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Palladium(II)-Catalyzed Direct Carboxylation of Alkenyl C−H Bonds with CO_2

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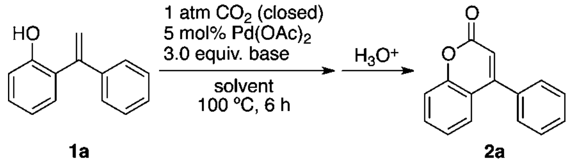
Supporting Information

ABSTRACT: Pd-catalyzed direct carboxylation of alkenyl C−H bonds with carbon dioxide was realized for the first time. Treatment of 2-hydroxystyrenes and a catalytic amount of $Pd(OAc)_2$ with Cs_2CO_3 under atmospheric pressure of CO_2 afforded corresponding coumarins in good yield. Furthermore, isolation of the key alkenylpalladium intermediate via C−H bond cleavage was achieved. The reaction was proposed to undergo reversible nucleophilic addition of the alkenylpalladium intermediate to CO_2.

The catalytic, direct carboxylation of C−H bonds under atmospheric pressure of carbon dioxide is highly attractive as a straightforward method for the synthesis of carboxylic acid derivatives.[1] Recently, several groups including ours reported transition metal catalyzed direct carboxylation of sp^2 C−H bonds of aromatic molecules; however, catalytic carboxylation of alkenyl sp^2 C−H bonds has not yet been realized.[2,3] Moreover, efficient direct carboxylation of unactivated C−H bonds required pyrophoric reducing reagent such as $AlMe_2(OMe)$ in order to generate the highly nucleophilic species.[2d,4] We focused on Pd(II) catalysts, as the nucleophilic carboxylation reaction of organopalladium(II) species has several precedents,[5] and Pd(II) could undergo alkenyl C−H bond cleavage without changing the valency of palladium.[6] We therefore expected that, by utilizing these characteristics, the catalytic direct carboxylation of alkenyl C−H bonds could be achieved without using reducing reagents. We have chosen 2-hydroxystyrenes as substrate with the expectation that the hydroxy group would behave as a directing group for C−H activation.[7−9]

We first examined the reaction employing α-phenyl-2-hydroxystyrene **1a** with 5 mol % of $Pd(OAc)_2$ in diglyme at 100 °C under CO_2 atmosphere in a closed system in the presence of various bases. We found that, by using KO*t*-Bu as base, the desired carboxylated product, 4-phenylcoumarin **2a**, was obtained in 16% yield (Table 1, entry 3). The efficiency of the reaction was improved dramatically by using Cs_2CO_3 as base to give **2a** in high yield (entry 6), but other bases were not effective for this reaction. Examination of solvents revealed that various kinds of solvents could be employed for this reaction. Whereas polar solvents such as DMF and DMSO gave the desired product in slightly lower yield, diglyme gave the best result for this reaction (entries 6−9). The reaction without $Pd(OAc)_2$ was carried out only to recover the starting material quantitatively.[10]

Table 1. Screening of Reaction Conditions



entry	solvent	base	**2a** (%)[a]	**1a** (%)[a]
1	diglyme	none	0	quant.
2	diglyme	LiO*t*-Bu	2	96
3	diglyme	KO*t*-Bu	16	75
4	diglyme	K_2CO_3	0	quant.
5	diglyme	$CsOH{\cdot}H_2O$	0	98
6	diglyme	Cs_2CO_3	86[b]	8
7	cyclooctane	Cs_2CO_3	80	14
8	1,4-dioxane	Cs_2CO_3	72	24
9	DMF	Cs_2CO_3	73	16
10	DMSO	Cs_2CO_3	69	25

[a] Based on ^1H NMR. [b] Isolated yield.

This reaction was applied to various functionalized 2-hydroxystyrenes. A wide range of substrates bearing an electron-donating or an electron-withdrawing group on the phenyl ring at α-position of 2-hydroxystyrene gave the corresponding coumarins in good yield (Table 2, entries 2−5). Furthermore, the substrates bearing a functional group such as 4-cyanophenyl, 3,4-methylenedioxyphenyl, pyrrole, and thiophene group also provided the desired carboxylation products without affecting these groups (entries 6−9). It should be noted that bromophenyl moiety was not affected under the reaction conditions, implying no formation of Pd(0) species (entry 10). α-Methyl and nonsubstituted 2-hydroxystyrenes also gave the corresponding coumarins (entries 11 and 12). Substitution of methyl or methoxy group on the phenol ring caused no problem with increased catalyst loadings, and 3-hydroxypyridine derivative **1p** afforded corresponding carboxylation product **2p** in moderate yield (entries 13−16). Unfortunately, β-substituted 2-hydroxystyrenes did not give the desired products.

To obtain information on the reaction mechanism, observation of the reaction intermediates was examined under stoichiometric conditions (Scheme 1). Treatment of α-phenyl-2-hydroxystyrene **1a** with $Pd(OAc)_2$ (1 equiv) in DMSO-d_6 at room temperature smoothly afforded the cyclometalated

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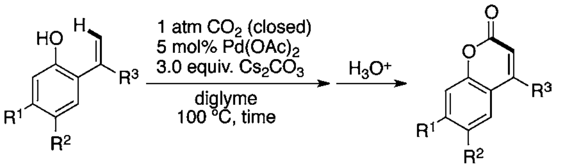
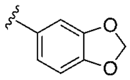
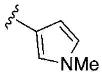
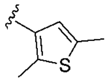
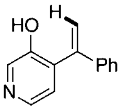
Table 2. Generality

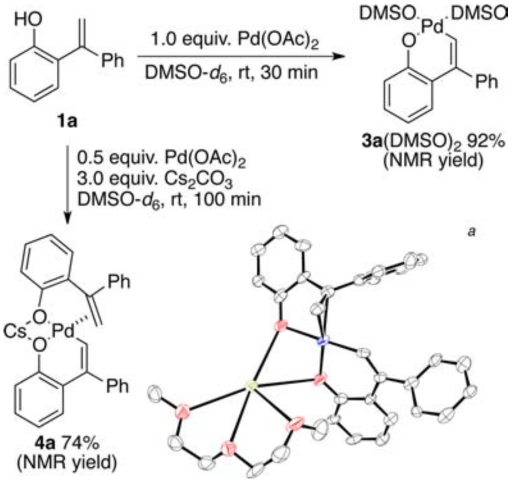


1a-p **2a-p**

Entry	R^1	R^2	R^3		time	Yield
1	H	H	Ph	**1a**	8 h	**2a** 86%
2			p-$MeOC_6H_4$	**1b**	7 h	**2b** 83%
3			p-MeC_6H_4	**1c**	12 h	**2c** 82%
4			o-MeC_6H_4	**1d**	18 h	**2c** 78%
5			p-$CF_3C_6H_4$	**1e**	6 h	**2e** 81%
6			p-NCC_6H_4	**1f**	6 h	**2f** 90%
7				**1g**	7 h	**2g** 88%
8			 NMe	**1h**	6 h	**2h** 74%
9			 S	**1i**	10 h	**2i** 81%
10			p-BrC_6H_4	**1j**	4 h	**2j** 82%
11[a]			Me	**1k**	10 h	**2k** 83%
12			H	**1l**	8 h	**2l** 73%
13	MeO	H	Ph	**1m**	6 h	**2m** 84%
14[b]	H	MeO	Ph	**1n**	12 h	**2n** 80%
15[b]	H	Me	Ph	**1o**	12 h	**2o** 75%
16[c]	 HO H N Ph			**1p**	15 h	**2p** 50%

[a]Cyclooctane was used as solvent. [b]7.5 mol % of $Pd(OAc)_2$ was employed. [c]10 mol % of $Pd(OAc)_2$ was employed.

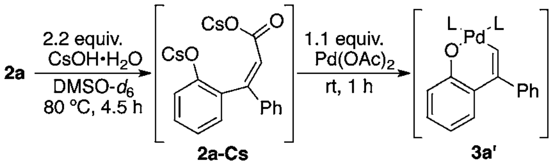
Scheme 1. Formation of Alkenylpalladium Complexes



[a]ORTEP diagram of alkenylpalladium complex **4a·diglyme** at the 50% probability level (H atoms have been omitted for clarity). The diagram shows half of a dimerized symmetric structure.

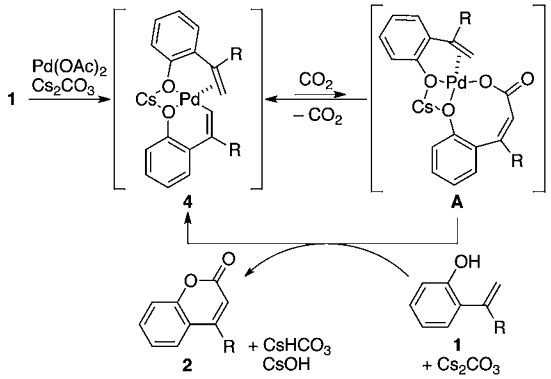
complex **3a**$(DMSO)_2$, which was generated via alkenyl C−H bond cleavage.[11,12] In contrast, the mixture of **1a** and 0.5 equiv of $Pd(OAc)_2$ with Cs_2CO_3 was found to give an alkenyl palladium intermediate **4a**, which was coordinated by a cesium salt of **1a**. Complex **4a** was also observed under the catalytic reaction conditions using DMSO-d_6 as a solvent and the structure was confirmed by X-ray analysis of a single crystal.[13] Quite interestingly, the carboxylation reactions of the complexes **3a** and **4a** themselves with CO_2 did not proceed at all;[13] however, they showed a similar catalytic activity just like $Pd(OAc)_2$ when they were employed as a catalyst under the conditions shown in Table 2.

Scheme 2. Decarboxylation of Palladium Carboxylate Complexes



As these intriguing results concerning stoichiometry were thought to be due to the reversible nucleophilic addition of the alkenylpalladium intermediate to CO_2 and its unfavorable equilibrium for carboxylation product, the following experiment was carried out to confirm this point. In situ formation of cesium carboxylate **2a-Cs** by treatment of $CsOH·H_2O$ and coumarin **2a**, followed by addition of $Pd(OAc)_2$ (1 equiv) was monitored by ^1H NMR in DMSO-d_6 (Scheme 2). As a result, the complex **3a′** similar to **3a**$(DMSO)_2$ was generated by rapid decarboxylation at room temperature.[14] This result confirmed the reversibility of the carboxylation reaction with CO_2 with the equilibrium in favor of the decarboxylation side.[15] Under the catalytic conditions, the equilibrium would become in favor of the carboxylation side due to the participation of the third molecule of substrate to regenerate complex **4a**.[16]

Scheme 3. Proposed Mechanism



Although further studies are required to clarify the precise mechanism of the reaction, our proposed mechanism is shown in Scheme 3. First the six-membered alkenyl palladium intermediate **4** is produced by chelation-assisted alkenyl C−H bond cleavage of 2-hydroxystyrene with $Pd(OAc)_2$ along with coordination of the second molecule of 2-hydroxystyrene **1** as its cesium salt. Subsequently, alkenyl palladium(II) **4** undergoes reversible nucleophilic carboxylation to afford palladium carboxylate intermediate **A**, which reacts with another molecule of 2-hydroxystyrene **1** and base to give coumarin with regeneration of the cyclometalated intermediate **4**.[17] The shift of the carboxylation−decarboxylation equilibrium to the carboxylation side could be attributed to the lactonization process.[18]

In conclusion, we have developed a catalytic direct carboxylation of unactivated alkenyl C−H bond of 2-hydroxystyrenes. This is the first example of Pd(II)-catalyzed alkenyl C−H bond functionalization with nucleophilic carboxylation. Furthermore, isolation of the alkenyl palladium intermediate suggested the importance of the regeneration step of intermediate **4** in this reaction. Further studies to reveal the detailed mechanism are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Preparative methods, spectral and analytical data for compounds **1**, **2**, **3a**, and **4a**, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) Under harsher conditions with KO*t*-Bu as base, a mixture of some carboxylated products was obtained. See Supporting Information.

(11) Alkenylpalladium complex **3a**(DMSO)$_n$ ($n < 2$; ^{1}H NMR spectrum and elemental analysis indicated $n \approx 1.7$) was isolated in 41% yield, which gave a single crystal suitable for X-ray analysis by ligand exchange of DMSO with 1,10-phenanthroline. See Supporting Information.

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(13) For full experimental details, see Supporting Information.

(14) ^{1}H NMR spectrum of **3a′**, whose "L" might be acetate anion, was in good agreement with a mixture of **3a**(DMSO)$_n$ and CsOAc (2 equiv) in DMSO-d_6.

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(16) Although none of the product was obtained at all when 50 mol % of $Pd(OAc)_2$ was employed, coumarin **2a** was obtained in 32% yield when 33 mol % of $Pd(OAc)_2$ was employed in cyclooctane. These results indicated that the third molecule of substrate was required for the formation of the coumarin by the reaction with complex **4a**.

(17) Direct observation of the reaction of **1a** in DMSO-d_6 revealed that coumarin **2a** was formed in 63% yield (determined by ^{1}H NMR) under the catalytic conditions without quenching by 1 N HCl.

(18) Exchange of palladium carboxylates with cesium carboxylates could also be an important step for the shift of the equilibrium, although direct observation of the reaction mixture did not show the presence of **2a-Cs** during the reaction.