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

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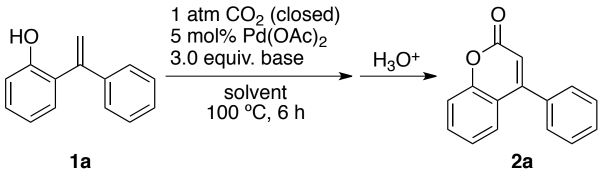
Supporting Information Placeholder

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.[7,8,9]

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. And it was 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. While 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



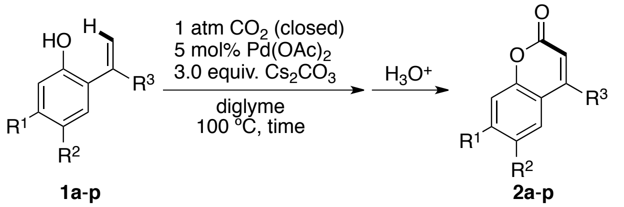
entry	solvent	base	**2a** (%)[a]	**1a** (%)[a]
1	diglyme	none	0	quant.
2	diglyme	LiO*t*-Bu	2	96
3	diglyme	KO*t*-Bu	16	75
4	diglyme	K_2CO_3	0	quant.
5	diglyme	$CsOH•H_2O$	0	98
6	diglyme	Cs_2CO_3	86[b]	8
7	cyclooctane	Cs_2CO_3	80	14
8	1,4-dioxane	Cs_2CO_3	72	24
9	DMF	Cs_2CO_3	73	16
10	DMSO	Cs_2CO_3	69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

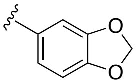
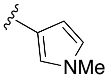
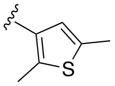
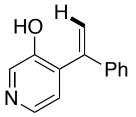
[a] Based on ^1H NMR. [b] Isolated yield.

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 non-substituted 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.

Table 2. Generality

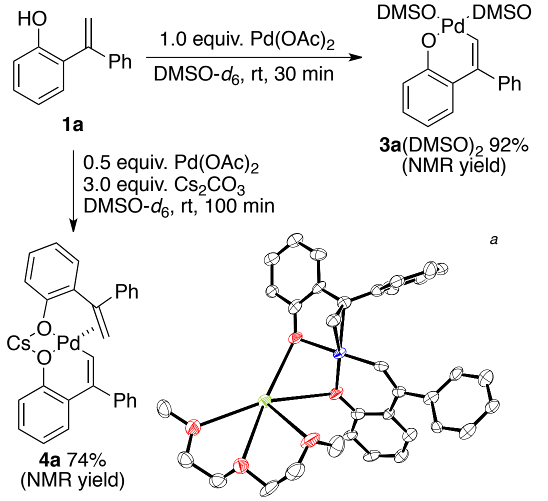


Entry	R^1	R^2	R^3		time	Yield
1	H	H	Ph	**1a**	8 h	**2a** 86%
2			*p*-$MeOC_6H_4$	**1b**	7 h	**2b** 83%
3			*p*-MeC_6H_4	**1c**	12 h	**2c** 82%
4			*o*-MeC_6H_4	**1d**	18 h	**2c** 78%
5			*p*-$CF_3C_6H_4$	**1e**	6 h	**2e** 81%
6			*p*-NCC_6H_4	**1f**	6 h	**2f** 90%
7				**1g**	7 h	**2g** 88%
8				**1h**	6 h	**2h** 74%
9				**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]				**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.

In order 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 complex **3a**$(DMSO)_2$, which was generated via alkenyl C-H bond cleavage.[11,12] In contrast, the mixture of **1a** and 0.5 equivalent 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.

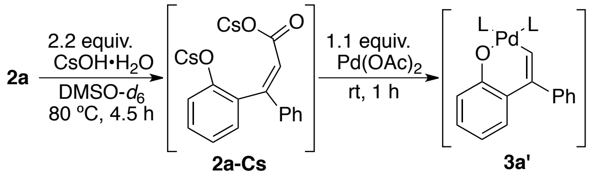
Scheme 1. Formation of Alkenylpalladium Complexes



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

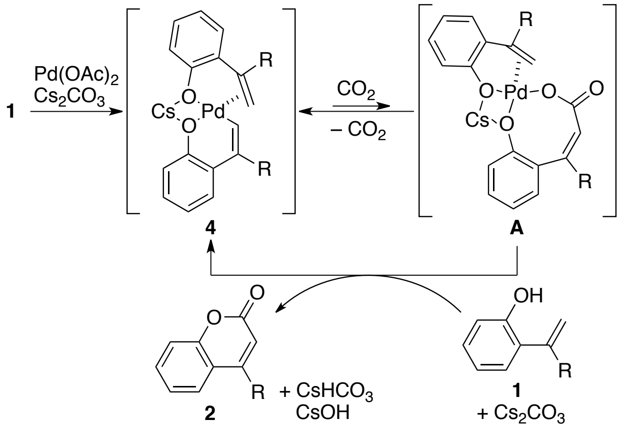
As these intriguing results concerning stoichiometry were thought to be due to the reversible nucleophilic addition of the alkenylpalladium intermediate to CO_2 and its unfavorable equilibrium for carboxylation product, the following experiment was carried out to confirm this point. Thus, in-situ formation 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 2. Decarboxylation of Palladium Carboxylate Complexes



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]

Scheme 3. Proposed Mechanism



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

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REFERENCES

(1) For reviews on transition metal-promoted CO_2-fixation reactions, see; (a) Braunstein, P.; Matt, D.; Nobel, D. *Chem. Rev.* **1988**, *88*, 747. (b) Yin, X.; Moss, J. R. *Coord. Chem. Rev.* **1999**, *181*, 27. (c) Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365. (d) *Carbon Dioxide as Chemical Feedstock*; Aresta, M., Ed.; Wiley-VCH: Weinheim, 2010. (e) Correa, A.; Martín, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6201. (f) Riduan, S. N.; Zhang, Y. *Dalton Trans.* **2010**, *39*, 3347. (g) Huang, K.; Sun, C.-L.; Shi, Z.-J. *Chem. Soc. Rev.* **2011**, *40*, 2435. (h) Cokoja, M.; Bruckmeier, C.; Rieger, B.; Herrmann, W. A.; Kühn, F. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8510. (i) Tsuji, Y.; Fujihara, T. *Chem. Commun.* **2012**, *48*, 9956.

(2) (a) Zhang, L.; Cheng, J.; Ohishi, T.; Hou, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 8670. (b) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R. L.; Cazin, C. S. J.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8674. (c) Boogaerts, I. I. F.; Nolan, S. P. *J. Am. Chem. Soc.* **2010**, *132*, 8858. (d) Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251. (e) Inomata, H.; Ogata, K.; Fukuzawa, S.-I.; Hou, Z. *Org. Lett.* **2012**, *14*, 3986.

(3) Fujiwara and co-workers reported Pd-catalyzed direct carboxylation of arenes, albeit with low conversion, see; Sugimoto, H.; Kawata, I.; Taniguchi, H.; Fujiwara, Y. *J. Organomet. Chem.* **1984**, *266*, C44.

(4) Direct carboxylation reactions of C-H bonds without reducing reagents were reported but they were limited to substrates that have rather acidic protons (pK_a of about 30), see ref 2a, 2b, 2c, and 2e.

(5) For recent selected examples of Pd-catalyzed carboxylation reactions with CO_2, see; (a) Johansson, R.; Jarenmark, M.; Wendt, O. F. *Organometallics* **2005**, *24*, 4500. (b) Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 7826. (c) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254. (d) Correa, A.; Martín, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974. (e) Takaya, J.; Sasano, K.; Iwasawa, N. *Org. Lett.* **2011**, *13*, 1698. (f) Hruszkewycz, D. P.; Wu, J.; Hazari, N.; Incarvito, C. D. *J. Am. Chem. Soc.* **2011**, *133*, 3280. (g) Feng, X.; Sun, A.; Zhang, S.; Yu, X.; Bao, M. *Org. Lett.* **2013**, *15*, 108, and references cited therein.

(6) For Pd-catalyzed alkenyl C-H bond olefination reactions via alkenyl C-H bond cleavage, see; (a) Silva, M. J.; Gonçalves, J. A.; Alves, R. B.; Howarth, O. W.; Gusevskaya, E. V. *J. Organomet. Chem.* **2004**, *689*, 302. (b) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623. (c) Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372. (d) Li, M.; Li, L.; Ge, H. *Adv. Synth. Catal.* **2010**, *352*, 2445. (e) Xu, Y.-H.; Wang, W.-J.; Wen, Z.-K.; Hartley, J. J.; Loh, T.-P. *Tetrahedron Lett.* **2010**, *51*, 3504. (f) Yu, H.; Jin, W.; Sun, C.; Chen, J.; Du, W.; He, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5792. (g) Xu, Y.-H.; Chok, Y. K.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 1822. (h) Yu, Y.-Y.; Niphakis, M. J.; Georg, G. I. *Org. Lett.* **2011**, *13*, 5932. (i) Zhang, Y.; Cui, Z.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 1838. (j) Gigant, N.; Gillaizeau, I. *Org. Lett.* **2012**, *14*, 3304. (k) Chen, Y.; Wang, F.; Jia, A.; Li, X. *Chem. Sci.* **2012**, *3*, 3231. (l) Wen, Z.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Eur. J.* **2012**, *18*, 13284. (m) Moon, Y.; Kwon, D.; Hong, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11333. (n) Min, M.; Kim, Y.; Hong, S. *Chem. Commun.* **2013**, *49*, 196. (o) Shang, X.; Liu, Z.-Q. *Chem Soc. Rev.* **2013**, *42*, 3253. For Pd-catalyzed alkenyl C-H bond arylation reactions via alkenyl C-H bond cleavage, see; (p) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708. (q) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F.; *Angew. Chem., Int. Ed.* **2008**, *47*, 7230. (r) Zhou, H.; Chung, W.-J.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2009**, 3472. (s) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355. (t) Gamble, A. B.; Keller, P. A. *Chem. Commun.* **2010**, *46*, 4076. (u) Li, C.; Zhang, Y.; Li, P.; Wang, L. *J. Org. Chem.* **2011**, *76*, 4692. (v) Min, M.; Hong, S. *Chem. Commun.* **2012**, *48*, 9613. (w) Yu, Y.-Y.; Bi, L.; Georg, G. I. *J. Org. Chem.* **2013**, *78*, 6163. See also ref 6k, and 6m. For other examples including vinylpalladium species generated via alkenyl C-H bond cleavage, see; (x) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (y) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2012**, *14*, 4358.

(7) Recently, Alper's group reported Pd-catalyzed oxidative cyclocarbonylation of 2-hydroxystyrenes with carbon monoxide for the synthesis of coumarins, see; Ferguson, J.; Zeng, F.; Alper, H. *Org. Lett.* **2012**, *14*, 5602.

(8) For Pd-catalyzed C-H bond functionalization reactions with phenolic hydroxyl group as directing group, see; (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740. (b) Miura, M.; Tsuda, T.; Satoh, T.; Nomura, M. *Chem. Lett.* **1997**, 1103. (c) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (d) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961. (e) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250. (f) Wei, Y.; Yoshikai, N. *Org. Lett.* **2011**, *13*, 5504.

(9) Hoberg and co-workers reported nickel-mediated reaction of styrene with CO_2 to give cinnamic acid, which is an early example of a formal direct carboxylation of styrene using a stoichiometric amount of nickel although this reaction proceeded through oxidative cyclization followed by β-hydride elimination. See; Hoberg, H.; Peres, Y.; Milchereit, A. *J. Organomet. Chem.* **1986**, *307*, C38.

(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≈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-phenanthoroline. See Supporting Information.

(12) Newkome, G. R.; Theriot, K. J.; Cheskin, B. K.; Evans, D. W.; Gregory, R. B. *Organometallics* **1990**, *9*, 1375. See also ref 3g.

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

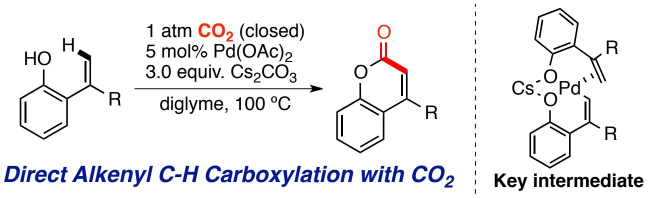
(14) ^{1}H NMR spectrum of **3a'**, whose "L" might be acetate anion, was in good agreement with a mixture of **3a**$(DMSO)_n$ and CsOAc (2 equiv.) in DMSO-d_6.

(15) For recent reviews on decarboxylative cross-coupling reactions, see; (a) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373. (b) Goossen, L. J.; Rodríguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (c) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395. (d) Rodríguez, N. Goossen, L. J. *Chem Soc. Rev.* **2011**, *40*, 5030. (e) Shang, R.; Liu, L. *Sci. China Chem.* **2011**, *54*, 1670. (f) Cornella, J.; Larrosa, I. *Synthesis* **2012**, 653.

(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.


HO
H
R
1 atm CO_2 (closed)
5 mol% $Pd(OAc)_2$
3.0 equiv. Cs_2CO_3
diglyme, 100 ºC
O
O
R
Direct Alkenyl C-H Carboxylation with CO_2
R
Cs
O
Pd
O
R
Key intermediate