Synthetic Methods

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Palladium-Catalyzed Hydrocarboxylation of Alkynes with Formic Acid**

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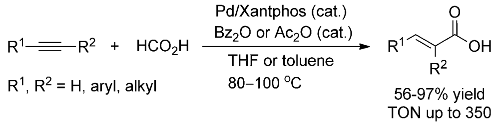
Abstract: *A palladium-catalyzed hydrocarboxylation of alkynes with formic acid has been developed. The method provides acrylic acid and derivatives in good yields with high regioselectivity without the need to handle toxic CO gas.*

Acrylic acid, an important commodity chemical, is produced on a scale of more than 3 million tons per year and is widely used as a base material for the production of paints, plastics, superabsorbent polymers, and rubbers.[1] In industry, acrylic acid is prepared by partial oxidation of propene,[2] which is refined from petroleum. However, the growing demand for plastics and superabsorbent polymers, and the diminishing supply of petroleum have stimulated intense interest in sustainable processes for the production of acrylic acid. Catalytic hydrocarboxylation of acetylene with carbon monoxide (CO), a method developed by Reppe and co-workers, is an atom-economical approach to acrylic acid.[3] However, this nonpetroleum-based process has a major drawback in that it uses high-pressure CO gas, which is toxic. In contrast, formic acid is a nontoxic, renewable liquid and can be produced by catalytic hydrogenation of CO_2[4] and oxidation of biomass.[5] Formic acid is an ideal replacement for CO gas and has been used in organic synthesis.[6] For example, formic acid was used as an in situ source of CO in the hydrocarboxylation and hydroformylation of olefins.[7] However, the catalytic hydrocarboxylation of acetylene with formic acid to form acrylic acids remains unexplored.[8] In 1993, Alper et al. reported that alkynes can be hydrocarboxylated to form unsaturated carboxylic acids with formic acid in the presence of a palladium catalyst under 6–8 atm of CO gas. However, CO gas is essential for this reaction: virtually no reaction occurs in its absence.[9]

Herein we report that the hydrocarboxylation of acetylene with formic acid can be achieved in the presence of palladium catalysts and a catalytic amount of benzoic anhydride (Scheme 1). The conversion of acetylene into acrylic acid occurred with turnover numbers (TONs) of up to 350 under mild reaction conditions. We found that this catalytic system could also be used for efficient hydrocarboxylation of other terminal alkynes, as well as internal alkynes, thus providing α,β-unsaturated acids in up to 97% yield.



Scheme 1. Palladium-catalyzed hydrocarboxylation of alkynes with formic acid.

We initially carried out the hydrocarboxylation of acetylene (10 atm) with formic acid at 80°C in toluene with $Pd(OAc)_2$ as a catalyst precursor and acetic anhydride (Ac_2O) as a promoter. Screening of various mono- and bidentate phosphine ligands showed that the nature of the ligand markedly affected the reaction (Figure 1; see also the Supporting Information). Only a few ligands afforded the desired acrylic acid product, and the biphosphine ligand Xantphos, which has a large bite angle, gave the best result (TON = 24; Table 1, entry 2). No reaction occurred in the absence of an anhydride (compare entries 1 and 2), which is necessary for the decomposition of formic acid to CO. In addition to acetic anhydride, trifluoroacetic anhydride (TFAA) and benzoic anhydride (Bz_2O) could also be used, and Bz_2O gave a slightly higher TON than acetic anhydride (compare entries 2 and 4). The effect of solvent on the hydrocarboxylation of acetylene was also evaluated: when the reaction was carried out in either Et_2O, DMF, or THF, the

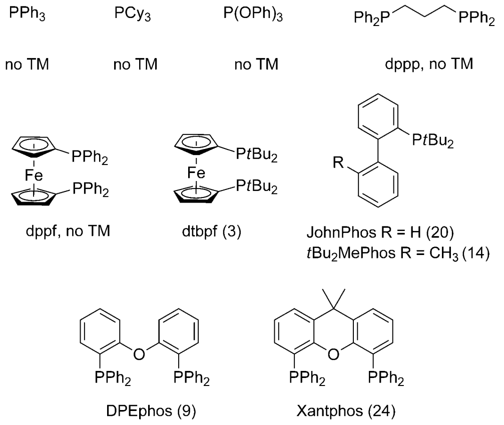


Figure 1. Phosphine ligands tested in the hydrocarboxylation of acetylene. Numbers within parentheses are TONs.

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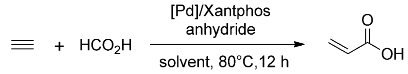
Table 1: Optimization of reaction conditions for hydrocarboxylation of acetylene.[a]



Entry	[Pd]	Xantphos/[Pd]	Anhydride	Solvent	TON[b]
1	Pd(OAc)$_2$	2	–	toluene	0
2	Pd(OAc)$_2$	2	Ac$_2$O	toluene	24
3	Pd(OAc)$_2$	2	TFAA	toluene	14
4	Pd(OAc)$_2$	2	Bz$_2$O	toluene	27
5	Pd(OAc)$_2$	2	Bz$_2$O	Et$_2$O	37
6	Pd(OAc)$_2$	2	Bz$_2$O	DMF	43
7	Pd(OAc)$_2$	2	Bz$_2$O	THF	46
8	Pd(OAc)$_2$	2	Bz$_2$O	HCO$_2$H	10
9	Pd(OAc)$_2$	2	Bz$_2$O	CH$_3$CN	7
10	[Pd(acac)$_2$]	2	Bz$_2$O	THF	37
11	[PdCl$_2$(PhCN)$_2$]	2	Bz$_2$O	THF	58
12	[Pd$_2$(dba)$_3$]·CHCl$_3$	2	Bz$_2$O	THF	85
13	[Pd$_2$(dba)$_3$]·CHCl$_3$	5	Bz$_2$O	THF	101
14	[Pd$_2$(dba)$_3$]·CHCl$_3$	10	Bz$_2$O	THF	140

[a] Reaction conditions: initial pressure $P(C_2H_2) = 10$ atm (12 mmol), [Pd] (5 μmol), anhydride (0.1 mmol), HCO$_2$H (1.5 mmol), solvent (3 mL). [b] Yield was determined by GC analysis using *n*-hexadecane as an internal standard. DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

TON was higher than that in toluene (entries 5–7). However, reactions in pure formic acid and in CH$_3$CN had lower TONs (entries 8 and 9). Various palladium catalyst precursors were compared, and [Pd$_2$(dba)$_3$]·CHCl$_3$ was found to be the best, thus giving a TON of 85 (entries 10–12). Increasing the ratio of the ligand to palladium from 2 to 5 and 10 markedly improved the TON of the reaction, to 101 and 140 (entries 13 and 14), respectively.

We also studied the effects of reaction temperature, acetylene pressure, formic acid concentration, and reaction time on the TON. A plot of TON versus reaction temperature showed that 100 °C was optimal (Figure 2). The pressure of acetylene strongly affected the TON, which increased with increasing acetylene pressure up to 15 atm and then reached a plateau (Figure 3).

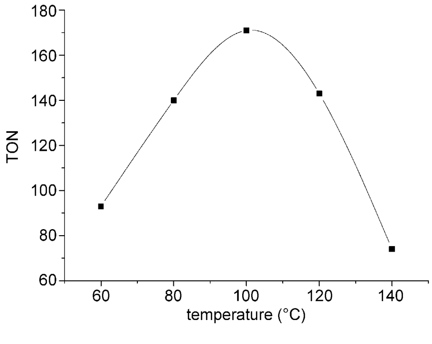


Figure 2. The effect of reaction temperature on the hydrocarboxylation of acetylene. Reaction conditions: [Pd$_2$(dba)$_3$]·CHCl$_3$ (2.5 μmol), Xantphos (50 μmol), benzoic anhydride (0.1 mmol), HCO$_2$H (1.5 mmol), acetylene (initial pressure 10 atm, ca.12 mmol), in THF (3 mL) for 12 h.

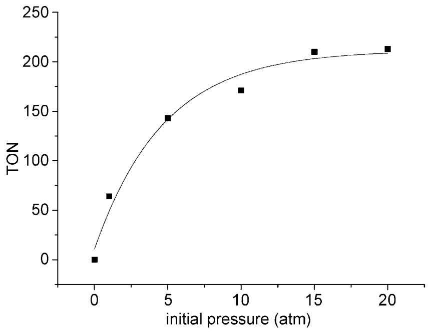


Figure 3. The effect of the initial pressure of acetylene on the hydrocarboxylation reaction. Reaction conditions: [Pd$_2$(dba)$_3$]·CHCl$_3$ (2.5 μmol), Xantphos (50 μmol), benzoic anhydride (0.1 mmol), HCO$_2$H (1.5 mmol), in THF (3 mL) at 100 °C for 12 h.

A plot of TON versus formic acid concentration clearly indicated that the optimal concentration was approximately 1 mmol mL^{-1} (Figure 4). Finally, from a plot of TON against the reaction time, we observed that TON increased with increasing reaction time, thus reaching a plateau of 350 after 12 h (Figure 5).

Encouraged by the results obtained with acetylene, we investigated the hydrocarboxylation of other alkynes with

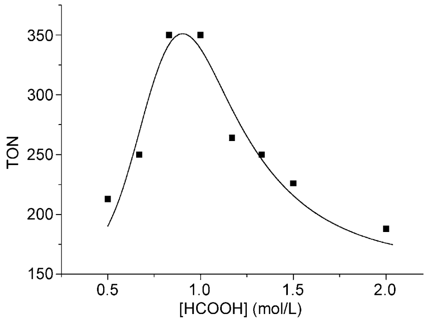


Figure 4. The effect of the concentration of formic acid on the hydrocarboxylation reaction. Reaction conditions: [Pd$_2$(dba)$_3$]·CHCl$_3$ (2.5 μmol), Xantphos (50 μmol), benzoic anhydride (0.1 mmol), acetylene (initial pressure 15 atm, ca. 18 mmol), in THF (3 mL) at 100 °C for 12 h.

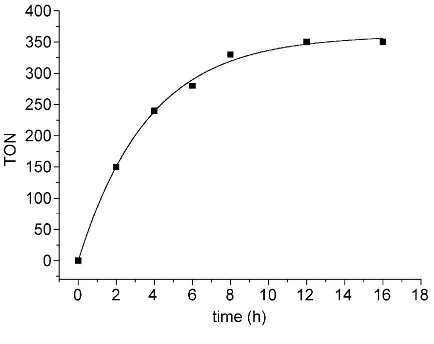
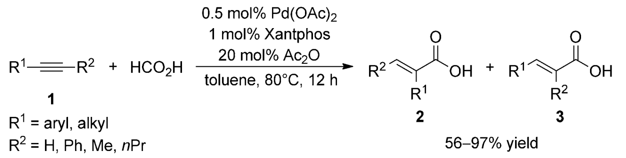


Figure 5. The effect of reaction time on the hydrocarboxylation reaction. Reaction conditions: [Pd$_2$(dba)$_3$]·CHCl$_3$ (2.5 μmol), Xantphos (50 μmol), benzoic anhydride (0.1 mmol), HCO$_2$H (3 mmol), acetylene (initial pressure 15 atm, ca.18 mmol), in THF (3 mL) at 100 °C.

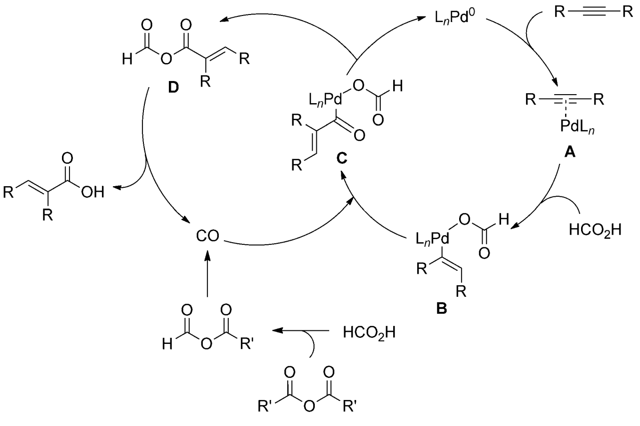
Table 2: Catalytic hydrocarboxylation of terminal and internal alkynes with formic acid.[a]



Entry	**1**	R^1	R^2	**2/3**	Yield [%][b]
1	**1b**	C_6H_5	H	93:7	76
2	**1c**	4-MeC_6H_4	H	96:4	84
3	**1d**	3-MeC_6H_4	H	95:5	82
4	**1e**	2-MeC_6H_4	H	98:2	56
5	**1f**	4-MeOC_6H_4	H	98:2	84
6	**1g**	4-ClC_6H_4	H	93:7	71
7[c]	**1h**	*n*Bu	H	100:0	70
8[c]	**1i**	*t*Bu	H	10:90	62
9	**1j**	C_6H_5	C_6H_5	–	97
10[d]	**1k**	C_6H_5	Me	63:37	87
11[c]	**1l**	*n*Pr	*n*Pr	–	64
12[c]	**1m**	*t*Bu	Me	0:100	61

[a] Reaction conditions: alkyne (0.5 mmol), Pd(OAc)$_2$ (0.5 mol%), Xantphos (1 mol%), HCO$_2$H (0.75 mmol), Ac$_2$O (20 mol%), toluene (3 mL), 80°C, 12 h. [b] Yield of the isolated product. Selectivity determined by NMR spectroscopy. [c] 5 mol% Pd(OAc)$_2$, 10 mol% Xantphos. [d] 24 h.

formic acid (Table 2). Reaction of phenylacetylene (**1b**) with formic acid proceeded smoothly in toluene at 80°C in the presence of 0.5 mol% Pd(OAc)$_2$, 1 mol% Xantphos, and 20 mol% Ac$_2$O to give the phenylacrylic acids **2b** and **3b** in a combined 76% yield (entry 1). The reaction was highly regioselective, the major product being α-phenylacrylic acid (**2b**, 93%), thus arising from the addition of the carboxyl group to the substituted side of the triple bond. Other monosubstituted aryl acetylenes also underwent hydrocarboxylation, thus mainly producing α-substituted acrylic acids in good yields (entries 2–6). Compared with aromatic acetylenes, aliphatic acetylenes were less reactive and required higher catalyst loading (5 mol%, entries 7 and 8). The hydrocarboxylation of 1-hexyne exclusively provided α-*n*-butyl acrylic acid (**2h**; entry 7), whereas sterically hindered *tert*-butylacetylene gave β-*tert*-butylacrylic acid (**3i**) as the major product (entry 8). Acetylenes with sterically bulky substituents, such as **1e** which has a 2-methylphenyl group, and **1i** which has a *tert*-butyl group, afforded relatively low product yields (entries 4 and 8). In addition to terminal alkynes, disubstituted alkynes also underwent hydrocarboxylation reactions with formic acid in good to excellent yields (61–97%; entries 9–12). Again, the aromatic acetylenes were more reactive and gave higher yields (entries 9 and 10) than the aliphatic acetylenes, which required higher catalyst loading (5 mol%; entries 11 and 12). Very high regioselectivity was obtained in the hydrocarboxylation of an internal acetylene with a *tert*-butylgroup (**2/3** = 0:100; entry 12).



Scheme 2. Proposed mechanism.

Although the exact mechanism of the reaction is unclear, we propose the mechanism illustrated in Scheme 2. Acetylene is activated by the formation of a palladium complex, which reacts with formic acid to generate the intermediate **B**.[9b,10] At the same time, the anhydride R′CO$_2$COR′ reacts with formic acid to produce the mixed anhydride HCO$_2$COR′, which decomposes to CO in situ.[11] Coordination of CO to the palladium atom of **B** and subsequent insertion into the Pd–C bond form the intermediate **C**. Reductive coupling of **C** gives the anhydride **D**, which decomposes to the acrylic acid product and CO, and regenerates the palladium catalyst.[12]

In conclusion, we have developed a palladium-catalyzed hydrocarboxylation reaction of alkynes with formic acid. The reaction provides a new approach to acrylic acids, an important chemical feedstock, in high yields with high regioselectivities. Further studies to determine the mechanism and enhance the catalytic activity are in progress in our laboratory.

Experimental Section

Hydrocarboxylation of acetylene: In a glove box, a glass vessel was charged with the catalyst [Pd$_2$(dba)$_3$]·CHCl$_3$ (2.6 mg, 2.5 μmol) and Xantphos (29 mg, 50 μmol). The vessel was placed into an autoclave and was purged three times with argon. A solution of HCO$_2$H (138 mg, 3 mmol) and Bz$_2$O (22.6 mg, 0.1 mmol) in dry THF (3 mL) was added through the injection port. The autoclave was flushed with acetylene three times before it was charged with acetylene to 15 atm. The reaction mixture was stirred at 100°C. After 12 h, the autoclave was cooled to room temperature, and the pressure was released. *n*-Hexadecane was added as an internal standard, and an aliquot of the mixture was taken and filtered through a short silica column, and the filtrate was submitted to analysis of the yield of acrylic acid by GC.

Keywords: alkynes · carboxylic acids · palladium · P ligands · synthetic methods

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[1] a) W. Bauer Jr., in *Kirk-Othmer Encyclopedia of Chemical Technology*, *Vol. 1* (*Ed.:* A. Seidel), Wiley, Hoboken, **2004**, pp. 342–369; b) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann, F. E. Kuhn, *Angew. Chem. Int. Ed.* **2011**, *50*, 8510–8537; *Angew. Chem.* **2011**, *123*, 8662–8690.

[2] W. Bertleff, M. Roeper, X. Sava in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2000**.

[3] a) W. Reppe, *Experientia* **1949**, *5*, 93–110; b) W. Reppe, *Justus Liebigs Ann. Chem.* **1953**, *582*, 1–37; c) W. Reppe, N. v. Kutepow, A. Magin, *Angew. Chem. Int. Ed. Engl.* **1969**, *8*,

727–733; *Angew. Chem.* **1969**, *81*, 717–723; d) B. E. Ali, H. Alper in *Transition Metals for Organic Synthesis Vol. 1* (Eds.: M. Beller, C. Bolm), Wiley, New York, **2004**, pp. 113–130; e) A. Brennführer, H. Neumann, M. Beller, *ChemCatChem* **2009**, *1*, 28–41; f) S. Doherty, J. G. Knight, C. H. Smyth in *Modern Carbonylation Methods* (Ed.: L. Kollár), Wiley-VCH, Weinheim, **2010**, pp. 251–290; g) C.-M. Tang, X.-L. Li, G.-Y. Wang, *Korean J. Chem. Eng.* **2012**, *29*, 1700–1707; h) I.-T. Trotuş, T. Zimmermann, F. Schüth, *Chem. Rev.* **2014**, *114*, 1761–1782.

[4] A. Behr, K. Nowakowski, *Adv. Inorg. Chem.* **2014**, *66*, 223–258.

[5] M. Grasemann, G. Laurenczy, *Energy Environ. Sci.* **2012**, *5*, 8171–8181.

[6] For reviews, see: K. F. Eidman in *Handbook of Reagents for Organic Synthesis Acidic and Basic Reagents*, Wiley, Chichester, UK, **1999**, pp. 155–157.

[7] For reviews, see: a) T. Morimoto, K. Kakiuchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 5580–5588; *Angew. Chem.* **2004**, *116*, 5698–5706; b) L.-P. Wu, Q. Liu, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 6310–6320; *Angew. Chem.* **2014**, *126*, 6426–6436; For recent reports, see: c) M. G. Mura, L. D. Luca, G. Giacomelli, A. Porcheddu, *Adv. Synth. Catal.* **2012**, *354*, 3180–3186; d) Y. Wang, W. Ren, J. Li, H. Wang, Y. Shi, *Org. Lett.* **2014**, *16*, 5960–5963.

[8] For reports on hydroesterification of alkynes employing formates, see: a) Y. Na, S. Ko, L. K. Hwang, S. Chang, *Tetrahedron Lett.* **2003**, *44*, 4475–4478; b) Y. Katafuchi, T. Fujihara, T. Iwai, J. Terao, Y. Tsuji, *Adv. Synth. Catal.* **2011**, *353*, 475–482.

[9] a) D. Zargarian, H. Alper, *Organometallics* **1993**, *12*, 712–724; b) B. El Ali, G. Vasapollo, H. Alper, *J. Org. Chem.* **1993**, *58*, 4739–4741.

[10] R.-W. Shen, T.-Q. Chen, Y.-L. Zhao, R.-H. Qiu, Y.-B. Zhou, S.-F. Yin, X.-B. Wang, M. Goto, L.-B. Han, *J. Am. Chem. Soc.* **2011**, *133*, 17037–17044.

[11] a) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Lett.* **2003**, *5*, 4269–4272; b) S. Korsager, R. H. Taaning, T. Skrydstrup, *J. Am. Chem. Soc.* **2013**, *135*, 2891–2894.

[12] To prove the involvement of CO in the mechanism, we carried the hydrocarboxylation of acetylene using 1 atm CO instead of benzoic anhydride [conditions: $P(\mathrm{CO}) = 1$ atm, $P(\mathrm{C_2H_2}) =$ 15 atm (18 mmol), $[\mathrm{Pd_2(dba)_3}]\cdot\mathrm{CHCl_3}$ (5 µmol), Xantphos (50 µmol), $\mathrm{HCO_2H}$ (2.5 mmol), THF (3 mL)]. The desired product is obtained with a TON of 370.

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