Organic LETTERS

Facile Palladium-Catalyzed Hydrocarboxylation of Olefins without External CO Gas

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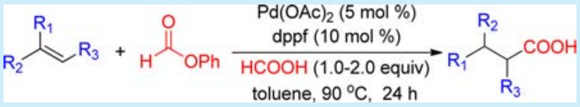
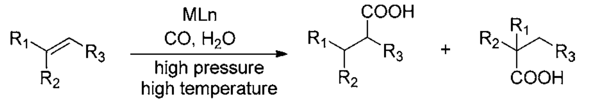
Supporting Information

ABSTRACT: An effective Pd-catalyzed hydrocarboxylation of olefins with phenyl formate and formic acid is described. A variety of carboxylic acids are obtained in good yields with high regioselectivities under operationally simple conditions without the use of toxic CO gas.



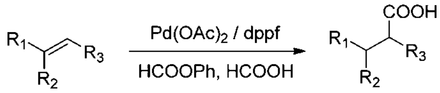
Carboxylic acids are an important class of organic molecules and are present in a wide variety of biologically significant compounds.[1] While various synthetic methods have been developed for this class of molecules, hydrocarboxylation via direct addition of an H and a COOH group onto a C−C double bond also presents an attractive approach.[2,3] However, such processes have been frequently carried out with CO gas under high pressure and high temperatures (Scheme 1), which hinders their applications and studies in the laboratories because of the difficulty in transporting, storing, and handling toxic CO gas. The development of effective, mild, and operationally simple hydrocarboxylation processes without the use of external CO gas is highly desirable.[4] Thus, far, there are only limited reports on hydrocarboxylation of olefins using formic acid or esters as source of CO, mostly with Ir and Rh as catalysts at >100 °C.[5,6] As part of our efforts in the carbonylation of olefins without external CO gas,[7−9] we have found that a wide variety of olefins can be efficiently hydrocarboxylated with HCOOPh and HCOOH in the presence of Pd catalyst under mild reaction conditions to give the corresponding carboxylic acids in good yields with high regioselectivities (Scheme 2). Herein, we report our preliminary results on this subject.

Scheme 1. Metal-Catalyzed Hydrocarboxylation with CO



α-Methylstyrene (**1a**) was used as the test substrate. Treating **1a** with HCOOPh (**4a**), 5 mol % of $Pd(OAc)_2$, and 20 mol % of PPh_3 in toluene at 90 °C for 24 h only gave phenyl 3-phenylbutanoate in 12% yield (Table 1, entry 1). However, the corresponding acid (3-phenylbutanoic acid) was isolated in 57% yield when the reaction was carried out in the presence of 1.2 equiv of HCOOH (Table 1, entry 2). $HCOOCH_3$ (**4b**), HCOOEt (**4c**), and HCOOBn (**4d**) were found to be ineffective for hydrocarboxylation under the reaction conditions (Table 1, entries 3−5), likely due to the fact that the OCH_3, OEt, and OBn groups are less electron-withdrawing than the OPh group. Among various Pd catalysts examined (Table 1, entries 6−11), the best result was obtained with 5 mol % of $Pd(OAc)_2$ and 10 mol % of dppf, giving the carboxylic acid in 96% yield with 1.2 equiv of HCOOPh and 1.2 equiv of HCOOH in toluene at 90 °C for 24 h (Table 1, entry 11). While lower yields were obtained, the reaction could proceed at lower reaction temperatures (Table 1, entries 13 and 14). When the reaction was carried out in the absence of HCOOPh (**4a**), carboxylic acid **2a** was obtained in 35% yield (Table 1, entry 15). When AcOH was used, **2a** was isolated in 29% yield (Table 1, entry 16).

Scheme 2. Palladium-Catalyzed Hydrocarboxylation without CO



The hydrocarboxylation reaction can be extended to various substituted α-methylstyrenes and related olefins, giving the corresponding carboxylic acids in 60−99% yield (Table 2, entries 1−8) (the X-ray structure of acid **2b** is shown in Figure 1). Essentially, only linear carboxylic acids were obtained in these cases. Nonconjugated 1,1-disubstituted terminal olefins were also effective substrates for the hydrocarboxylation, giving the acid products in good yields with high regioselectivities (Table 2, entries 9−11). The reaction can also be applied to electron-deficient α,β-unsaturated ester, giving the acid in 84%

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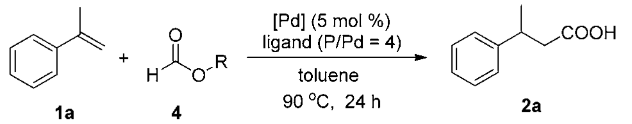
Table 1. Screening of Reaction Conditions[a]



4a, HCOOPh **4b**, $HCOOCH_3$
4c, HCOOEt **4d**, HCOOBn

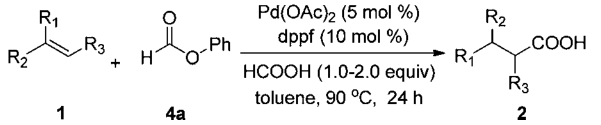
entry	4	[Pd]	ligand	additive (equiv)	yield (%)[b,c]
1	**4a**	$Pd(OAc)_2$	PPh_3		*d*
2	**4a**	$Pd(OAc)_2$	PPh_3	HCOOH (1.2)	57
3	**4b**	$Pd(OAc)_2$	PPh_3	HCOOH (1.2)	NR
4	**4c**	$Pd(OAc)_2$	PPh_3	HCOOH (1.2)	NR
5	**4d**	$Pd(OAc)_2$	PPh_3	HCOOH (1.2)	NR
6	**4a**	$Pd(PPh_3)_4$	PPh_3	HCOOH (1.2)	33
7	**4a**	$PdCl_2(CH_3CN)_2$	PPh_3	HCOOH (1.2)	20
8	**4a**	$PdCl_2$	PPh_3	HCOOH (1.2)	trace
9	**4a**	$Pd(OAc)_2$	dppe	HCOOH (1.2)	NR
10	**4a**	$Pd(OAc)_2$	dppb	HCOOH (1.2)	78
11	**4a**	$Pd(OAc)_2$	dppf	HCOOH (1.2)	96
12	**4a**	$Pd(OAc)_2$	dppf	HCOOH (2.0)	97
13[e]	**4a**	$Pd(OAc)_2$	dppf	HCOOH (2.0)	80
14[f]	**4a**	$Pd(OAc)_2$	dppf	HCOOH (2.0)	45
15	-	$Pd(OAc)_2$	dppf	HCOOH (2.0)	35
16	**4a**	$Pd(OAc)_2$	dppf	AcOH (2.0)	29

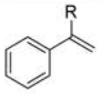
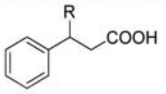
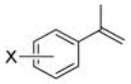
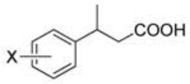
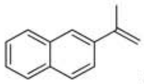
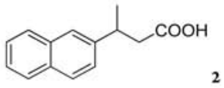
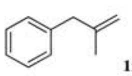
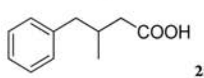
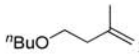
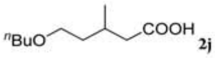
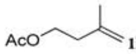
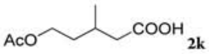
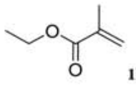
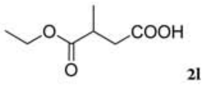
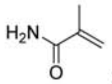
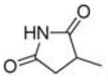
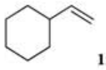
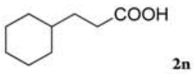
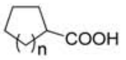
[a] The reactions were carried out with **1a** (0.50 mmol), **4** (0.60 mmol), [Pd] (0.025 mmol), ligand (0.050 or 0.10 mmol, P/Pd = 4/1), and additive (0.60 mmol) in toluene (0.50 mL) at 90 °C for 24 h unless otherwise stated. [b] Isolated yield. [c] The other regioisomer was barely detectable by ^{1}H NMR analysis of the crude reaction mixture if there was any. [d] The corresponding ester (phenyl 3-phenylbutanoate) was obtained in 12% yield. [e] The reaction was carried out at 70 °C for 24 h. [f] The reaction was carried out at 50 °C for 24 h.

yield (Table 2, entry 12). When a related *α*,*β*-unsaturated amide was subjected to the reaction conditions, the pyrrolidine-2,5-dione product was obtained in 84% yield (Table 2, entry 13). In the case of vinylcyclohexane, two regioisomers were obtained in 69% yield with a ratio of 5:1, favoring the linear carboxylic acid (Table 2, entry 14). Cycloalkenes were also effectively hydrocarboxylated to give the corresponding acids in 72−87% yields (Table 2, entries 15−18).

A precise understanding of the reaction mechanism awaits further study. A couple of reaction pathways can be perceived. A plausible catalytic cycle is proposed in Scheme 3. The Pd(0) oxidatively inserted into HCOOPh to form palladium hydride complex **5**, which rearranged to palladium carbonyl complex **6**.[10] The olefin substrate was subsequently hydropalladated to give complex **7**, which underwent a migratory insertion to form acylpalladium complex **8**. The replacement of the PhO group on the palladium of **8** by formate led to the formation of complex **9**, which underwent reduction elimination to form anhydride **10** and to regenerate the Pd(0) catalyst. Anhydride **10** was converted to carboxylic acid **2a** via decomposition[11] and/or by reacting with PhOH. HCOOH appeared to be very important for the efficient generation of the carboxylic acid. Without HCOOH, only small amount of the phenyl ester was formed (Table 1, entry 1), resulting from the reductive elimination of complex **8**. When the reaction was carried out with catalytic amount of phenyl formate (**4a**) (20 mol %), carboxylic acid **2a** was isolated in 80% yield (Scheme 4), which appears to be consistent with the regeneration of phenyl formate during the reaction as proposed in Scheme 3.

Table 2. Hydrocarboxylation of Olefins[a]



entry	1	product	yield (%)[b]
1	 R = Me **1a**	 **2a**	97
2	R = Et **1b**	**2b**	75
3	 X = *o*-Me **1c**	 **2c**	99
4	X = *m*-Me **1d**	**2d**	89
5	X = *p*-Me **1e**	**2e**	86
6	X = *p*-OMe **1f**	**2f**	70
7	X = *p*-Cl **1g**	**2g**	86
8	 **1h**	 **2h**	60
9	 **1i**	 **2i**	87
10	 **1j**	 **2j**	61
11	 **1k**	 **2k**	80
12	 **1l**	 **2l**	84
13	 **1m**	 **2m**	84
14	 **1n**	 **2n**	65 (5:1)[c]
15	 n = 1, **1o**	 **2o**	81
16	n = 2, **1p**	**2p**	87
17	n = 3, **1q**	**2q**	84
18	n = 4, **1r**	**2r**	72

[a] The reactions were carried out with **1** (0.50 mmol), **4a** (0.60 mmol), $Pd(OAc)_2$ (0.025 mmol), dppf (0.050 mmol), and HCOOH (1.00 mmol) in toluene (0.50 mL) at 90 °C for 24 h unless otherwise stated. For entries 2, 11, and 14, 0.50 mmol of HCOOH was used. [b] Isolated yield. [c] The ratio of two regioisomers was determined by ^{1}H NMR analysis. For entries 1−13, the other regioisomer was barely detectable if there was any.

In summary, we have developed an efficient Pd-catalyzed hydrocarboxylation of olefins under mild reaction conditions. A wide variety of carboxylic acids has been obtained in 60−99% yields with generally high regioselectivities. The reaction process requires no handling of toxic CO gas. The reaction is

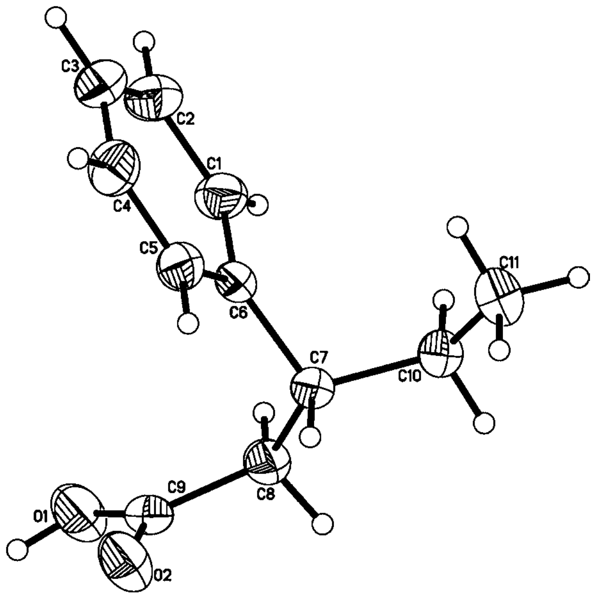
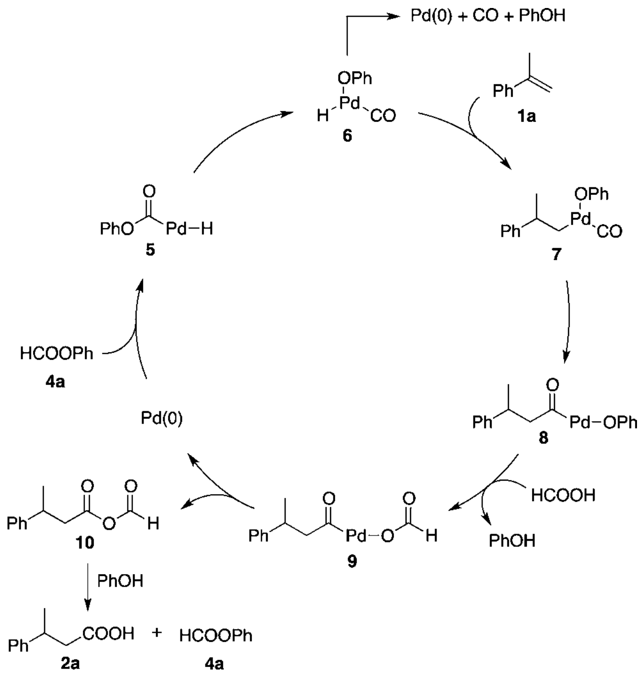
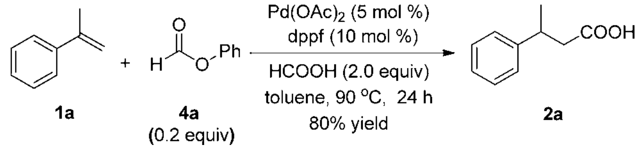


Figure 1. X-ray structure of compound **2b**.

Scheme 3. Proposed Catalytic Cycle for Hydrocarboxylation



Scheme 4. Hydrocarboxylation with a Catalytic Amount of Phenyl Formate (4a)



also operationally simple and is potentially useful for organic synthesis. Further efforts will be devoted to understanding the reaction mechanism, expanding the substrate scope, and developing an asymmetric process of this reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, X-ray structures, data for the determination of enantiomeric excess, and NMR spectra. 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) Some CO was also released from complex **6** during the reaction.

(11) For leading references, see: (a) Baird, J. M.; Kern, J. R.; Lee, G. R.; Morgans, D. J.; Sparacino, M. L., Jr. *J. Org. Chem.* **1991**, *56*, 1928. (b) Reference 3d,e..