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Pd-Catalyzed Highly Chemo- and Regioselective Hydrocarboxylation of Terminal Alkyl Olefins with Formic Acid

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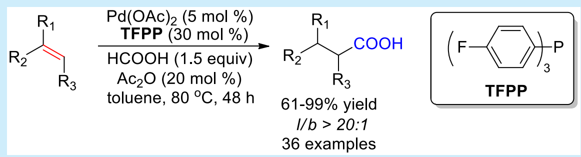
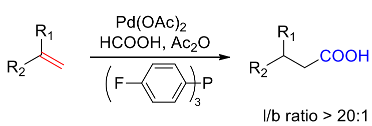
Supporting Information

ABSTRACT: An efficient Pd-catalyzed hydrocarboxylation of alkenes with HCOOH is described. A wide variety of linear carboxylic acids bearing various functional groups can be obtained with excellent chemo- and regioselectivities under mild reaction conditions. The reaction process is operationally simple and requires no handling of toxic CO.

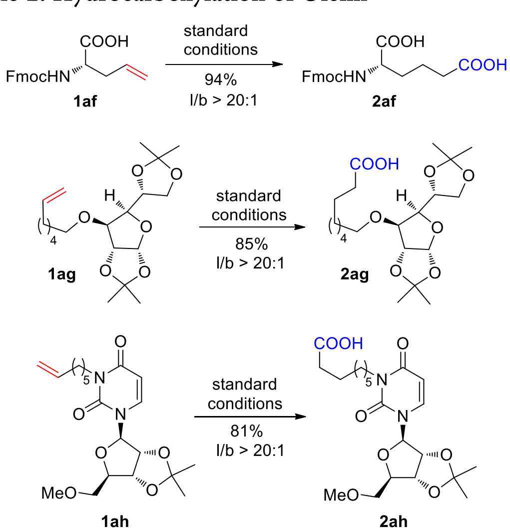


As an important functional moiety, carboxylic acids are present in various biologically active compounds, pharmaceuticals, fine chemicals, and materials. They also serve as important intermediates in organic synthesis. The development of efficient methods for the synthesis of carboxylic acids is of great significance. Hydrocarboxylation of olefins provides a straightforward and attractive route to this class of compounds.[1] Significant progress has been made with both CO and its surrogates.[2−6] Recently, we have reported that hydrocarboxylations can be achieved by direct addition of HCOOH onto olefins with Pd catalyst in the presence of HCOOPh[6a,c,e,g] or Ac_2O.[6b,f,7]

Scheme 1. Pd-Catalyzed Regioselective Hydrocarboxylation of Olefins



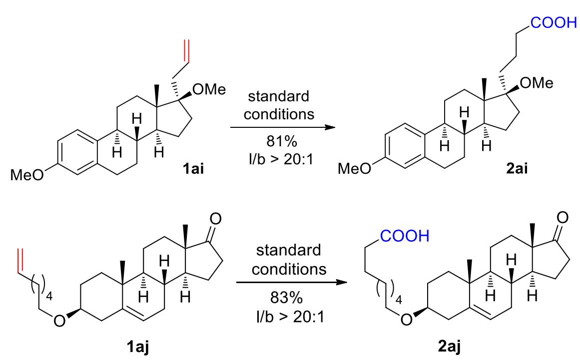
Scheme 2. Hydrocarboxylation of Olefin



While great progress has been made in the area of hydrocarboxylation, there are still challenges remaining. For example, in general, synthetically useful hydrocarboxylation of terminal alkyl olefins with high efficiency and regioselectivity under mild reaction conditions to generate linear carboxylic acids is still elusive. In this work, we now report that an efficient regioselective hydrocarboxylation of terminal alkyl olefins with broad substrate scope and potential synthetic value has been developed (Scheme 1).

1-Octene (**1a**) was used as the test substrate for the initial studies. Various ligands were investigated with 5 mol % of $Pd(OAc)_2$, 2.0 equiv of HCOOH, and 1.0 equiv of Ac_2O in

Scheme 3. Hydrocarboxylation of Steroidal Olefin



Scheme 4. Gram-Scale Hydrocarboxylation of Olefin

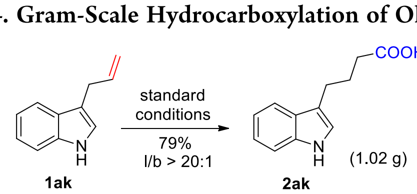


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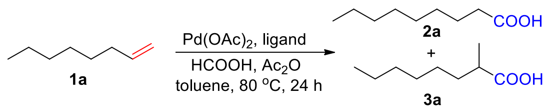
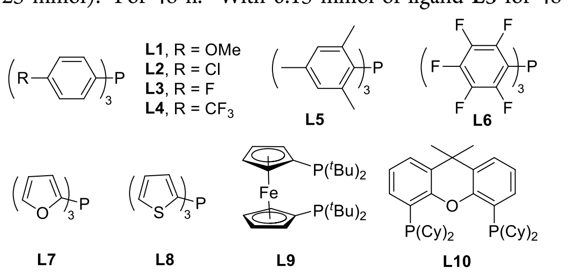
Table 1. Studies of the Reaction Conditions[a]



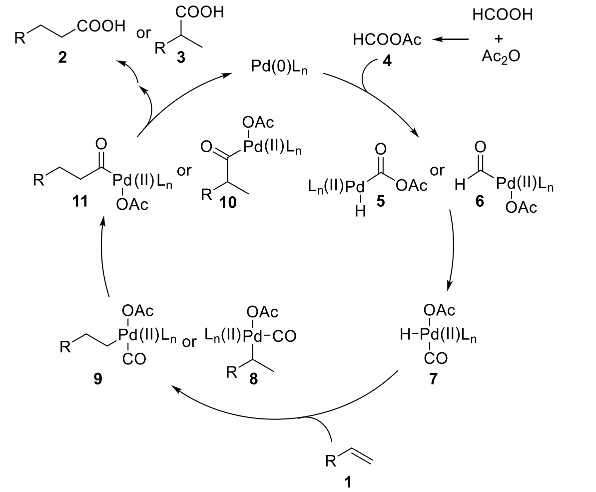
entry	ligand	HCOOH (equiv)	Ac_2O (equiv)	yield (%) (2a:3a)[b]
1	PPh_3	2.0	1.0	43 (5:1)
2	$(o\text{-tolyl})_3P$	2.0	1.0	0
3	$(p\text{-tolyl})_3P$	2.0	1.0	23 (6:1)
4	**L1**	2.0	1.0	70 (4:1)
5	**L2**	2.0	1.0	42 (5:1)
6	**L3**	2.0	1.0	64 (8:1)
7	**L4**	2.0	1.0	33 (2:1)
8	**L5**	2.0	1.0	0
9	**L6**	2.0	1.0	0
10	**L7**	2.0	1.0	12 (10:1)
11	**L8**	2.0	1.0	0
12	dppe	2.0	1.0	16 (3:1)
13	dppp	2.0	1.0	45 (2:1)
14	dppb	2.0	1.0	73 (4:1)
15	dppf	2.0	1.0	71 (5:1)
16	**L9**	2.0	1.0	0
17	xantphos	2.0	1.0	63 (6:1)
18	**L10**	2.0	1.0	0
19	BINAP	2.0	1.0	10 (2:1)
20[c]	**L3**	2.0	1.0	54 (5:1)
21[d]	**L3**	2.0	1.0	68 (5:1)
22[e]	**L3**	2.0	1.0	39 (9:1)
23	**L3**	2.0	0.5	78 (9:1)
24	**L3**	1.5	0.5	68 (12:1)
25	**L3**	1.0	0.5	44 (12:1)
26	**L3**	1.5	0.7	60 (8:1)
27	**L3**	1.5	0.3	52 (16:1)
28	**L3**	1.5	0.2	48 (>20:1)
29[f]	**L3**	1.5	0.2	65 (>20:1)
30[g]	**L3**	**1.5**	**0.2**	**92 (>20:1)**

[a]The reactions were carried out with **1a** (0.50 mmol), $Pd(OAc)_2$ (0.025 mmol), ligand (0.050 or 0.10 mmol, P/Pd = 4:1), HCOOH (0.50–1.0 mmol), and Ac_2O (0.10–0.50 mmol) in toluene (0.50 mL) at 80 °C for 24 h unless otherwise stated. [b]Isolated yield. The ratio of **2a** to **3a** was determined by ^{1}H NMR analysis of the isolated products (see ref 8). [c]With $Pd(TFA)_2$ (0.025 mmol). [d]With APD [allylpalladium(II) chloride dimer] (0.0125 mmol). [e]With $Pd_2(dba)_3$ (0.0125 mmol). [f]For 48 h. [g]With 0.15 mmol of ligand **L3** for 48 h.



toluene at 80 °C for 24 h (Table 1, entries 1–19). Studies showed that the ligand had a profound effect on the reaction efficiency and regioselectivity. No acid products **2a** and **3a** were detected with a number of ligands (Table 1, entries 2, 8, 9, 11, 16, and 18). Among the ligands examined, tris(4-fluorophenyl)-phosphine (TFPP) (**L3**) and tri(2-furyl)phosphine (**L7**) gave higher regioselectivity for linear acid **2a** (Table 1, entries 6 and 10). Since ligand **L3** gave significantly higher yield than **L7**,

Scheme 5. Proposed Catalytic Cycle for the Hydrocarboxylation



further investigation was carried out with **L3**. Among the Pd sources investigated, $Pd(OAc)_2$ gave overall the best result (Table 1, entry 6 vs entries 20–22). The reaction yield and regioselectivity also varied with the amounts of HCOOH and Ac_2O (Table 1, entries 23–28). With 1.5 equiv of HCOOH and 0.2 equiv of Ac_2O, linear acid **2a** was isolated in 48% yield, but with remarkably high regioselectivity (>20:1) (Table 1, entry 28). The yield was increased to 92% with more ligand added and prolonged reaction time (Table 1, entry 30).

As shown in Table 2, the hydrocarboxylation can be extended to a wide variety of alkyl terminal alkenes, giving the corresponding linear acids in 66–96% yields with >20:1 l/b ratio (Table 2, entries 1–17).[9] The reaction is compatible with various functional groups including Cl, OMe, OTBDPS, CHO, acetal, COOH, COOR, CN, phosphonate, and urea. The hydrocarboxylation was also effective toward 1,1-disubstituted olefins, giving the corresponding acids in 63–99% yields (Table 2, entries 18–21). Cycloalkenes can also be hydrocarboxylated to give acid products in 81–84% yields (Table 2, entries 22–23). Terminal olefins can be selectively hydrocarboxylated when 1,2-disubstituted or trisubstituted olefins were also present in the substrates, giving monoacids in 61–82% yields (Table 2, entries 24–28). In the case of 2-methylhexa-1,5-diene (**1ad**), the monoterminal olefin can be preferentially hydrocarboxylated over the 1,1-disubstituted terminal olefin, giving acid **2ad** in 70% yield (Table 2, entry 29). The site-selective hydrocarboxylation was also observed for triene substrate **1ae**, providing monoacid **2ae** in 69% yield (Table 2, entry 30).

The hydrocarboxylation can also be applied to highly functionalized amino acid, carbohydrate, nucleoside, and steroid derivatives **1af**, **1ag**, **1ah**, **1ai**, and **1aj**, giving the corresponding acids in 81–94% yields with >20:1 regioselectivities (Schemes 2 and 3). The current process could provide a useful method for the synthesis of acid derivatives from biologically active compounds. As shown in Scheme 4, the reaction process can be carried out on a gram scale. Acid **2ak** was obtained in 79% yield from 3-allyl-1*H*-indole (**1ak**).

A precise reaction mechanism and the origin of the regioselectivity are not clear at this moment and await further study. One plausible catalytic cycle is shown in Scheme 5 as previously proposed.[6f] The oxidative addition of Pd(0) to HCOOAc (**4**) (generated from HCOOH and Ac_2O) led to the formation of palladium complexes **5** and/or **6**, which rearranged

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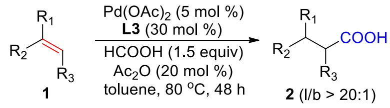
Table 2. Pd-Catalyzed Chemo- and Regioselective Hydrocarboxylation of Olefins[a]



entry	1	2	yield	entry	1	2	yield
1	1a	2a	92	16	1p	2p	93
2	1b	2b	92	17[d]	1q	2q	85
3	1c	2c	85	18[d]	1r	2r	84
4	1d	2d	90	19[d]	1s	2s	63
5	1e	2e	78	20	1t	2t	99
6	1f	2f	90	21[e]	1u	2u	72
7	1g	2g	73	22[d]	1v	2v	84
8	1h	2h	95	23[d]	1w	2w	81
9	1i	2i	92	24	1x	2x	61
10	1j	2j	82	25	1y	2y	66
11	1k	2k	95	26	1z	2z	70
12[c]	1l	2l	78	27[c]	1ab	2ab	75
13	1m	2m	66	28	1ac	2ac	82
14	1n	2n	75	29[f]	1ad	2ad	70
15	1o	2o	96	30	1ae	2ae	69

[a]The reactions were carried out with substrate **1** (0.50 mmol), $Pd(OAc)_2$ (0.025 mmol), **L3** (0.15 mmol), HCOOH (0.75 mmol), and Ac_2O (0.10 mmol) in toluene (0.50 mL) at 80 °C for 48 h unless otherwise stated. [b]Isolated yields. The l/b ratios were determined by ^1H NMR analysis of the crude reaction mixture and isolated products. [c]With 0.50 mmol of HCOOH. [d]With 1.0 mmol of HCOOH in 0.10 mL of toluene at 80 °C for 72 h. [e]With 1.0 mmol of HCOOH and 0.50 mmol of Ac_2O in 0.50 mL of toluene at 90 °C for 48 h. [f]With 0.50 mmol of HCOOH, 0.050 mmol of Ac_2O, and 0.025 mmol of Bu_4NI at 80 °C for 48 h.

to complex **7**. The olefin substrate was subsequently hydropalladated by **7** to form complexes **8** and **9**. Upon migratory insertion, complexes **8** and **9** were converted to acyl Pd complexes **10** and **11**. Acids **2** and **3** were then generated from **10** and **11**, respectively, via reductive elimination with the regeneration of Pd(0) catalyst.

In summary, we have developed an efficient hydrocarboxylation process for alkyl terminal olefins with HCOOH and Ac_2O in the presence of $Pd(OAc)_2$ catalyst and tris(4-fluorophenyl)phosphine (**L3**) ligand, giving a wide variety of linear carboxylic acids in 61−99% yields with generally >20:1 regioselectivity under mild reaction conditions. Various functional groups are well tolerated in the reaction. Monoterminal olefins can be selectively hydrocarboxylated in the presence of other olefins. The reaction is operationally simple and can be carried out on a gram scale, requiring no handling of toxic CO.

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The current process could provide a practical method for the synthesis of various biologically and chemically significant linear carboxylic acids. Further development of the hydrocarboxylation reaction process is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02101.

Experimental procedures, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1915010−1915011 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(8) Sometimes the ratio of **2a** to **3a** could not be precisely determined from the crude reaction mixtures by ^{1}H NMR due to the overlap of acid product signals with signals from other compounds such as solvents, unreacted olefins, etc. The ratio was thus determined by ^{1}H NMR of the isolated product via alkalinization−washing−acidifying−extraction. In principle, the ratio of **2a** to **3a** should remain the same during this purification process.

(9) For styrene, a mixture of branched and linear acids was obtained in 85% yield with 3.6:1 b/l ratio under the current reaction conditions.