross-coupling.

In summary, we have developed a novel methodology where the CO precursor serves a dual purpose: 1) providing CO for the carbonylation and 2) providing the nucleophilic coupling partner for the carbonylative Hiyama-Denmark cross-coupling reaction. This transformation provides a new perspective for the development of carbonylative cross-coupling reactions as it demonstrates the possibility for using a single, bifunctional reagent without the need for an ex-situ carbon monoxide supply. The developed reaction features high functional group tolerance, and it is successful with electron-rich, -neutral, and -poor aryl iodides, even when sterical hindrance is present in the *ortho*-position. Finally, our mechanistic studies are consistent with the hypothesized mode of operation.

Experimental Section

General procedure: In the glovebox, aryl iodide **1** (0.2 mmol, 1.0 equiv), silacarboxylic acid **2** (3.6 mmol, 1.8 equiv), PdI₂ (0.01 mmol, 5 mol %), Phenanthroline (0.01 mmol, 5 mol %), CuTc (0.02 mmol, 10 mol %), and CsF (0.54 mmol, 2.7 equiv) were added into an oven-dried 15 mL vial with a magnetic stirring bar, followed by addition of NMP (1.0 mL). The vial was sealed and heated to various temperature. After 1 h, the vial was cooled to room temperature. The residue was purified by flash column chromatography to give the desired product.

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