Palladium-Catalyzed Hydrocarboxylation of Alkynes with Formic Acid

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Alkynes are hydrocarboxylated with formic acid in the presence of catalytic amounts of Pd(OAc)$_2$ and suitable phosphine ligands (120 psi of CO gas pressure, 100–110 °C) to produce the corresponding unsaturated carboxylic acids in 60–90% yields. The products of terminal alkyne reactions are CR(COOH)=CH$_2$, 1, and (*E*)-CHR=CH(COOH), 2. The regioselectivity is approximately 90:10 in favor of 1 when R is a phenyl or a straight chain alkyl group; 2 is the favored product when R is *t*-Bu and the exclusive one when R is SiMe$_3$. The products of internal alkyne reactions are (*E*)-CR(COOH)=CHR', 3, and (*E*)-CHR=CR'(COOH), 4; the regioselectivity in this case is not as high as for terminal alkynes. Oxalic acid can be used instead of formic acid in both of these reactions. The most suitable phosphine ligands for alkyne hydrocarboxylation in the present system are PPh$_3$ and dppb (1,4-bis(diphenylphosphino)butane). In some cases, using a mixture of these two ligands remarkably improves the reaction yields; the implications of such ligand synergism are discussed. On the basis of deuterium labeling studies and other experimental results, a reaction mechanism has been proposed which involves the addition of the O–H bond of formic acid to the palladium center, forming a cationic hydrido(alkyne)-palladium intermediate. This intermediate is believed to undergo a sequence of reactions, including hydride and CO insertions, to furnish the organic product(s) and regenerate the active catalyst. The postulated insertion steps have been discussed in light of the present results and literature precedents.

Introduction

Although alkyne carbonylation was one of the first carbonylation reactions discovered,[1] the commercial utility of this process has remained quite underdeveloped. The main reasons for this are the relatively high cost of alkynes as feedstocks and the complex nature of their carbonylation reactions, which often yield an array of different products. The inherent complexity of these reactions is documented in Pino and Braca's authoritative review[2] of the early stages in the development of this field. Presently, only the carbonylation of acetylene, the simplest of alkynes, is carried out on a commercial scale to produce acrylic acid, which is used for the production of acrylic resins. The commercial viability of this reaction stems mainly from the symmetrical structure of acetylene, which avoids the problems associated with controlling the regio- and stereoselectivity in alkyne carbonylation reactions.

As part of our continuing efforts to effect net carbonylation reactions in the absence of CO gas, we have studied a number of carbonylation reactions in the presence of formic and oxalic acids and their corresponding esters. For instance, we have recently reported[3] the use of formic acid in the Pd-catalyzed carbonylation of terminal alkynes and showed that the use of "oxidative" conditions (CuCl$_2$/O$_2$) promoted the dicarbonylation of terminal alkynes to fumaric and maleic acids. In contrast, monocarbonylation prevails under "reductive" conditions (phosphine ligands, high temperatures and pressures of CO gas), as seen from the reports from this laboratory on the Pd-catalyzed carbonylation of alkynes with formate esters[4] and dialkyl oxalates.[5] The observation that under nonoxidative conditions alkynes react by monocarbonylation rather than dicarbonylation prompted a study of the reaction of alkynes with formic acid under reductive conditions. This study has resulted in a general procedure for alkyne hydrocarboxylation, as described below.

Experimental Section

General Comments. The solvents were distilled from appropriate drying agents under N$_2$. The gases (high-purity grade) were purchased from commercial sources and were passed through scrubbers (KOH, CaCl$_2$) prior to use. The alkynes (Farchan) were dried and distilled before use. D$_2$O (99.9%), DCOOH (95% in H$_2$O), and HCOOD (93%; contains 5% D$_2$O and 2% HCOOH) were purchased from MSD Isotopes and were used without further purification.

^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 200-MHz and XL 300-MHz spectrometers at ambient temperature. ^{1}H NMR data are reported in the following format: chemical shift (multiplicity, coupling constant(s), assignment). The chemical shifts (δ) are measured in parts per million (ppm) and referenced to the residual solvent proton resonances which are internally calibrated against tetramethylsilane; coupling constants are in hertz. ^{13}C NMR data are reported in the following

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format: chemical shift (assignment). The chemical shifts are measured in ppm and referenced to the triplet resonance of $CDCl_3$ or the singlet resonance of the carbonyl carbon of acetone-d_6, both of which are internally calibrated against tetramethylsilane. GC/MS analyses were performed on a VG 7070E mass analyzer, and high-resolution mass spectra were recorded on a Kratos Concept 2H mass spectrometer.

General Procedure for Catalytic Reactions. The catalytic reactions were carried out inside a Parr stainless steel autoclave equipped with a glass liner. The autoclave containing a stirring bar was charged with the solvent (ca. 5–10 mL) and the starting materials. The autoclave was assembled, purged with CO gas by three fill-vent cycles, charged with CO gas up to the appropriate pressure, and placed inside an oil bath sitting atop a heater/stirrer. The temperature of the oil bath was brought to the desired level and monitored during the reaction period. After the reaction time had lapsed, the autoclave was taken out of the oil bath and allowed to cool. The gas(es) was (were) vented, the autoclave was disassembled, and the products were isolated from the reaction mixture by conventional workup procedures (extraction with ca. 1 N aqueous NaOH solution, acidification, and extraction with Et_2O or EtOAc). The products were characterized by NMR, IR, and GC/MS spectroscopy.

α-Methylenebenzeneacetic Acid (Atropic Acid), 1a, and (*E*)-3-Phenyl-2-propenoic Acid (Cinnamic Acid), 2a. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (27 mg, 0.103 mmol), dppb (20 mg, 0.0469 mmol), phenylacetylene (98%, 255 mg, 2.45 mmol), formic acid (98%, 232 mg, 4.94 mmol), and DME (5 mL) for 18 h at 108 °C under 120 psi of CO gas pressure. **1a** and **2a** were obtained in a 93:7 ratio (combined yield = 96%). ^{1}H NMR (δ, $CDCl_3$): **1a**, 8–10 (broad, COO*H*), 7.4 (m, phenyl protons), 6.53 (d, $^2J_{H-H}$ = 1.2, vinylic proton cis to COOH), 6.01 (d, $^2J_{H-H}$ = 1.2, vinylic proton trans to COOH); **2a**, 8–10 (broad, COO*H*), 7.79 (d, $^3J_{H-H}$ = 15.9, vinylic proton cis to COOH), 7.4 (m, phenyl protons), 6.45 (d, $^3J_{H-H}$ = 16.0, vinylic proton gem to COOH). The present data match those reported in the literature.[6] High-resolution MS: calcd for $C_9H_8O_2$, *m/e* 148.161; found, 148.052 54.

α-Methylenebenzenebutanoic Acid, 1b, and (*E*)-5-Phenyl-2-pentenoic Acid, 2b. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (28 mg, 0.107 mmol), 4-phenyl-1-butyne (98%, 333 mg, 2.56 mmol), formic acid (98%, 160 mg, 3.47 mmol), and DME (6 mL) for 22 h at 105 °C under 120 psi of CO gas pressure. **1b** and **2b** were obtained in a 94:6 ratio (combined yield = 86%). ^{1}H NMR (δ, $CDCl_3$): **1b**, 10.7 (br, COO*H*), 7.30 (m, phenyl protons), 6.32 (d, $^2J_{H-H}$ = 1.5, vinylic proton cis to COOH), 5.62 (d, $^2J_{H-H}$ = 1.1, vinylic proton trans to COOH), 2.84 (m, CH_2C(COOH)=), 2.65 (m, Ph-CH_2); **2b**; 10.8 (br, COO*H*), 7.21 (m, phenyl protons), 5.85 (d, $^3J_{H-H}$ = 15.7, =*CH*(COOH)), 2.78 (m, CH_2CH=), 2.65 (m, PhCH_2). The resonance due to the second vinylic proton (dt, =*CH*CH_2) is presumed to be buried under the phenyl resonances. The present data match those reported in the literature.[6a,7] ^{13}C NMR (δ, $CDCl_3$): **1b**, 172.8 (*C*OOH), 141.2 (CH_2-*C*(COOH)=), 139.2 (ipso carbon of the phenyl ring), 128.5 and 128.4 (*o*- and *m*-carbon atoms of the phenyl ring), 128.0 (*p*-carbon atom of the phenyl ring), 126.0 (=CH_2), 34.8 and 33.5 (PhCH_2CH_2); **2b**, 172.2 (*C*OOH), 151.2 (=CH(COOH)), 140.2 (ipso carbon of the phenyl ring), 128.4 and127.9 (*o*- and *m*-carbon atoms of the phenyl ring), 126.2 (*p*-carbon atom of the phenyl ring), 121.1 (CH_2-*C*H=), 34.1 and 34.0 (PhCH_2CH_2). GC/MS (*m/e*): trimethylsilyl ester of **1b**, $M^{\cdot+}$ = 248; trimethylsilyl ester of **2b**, $M^{\cdot+}$ − CH_3 = 233.

2-Methyleneoctanoic Acid, 1c, and (*E*)-2-Nonenoic Acid, 2c. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (56 mg, 0.214 mmol), 1-octyne (98%, 328 mg, 2.98 mmol), formic acid (98%, 196 mg, 4.26 mmol), and DME (6 mL) for 29 h at 105 °C under 120 psi of CO gas pressure. **1c** and **2c** were obtained in an 87:13 ratio (combined yield = 83%). ^{1}H NMR (δ, $CDCl_3$): **1c**, 6.26 (d, $^2J_{H-H}$ = 1.4, vinylic proton cis to COOH), 5.62 (d, $^2J_{H-H}$ = 1.4, vinylic proton trans to COOH), 2.27 (t, $^3J_{H-H}$ = 7.3, CH_2C(COOH)=), 1.45–1.26 (m, $CH_3(CH_2)_4$), 0.86 (t, $^3J_{H-H}$ = 6.4, CH_3); **2c**, 7.07 (dt, $^3J_{H-H}$ = 15.6 and 7.0, =*CH*CH_2–), 5.80 (dt, $^3J_{H-H}$ = 15.6 and 1.6, =C(COOH)*H*), 2.29 (m, =$CHCH_2$–), 1.45–1.26 and (m, $CH_3(CH_2)_4$), 0.86 (t, $^3J_{H-H}$ = 6.4, CH_3). The present data match those reported in the literature.[6a] ^{13}C NMR (δ, $CDCl_3$): **1c**, 173.2 (*C*OOH), 140.3 (CH_2-*C*(COOH)=), 126.9 (=CH_2), 31.6 (CH_2C(COOH)=), 31.4 (-CH_2CH_2C-(COOH)=), 28.9 and 28.3 ($CH_3CH_2CH_2CH_2$), 22.6 (CH_3CH_2), 14.1 (CH_3). GC/MS (*m/e*): trimethylsilyl ester of **1c**, $M^{\cdot+}$ = 228; trimethylsilyl ester of **2c**, $M^{\cdot+}$ − CH_3 = 213.

5-Cyano-2-methylenepentanoic Acid, 1d, and (*E*)-6-Cyano-2-hexenoic Acid, 2d. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (56 mg, 0.214 mmol), 5-cyano-1-pentyne (98%, 268 mg, 2.88 mmol), formic acid (98%, 218 mg, 4.73 mmol), and DME (5 mL) for 16 h at 100 °C under 120 psi of CO gas pressure. **1d** and **2d** were obtained in a 94:6 ratio (combined yield = 86%). ^{1}H NMR (δ, $CDCl_3$): **1d**, 10.9 (br, COO*H*), 6.34 (s, vinylic proton cis to COOH), 5.72 (d, $^2J_{H-H}$ = 1.1, vinylic proton trans to COOH), 2.43 (t, $^3J_{H-H}$ = 7.4, -CH_2C-(COOH)=), 2.33 (t, $^3J_{H-H}$ = 7.0, NC-CH_2), 1.84 (quintet, $^3J_{H-H}$ = 7.4, NC-CH_2CH_2); **2d**, 10.9 (br, COO*H*), 6.99 (dt, $^3J_{H-H}$ = 15.7 and 6.8, =*CH*CH_2–), 5.87 (dt, $^3J_{H-H}$ = 15.7 and 0.8, =C(COOH)-*H*), 2.39 (m, =$CHCH_2$–), 2.33 (t, $^3J_{H-H}$ = 7.0, NC-CH_2), 1.84 (quintet, $^3J_{H-H}$ = 7.4, NC-CH_2CH_2). The present data match those reported in the literature.[8] ^{13}C NMR (δ, $CDCl_3$): **1d**, 172.1 (*C*OOH), 137.8 (-CH_2C(COOH)=), 129.1 (=CH_2), 119.3 (*C*N), 30.5 (CH_2C(COOH)=), 24.1 (NC-CH_2), 16.5 (NCCH_2CH_2). GC/MS (*m/e*): trimethylsilyl esters of **1d** and **2d**, $M^{\cdot+}$ − CH_3 = 196.

5-Chloro-2-methylenepentanoic Acid, 1e, and (*E*)-6-Chloro-2-hexenoic Acid, 2e. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (55 mg, 0.210 mmol), 5-chloro-1-pentyne (98%, 283 mg, 2.76 mmol), formic acid (98%, 198 mg, 4.30 mmol), and DME (5 mL) for 16 h at 95 °C under 120 psi of CO gas pressure. **1e** and **2e** were obtained in an 89:11 ratio (combined yield = 77%). ^{1}H NMR (δ, $CDCl_3$): **1e**, 6.33 (s, vinylic proton cis to COOH), 5.71 (d, $^2J_{H-H}$ = 1.1, vinylic proton trans to COOH), 3.52 (t, $^3J_{H-H}$ = 6.5, Cl-CH_2), 2.44 (t, $^3J_{H-H}$ = 6.9, -CH_2C(COOH)=), 1.94 (quintet, $^3J_{H-H}$ = 7.3, Cl-CH_2CH_2-CH_2); **2e**, 7.03 (dt, $^3J_{H-H}$ = 15.6 and 7.0, =*CH*-CH_2), 5.86 (dt, $^3J_{H-H}$ = 15.6, $^4J_{H-H}$ = 1.5, =*CH*(COOH)), 3.52 (t, $^3J_{H-H}$ = 6.5, Cl-CH_2), 2.44 (t, $^3J_{H-H}$ = 6.9, -CH_2C(COOH)=), 1.94 (quintet, $^3J_{H-H}$ = 7.3, Cl-$CH_2CH_2CH_2$). The present data match those reported in the literature.[9] ^{13}C NMR (δ, $CDCl_3$): **1e**, 172.7 (*C*OOH), 138.3 (-CH_2C(COOH)=), 128.5 (=CH_2), 44.1 (ClCH_2), 30.9 (CH_2C(COOH)=), 28.7 (ClCH_2CH_2); **2e**, 171.2 (*C*OOH), 151.0 (-CH_2C(OOH)=), 121.6 (=CH_2), 43.6 (ClCH_2), 30.5 (CH_2C-(COOH)=), 29.3 (ClCH_2CH_2). GC/MS (*m/e*): trimethylsilyl esters of **1e** and **2e**, $M^{\cdot+}$ − CH_3 = 205.

3-Methyl-2-methylenevaleric Acid (3-Methyl-2-methylenepentanoic Acid), 1f, and (*E*)-4-Methyl-2-hexenoic Acid, 2f. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (28 mg, 0.107 mmol), dppb (25 mg, 0.0586 mmol), 3-methyl-1-pentyne (98%, 210 mg, 2.56 mmol), formic acid (98%, 211 mg, 4.58 mmol), and DME (5 mL) for 17 h at 106 °C under 120 psi of CO gas pressure. **1f** and **2f** were obtained in an 87:13 ratio (combined yield = 70%). ^{1}H NMR (δ, $CDCl_3$): **1f**, 6.31 (d, $^2J_{H-H}$ = 1.0, vinylic proton cis to COOH), 5.59 (d, $^2J_{H-H}$ = 0.8, vinylic proton trans to COOH), 2.58 (m, -*CH*(Me)-CH_2), 1.39 (m, CH_3CH_2CH(Me)), CH_3CH_2), 1.06 (d, $^3J_{H-H}$ = 6.5, CH(Et)CH_3), 0.84 (t, $^3J_{H-H}$ = 7.5, CH_3CH_2); **2f**, 6.97 (dd, $^3J_{H-H}$ = 15.7 and 7.9, =*CH*{CH(Me)Et}), 5.77 (dd, $^3J_{H-H}$ = 15.7, $^4J_{H-H}$ = 1.2, =*CH*(COOH)), 2.20 (m, -*CH*(Me)CH_2), 1.55 (m, CH_3CH_2-CH(Me)), 1.04 (d, $^3J_{H-H}$ = 9.7, CH(Et)CH_3), 0.86 (t, $^3J_{H-H}$ = 7.5, CH_3CH_2). The present data match those found in the literature.[6b,10] ^{13}C NMR (δ, $CDCl_3$): **1f**, 173.4 (*C*OOH), 145.2 (-CH-(Me)*C*(COOH)=), 125.3 (=CH_2), 35.7 (*C*H(Me)Et), 28.6

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(CH_3CH_2), 19.3 ($CH_3CH(Et)$), 11.6 (CH_3CH_2); **2f**, 172.7 (COOH), 157.5 (CH(COOH)=), 119.1 (=CH(CHMe)), 38.2 (CH(Me)Et), 28.7 (CH_3CH_2), 18.7 ($CH_3CH(Et)$), 11.8 (CH_3CH_2). GC/MS (*m/e*): trimethylsilyl esters of **1f** and **2f**, $M^{\cdot+}$ = 200.

3,3-Dimethyl-2-methylenebutanoic Acid, 1g, and (*E*)-4,4-Dimethylpentenoic Acid, 2g. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (27 mg, 0.103 mmol), dppb (23 mg, 0.0539 mmol), 3,3-dimethylbutyne (240 mg, 2.93 mmol), formic acid (98%, 253 mg, 5.50 mmol), and DME (5 mL) for 17.5 h at 102 °C under 120 psi of CO gas pressure. **1g** and **2g** were obtained in a 21:79 ratio (combined yield = 70%) ^1H NMR (δ, $CDCl_3$): **1g**, 6.16 (s, vinylic proton cis to COOH), 5.62 (d, $^2J_{H-H}$ = 0.9, vinylic proton trans to COOH), 1.20, (s, $C(CH_3)_3$); **2g**, 7.07 (d, $^3J_{H-H}$ = 15.9, vinylic proton cis to COOH), 5.72 (d, $^3J_{H-H}$ = 15.9, =CH(COOH)), 1.07 (s, $C(CH_3)_3$). The present data match those reported in the literature.[11] ^{13}C NMR (δ, $CDCl_3$): **1g**, 173.6 (COOH), 148.9 (=C(CMe_3)(COOH)), 124.2 ($=CH_2$), 34.6 (CMe_3), 29.3 ($C(CH_3)_3$); **2g**, 173.1 (COOH), 161.9 (=CH(COOH)), 116.1 (=CHC($Me)_3$), 33.9 (CMe_3), 28.5 ($C(CH_3)_3$). GC/MS (*m/e*): trimethylsilyl esters of **1g** and **2g**; $M^{\cdot+}$ = 200.

(*E*)-3-(Trimethylsilyl)-2-propenoic Acid, 2h. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (28 mg, 0.107 mmol), dppb (23 mg, 0.0539 mmol), (trimethylsilyl)-acetylene (98%, 281 mg, 2.87 mmol), formic acid (98%, 266 mg, 5.77 mmol), and DME (5 mL) for 24 h at 101 °C under 120 psi of CO gas pressure. **2h** was obtained in 63% yield. ^1H NMR (δ, $CDCl_3$): **2h**, 7.37 (d, $^3J_{H-H}$ = 18.9, $SiMe_3CH$=), 6.22 (d, $^3J_{H-H}$ = 18.9, =CH(COOH)), 0.12 (s, $Si(CH_3)_3$). The present data match those reported in the literature.[12] ^{13}C NMR (δ, $CDCl_3$): **2h**, 171.3 (COOH), 153.0 (=CH(COOH)), 133.2 (=CH($SiMe_3$), -2.0 ($Si(CH_3)_3$). GC/MS (*m/e*): trimethylsilyl ester of **2h**, $M^{\cdot+}$ - Me = 201.

(*E*)-2-Ethylidenehexanoic Acid, 3a, and (*E*)-2-Methyl-2-heptenoic Acid, 4a. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (28 mg, 0.107 mmol), dppb (23 mg, 0.0539 mmol), 2-heptyne (257 mg, 2.68 mmol), formic acid (98%, 250 mg, 5.43 mmol), and DME (6 mL) for 23 h at 107 °C under 120 psi of CO gas pressure. **3a** and **4a** were obtained in a 38:62 ratio (combined yield = 82%). ^1H NMR (δ, $CDCl_3$): **3a**, 6.98 (q, $^3J_{H-H}$ = 7.2, =CHMe), 2.28 (t, $^3J_{H-H}$ = 7.1, =C(COOH)-CH_2), 1.81 (m, CH_3-C=), 1.34 (m, $CH_3(CH_2)_2$), 0.89 (t, $^3J_{H-H}$ = 7.0, CH_2CH_3); **4a**, 6.89 (tq, $^3J_{H-H}$ = 7.5, $^4J_{H-H}$ = 1.4, =$CHCH_2$), 2.18 (q, $^3J_{H-H}$ = 6.8, =CH-CH_2), 1.81 (m, =C(COOH)-CH_3), 1.34 (m, $CH_3(CH_2)_2$), 0.89 (t, $^3J_{H-H}$ = 7.1, CH_2CH_3). The present data match those reported in the literature.[6a,13] ^{13}C NMR (δ, $CDCl_3$): **3a**, 173.8 (COOH), 140.0 (=CHMe), 132.9 (=C(Me)-COOH), 31.1 (CH_2CH=), 25.8 ($CH_3CH_2CH_2$), 22.6 (CH_3CH_2), 14.4 (CH_3-CH=), 13.9 CH_3CH_2); **4a** (ref 14), 174.0 (COOH), 145.5 (=CHCH$_2$-), 126.9 (=C(Me)COOH), 30.5 (CH_2CH=), 28.6 (CH_3-CH_2CH_2), 22.4 (CH_3CH_2), 13.8 (CH_3CH_2), 11.9 (CH_3-C=). GC/MS (*m/e*): trimethylsilyl esters of **3a** and **4a**, $M^{\cdot+}$ = 214.

(*E*)-2-(1-Methylethyl)-2-butenoic Acid, 3b, and (*E*)-2,4-Dimethyl-2-pentenoic Acid, 4b. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (31 mg, 0.118 mmol), dppb (23 mg, 0.0539 mmol), 4-methyl-2-pentyne (224 mg, 2.73 mmol), formic acid (98%, 262 mg, 5.69 mmol), and DME (5 mL) for 20 h at 101 °C under 120 psi of CO gas pressure. **3b** and **4b** were obtained in a 20:80 ratio (combined yield = 58%). ^1H NMR (δ, $CDCl_3$): **3b**, 6.84 (q, $^3J_{H-H}$ = 7.1, vinylic proton), 2.91 (septet, $^3J_{H-H}$ = 7.1, Me_2CH-C(COOH)=), 1.79 (d, 7.1, CH_3CH=), 1.16 (d, $^3J_{H-H}$ = 7.0, $(CH_3)_2CH$-C(COOH)=); **4b**, 7.00 (dq, $^3J_{H-H}$ = 9.8, $^4J_{H-H}$ = 1.4, vinylic proton), 2.63 (m, Me_2CH-CH=), 1.82 (d, $^4J_{H-H}$ = 1.4, CH_3C(COOH)=), 1.07 (d, $^3J_{H-H}$ = 6.6, $(CH_3)_2$-CH-CH=). The present data match those reported in the literature.[14] ^{13}C NMR (δ, $CDCl_3$): **3b**, 173.4 (COOH), 137.8 (=C(COOH)-(*i*-Pr)), 124.8 (=CHMe), 26.7 ($CHMe_2$), 20.5 ($(CH_3)_2CH$), 14.0 (=$CHCH_3$); **4b**, 174.2 (COOH), 151.6 (=CH-(*i*-Pr)), 138.6 (=CMe(COOH)), 28.0 ($CH(Me)_2$), 21.7 ($(CH_3)_2$-CH), 11.8 (CH_3-C(COOH)=). GC/MS (*m/e*): trimethylsilyl esters of **3b** and **4b**, $M^{\cdot+}$ = 200.

(*E*)-α-Ethylidenebenzeneacetic Acid ((*E*)-2-Phenylcrotonic Acid), 3c, and (*E*)-2-Methyl-3-phenyl-2-propenoic Acid ((*E*)-α-Methylcinnamic Acid), 4c. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), dppb (23 mg, 0.0539 mmol), PPh_3 (30 mg, 0.115 mmol), 1-phenyl-1-propyne (99%, 300 mg, 2.59 mmol), formic acid (98%, 214 mg, 4.64 mmol), and DME (5 mL) for 16 h at 106 °C under 120 psi of CO gas pressure. **3c** and **4c** were obtained in a 42:58 ratio (combined yield = 96%). ^1H NMR (δ, $CDCl_3$): **3c**, 7.39 (m, phenyl protons), 7.31 (partly obscured by the multiplet resonance due to the aromatic protons) (m, =C(Me)H), 1.75 (d, $^3J_{H-H}$ = 7.2, =CH(CH_3)); **4c**, 7.80 (d, $^4J_{H-H}$ = 1.4, =CH(Ph)), 7.39 (m, phenyl protons), 2.12 (d, $^4J_{H-H}$ = 1.4, =C(COOH)CH_3). The present data match those reported in the literature[15] and confirm the (*E*) conformation assigned to these compounds. ^{13}C NMR (δ, $CDCl_3$): **3c**, 172.9 (COOH), 142.9 (=CHMe), 134.4 (=C(COOH)Ph), 129.0, 128.4, 128.7, 128.1 (carbons of the phenyl ring), 15.8 (=$CHCH_3$); **4c**, 174.6 (COOH), 141.2 (=CHPh), 135.5 (=C(COOH)Me), 129.8, 128.4, 127.6, 127.5 (carbons of the phenyl ring), 13.7 (=C(COOH)CH_3). Assignments of the nonaromatic carbons were confirmed by HETCOR and DEPT spectra. GC/MS (*m/e*): trimethylsilyl esters of **3c** and **4c**, $M^{\cdot+}$ = 234.

(*E*)-α-Propylidenebenzeneacetic Acid, 3d, and (*E*)-2-(Phenylmethylene)butanoic Acid ((*E*)-α-Ethylcinnamic Acid), 4d. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (28 mg, 0.107 mmol), dppb (23 mg, 0.0539 mmol), 1-phenyl-1-butyne (98%, 347 mg, 2.67 mmol), formic acid (98%, 256 mg, 5.58 mmol), and DME (5 mL) for 24 h at 101 °C under 120 psi of CO gas pressure. **3d** and **4d** were obtained in a 64:36 ratio (combined yield = 91%). ^1H NMR (δ, $CDCl_3$): **3d**, 10.3 (br, COOH), 7.33 (m, phenyl protons), 7.20 (t, $^3J_{H-H}$ = 7.5, =CH(Et)), 2.12 (quintet, $^3J_{H-H}$ = 7.6, =CH(CH_2-CH_3)), 1.02 (t, $^3J_{H-H}$ = 7.5, CH_2CH_3); **4d**, 10.3 (br, COOH), 7.77 (s, =CH(Ph)), 7.33 (m, phenyl protons), 2.55 (q, $^3J_{H-H}$ = 7.5, CH_2CH_3), 1.19 (t, $^3J_{H-H}$ = 7.5, CH_2CH_3). The present data match those reported in the literature.[7,16] ^{13}C NMR (δ, $CDCl_3$): **3d**, 172.8 (COOH), 149.3 (=CHEt), 134.7 (=C(COOH)Ph), 132.7, 129.7, 128.7, 128.5, 128.0 (phenyl carbons), 23.2 (CH_3CH_2), 13.2 (CH_3CH_2); **4d**, 174.1 (COOH), 140.8 (CHPh), 135.4 (=C(COOH)-Et), 133.9, 129.5, 129.4, 128.2, 127.6 (phenyl carbons), 20.6 (CH_3CH_2), 13.8 (CH_3CH_2). GC/MS (*m/e*): trimethylsilyl esters of **3d** and **4d**, $M^{\cdot+}$ = 248.

(*E*)-α-(Phenylmethylene)benzeneacetic Acid ((*E*)-2,3-Diphenyl-2-propenoic Acid), 3e. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (29 mg, 0.111 mmol), dppb (23 mg, 0.0539 mmol), diphenylacetylene (99%, 482 mg, 2.71 mmol), formic acid (98%, 227 mg, 4.94 mmol), and DME (5 mL) for 16.5 h at 100 °C under 120 psi of CO gas pressure. **3e** was obtained in 89% yield. ^1H NMR (δ, $CDCl_3$): 7.92 (s, =CH(Ph)), 7.37-7.06 (m, Ph). The present data match those reported in the literature.[17] ^{13}C NMR (δ, $CDCl_3$): 173.3 (COOH), 142.5 (=CPh(H)), 135.2, 134.2, 131.6 (ipso carbons of the two rings and CPh(COOH)), 130.8, 129.7, 128.7, 128.2 (*o*- and *m*-carbons of the two rings), 129.5, 128.4 (*p*-carbons of the two rings). MS (direct probe, electron impact) [*m/e* (relative intensity)]: 224.0 (100%), 179.0 (94%), 178.0 (73%).

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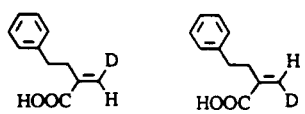
(16) Slougui, N.; Rousseau, G. *Synth. Commun.* **1982**, *12*, 401.
(17) Pouchert, C. J. *The Aldrich Library of NMR Spectra*, 2nd ed.; Aldrich: Milwaukee, WI, 1983; Vol. 2, 2(2)171D.

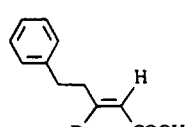
Deuterium Labeling Experiments. Preparation of $PhCH_2$-CH_2-CC-D. A septum-capped, 50-mL round-bottomed flask containing a stirring bar was purged with N_2 and flame dried for 20 min. The flask was removed from the flame, allowed to cool to room temperature under N_2, and placed in a cold bath (acetone/dry ice, ca. −60 °C). Freshly distilled THF (10 mL) and $PhCH_2$-CH_2-CC-H (98%, 899 mg, 6.91 mmol) were transferred into the flask via a syringe and stirred for 5 min. Then, *n*-BuLi (1.88 M, 3.7 mL; standardized immediately prior to the experiment by titration against $Ph_2CHCOOH$) was added dropwise to the reaction mixture and stirred at −60 °C for ca. 10 min. The temperature of the bath was then allowed to rise to ca. +2 °C whereupon D_2O (99.9% D, ca. 1 mL) was added to the mixture and stirred for 15 min. The final mixture was filtered and extracted with Et_2O and water, the ether layer was dried over $MgSO_4$ and filtered, and the solvent was removed to give a pale yellow liquid (736 mg, 81%). The ^1H NMR spectrum of this liquid indicated that greater than 95% deuterium incorporation had taken place at the acetylenic site; GC/MS of the liquid product confirmed this conclusion ($M^{\cdot+}$ = 131).

Catalytic Reaction of $PhCH_2CH_2$-CC-D with HCOOH. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (56 mg, 0.214 mmol), $PhCH_2CH_2$-CC-D (331 mg, 2.53 mmol), HCOOH (98%, 174 mg, 3.79 mmol), and DME (5 mL) for 15.5 h at 105 °C. Standard workup gave 368 mg of a pale yellow oil (solidified slowly). The ^1H NMR spectrum of this material was similar to that of **1b** except for the unequal intensities of the vinylic resonances: the resonance at 6.32 ppm was 1.28 times more intense than the one at 5.62 ppm. Integration of these resonances showed that the product was a 56:44 mixture of (*E*)- and (*Z*)-**1b**-D, respectively, in 82% combined yield. The GC/MS spectrum of these products confirmed deuterium incorporation: trimethylsilyl esters of (*E*)- and (*Z*)-**1b**-D, $M^{\cdot+}$ = 249.



(*E*)-**1b**-D (*Z*)-**1b**-D

Reaction of 4-Phenyl-1-butyne with D_2O. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (33 mg, 0.126 mmol), 4-phenyl-1-butyne (355 mg, 2.73 mmol), D_2O (99.9%, 151 mg, 7.55 mmol), and DME (6 mL) for 16 h at 97 °C. Standard workup gave 32 mg of a golden yellow oil (solidified slowly). The ^1H NMR spectrum of this material contained all the resonances for (*E*)- and (*Z*)-**1b**-D in addition to a broad resonance at 5.85 ppm which was assigned to **2b**-β-D. Integration of these resonances showed that the product was a 33:45:22 mixture of (*E*)- and (*Z*)-**1b**-D and **2b**-β-D, respectively (combined yield = 7%).

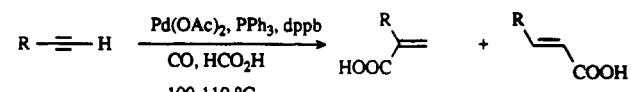


2b-β-D

Reaction of 4-Phenyl-1-butyne with HCOOD. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (28 mg, 0.107 mmol), 4-phenyl-1-butyne (355 mg, 2.73 mmol), HCOOD (5% D_2O, 2% HCOOH, 93% HCOOD; 209 mg, 4.45 mmol of HCOOD and 0.55 mmol of D_2O), and DME (5 mL) for 17 h at 100 °C. Standard workup gave 303 mg of a golden yellow oil (solidified slowly). The ^1H NMR spectrum of the latter confirmed the presence of (*E*)- and (*Z*)-**1b**-D, and **2b**-β-D in a 43:40:17 ratio, respectively (combined yield = 63%).

Reaction of 4-Phenyl-1-butyne with DCOOH. The general procedure was followed using $Pd(OAc)_2$ (6 mg, 0.027 mmol), PPh_3 (32 mg, 0.122 mmol), 4-phenyl-1-butyne (350 mg, 2.69 mmol), DCOOH (95% in H_2O; 198 mg, 4.20 mmol of DCOOH and 0.56 mmol of H_2O), and DME (6 mL) for 16 h at 102 °C. Standard workup gave a 91:9 mixture of **1b** and **2b**, respectively, in 79% yield; no deuterium incorporation had taken place.

Table I. $Pd(OAc)_2$-Catalyzed Hydrocarboxylation of Terminal Alkynes[a,b]

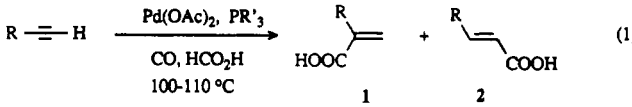


entry	R	yield (%)	turnover no.	1:2
a	Ph	96	90	93:7
b	$(CH_2)_2Ph$	86	83	94:6
c	$(CH_2)_5CH_3$	83	93	87:13
d	$(CH_2)_3CN$	86	93	94:6
e	$(CH_2)_3Cl$	77	79	89:11
f	CH(Me)Et	70	67	87:13
g	$C(Me)_3$	70	76	21:79
h	$SiMe_3$	63	67	0:100

[a] The detailed experimental procedures are described in the Experimental Section. The following were used in a typical experiment: $Pd(OAc)_2$ (0.027 mmol), PPh_3 (0.108 mmol), dppb (0.054 mmol), terminal alkyne (2.70 mmol), formic acid (5.40 mmol), and DME (5 mL). [b] No hydrocarboxylation takes place when R = OEt, COMe, $C(Me)=CH_2$, and COOH.

Results

Terminal alkynes can be hydrocarboxylated with formic acid in the presence of catalytic amounts of $Pd(OAc)_2$ and phosphine ligands. This reaction requires a temperature of 100–110 °C and 120 psi of CO gas pressure and gives 63–96% combined yields of the two regioisomers **1** and **2** (eq 1). The results of the catalytic hydrocarboxylation of terminal alkynes are summarized in Table I.



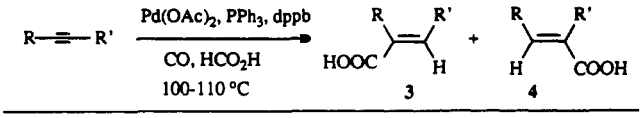
(1)

A close examination of these results reveals that the nature of the alkyne substituent R has a noticeable effect on the reaction yield, which decreases in the following order: Ph > $(CH_2)_5CH_3 \approx (CH_2)_nX$ > *s*-Bu = *t*-Bu > $SiMe_3$ (X = Ph, CN, Cl). On the basis of the reported *A*-values,[18] the relative effective bulk of these substituents increases in the following approximate order: Me ≈ Et ≈ straight chain alkyl < *i*-Pr ≈ *s*-Bu < $SiMe_3$ < Ph < *t*-Bu. A comparison of these two orders reveals that the effect of the R group on the yield of the hydrocarboxylation reaction is not strictly proportional to its relative steric bulk. Similarly, steric factors alone cannot explain the regioselectivity observed in these catalytic reactions. For instance, the regioselectivity is 87–94% in favor of the 1,1-disubstituted isomer, **1**, with both the straight chain alkyl substituents and the much bulkier Ph and *sec*-Bu groups (entries a–f). The 1,2-disubstituted isomer, **2**, becomes the preferred product with the *t*-Bu group and the exclusive product with $SiMe_3$ (entries g and h). It appears, therefore, that a combination of electronic and steric effects, as well as other factors, might be responsible for the observed trends in the reaction yield and regioselectivity.

Internal alkynes also undergo catalytic hydrocarboxylation in the presence of $Pd(OAc)_2$, PPh_3, dppb (1,4-bis(diphenylphosphino)butane), and HCOOH at 100–110 °C

(18) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1985; p 126, Table 2, and refs 159 and 173 therein.

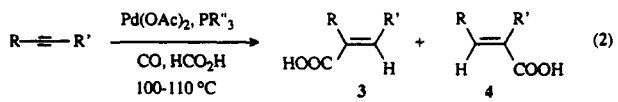
Table II. $Pd(OAc)_2$-Catalyzed Hydrocarboxylation of Internal Alkynes[a]



entry	alkyne R	alkyne R'	yield (%)	turnover no.	3:4
a	Bu	Me	82	82	38:62
b	*i*-Pr	Me	58	59	20:80
c	Ph	Me	96	93	42:58
d	Ph	Et	91	91	64:36
e	Ph	Ph	89	90	

[a] The detailed experimental procedures are described in the Experimental Section. The following were used in a typical experiment: $Pd(OAc)_2$ (0.027 mmol), PPh_3 (0.108 mmol), dppb (0.054 mmol), alkyne (2.70 mmol), formic acid (5.40 mmol), and DME (5 mL).

and 120 psi of CO gas; the products are the two regioisomers **3** and **4** (eq 2; Table II).



(2)

In principle, the hydrocarboxylation of internal alkynes can lead to a mixture of four isomeric products, two stereoisomers for each of the two possible regioisomers. Both the regio- and stereoselectivity of the reactions were determined from the ^1H NMR spectra of the reaction mixtures, on the basis of the following considerations. The regioisomers were readily distinguishable from the multiplicities and the coupling constants of their vinylic and allylic resonances. For instance, of the two products obtained from the hydrocarboxylation of 2-heptyne, one showed a quartet resonance at 6.98 ppm ($^3J_{H-H}$ = 7.2, 1 H) and a corresponding triplet resonance at 2.28 ppm ($^3J_{H-H}$ = 7.2, 2 H); these resonances clearly belong to **3a**, the regioisomer with the vinylic H positioned *gem* to the methyl substituent. The other product showed a triplet of quartets at 6.89 ppm ($^3J_{H-H}$ = 7.5, $^4J_{H-H}$ = 1.4, 1 H) and a corresponding quartet at 2.18 ppm ($^3J_{H-H}$ = 6.8, 2 H); these resonances were attributed to **4a**, the regioisomer with the vinylic H positioned *gem* to the butyl substituent. The stereoisomers were distinguishable on the basis of the chemical shift of the vinylic resonance, which is more downfield when the vinylic H is cis to the carbonyl moiety.[19] Thus, all of the internal alkynes tested in the present system lead to a single stereoisomer arising from an overall cis addition of the "H" and "COOH" moieties to give (*E*) alkenoic acids. In other words, the reaction of internal alkynes is stereospecific and regioselective. Therefore, symmetrical alkynes yield only one product, whereas unsymmetrically substituted internal alkynes give rise to two regioisomers.

As in the hydrocarboxylation of terminal alkynes, both the yield and the regioselectivity of this reaction vary with the alkyne substituents; in general, however, internal alkynes react less regioselectively than terminal alkynes. 2-Heptyne, for instance, gives an 82% combined yield and a 38:62 regioselectivity (entry a); the major product is the one in which the carboxyl group has been added to the acetylenic carbon bearing the less bulky substituent, **4**. The poor regioselectivity in this case may be rationalized in terms of the similar sizes of the two substituents Bu and Me; consistent with this rationale, a large difference

(19) Murray, T. F.; Norton, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 4107.

Table III. Effects of Various Phosphines on the Catalytic Hydrocarboxylation of 1-Octyne

entry	phosphine	yield (%)	turnover no.	1c:2c
1	PPh_3	83	93	87:13
2	$P(OPh)_3$	0		
3	PBu_3	0		
4	dppe	47	48	98:2
5	dppp	91	91	95:5
6	dppb	87	86	87:13
7	$Ph_2PCH{=}CHPPh_2$	9	9	

in the steric bulk of the two substituents would be expected to improve the regioselectivity. Indeed, replacing the Bu substituent in 2-heptyne with the more bulky *i*-Pr group improves the regioselectivity to 20:80, but it also causes a noticeable decline in the combined reaction yield (entry b). With 1-phenyl-1-propyne, on the other hand, the reaction yield is significantly higher and the regioselectivity is lower than would be expected on the basis of the relatively large size of the phenyl substituent (entry c). In comparison to the reaction of 2-heptyne, the effect of the Ph group on the regioselectivity seems to be much more similar to *n*-Bu than *i*-Pr. This anomalous behavior is also apparent in the reaction of 1-phenyl-1-butyne in which the major regioisomer is the one in which the carboxyl group has been added to the carbon bearing the Ph group (entry d). In summary, the effect of the Ph group on the reactivity of the alkyne is more like that of a small, straight chain alkyl group than a larger group such as *i*-Pr. In other words, the electronic properties of the Ph group seem to prevail over its steric aspects.

Most of the results presented in Tables I and II were obtained from reactions in which optimized experimental conditions were employed. The process by which these optimal conditions were determined is discussed in the following sections.

A. Role of Phosphine Ligands. Table III contains the results of a series of experiments carried out to examine the influence of the nature of phosphine ligands on the hydrocarboxylation of 1-octyne. The three monodentate phosphines PPh_3, PBu_3, and $P(OPh)_3$ were tested in order to establish the effect of phosphine basicity and cone angle on the reaction. In terms of the relative orders of ligand basicity ($PBu_3 > PPh_3 > P(OPh)_3$) and cone angle ($PPh_3 > PBu_3 > P(OPh)_3$), as estimated by Tolman,[20] only PPh_3 which has intermediate basicity and the largest cone angle promotes the hydrocarboxylation reaction (entries 1–3). This same ligand was also found to be the best in Watanabe's [Pt/Sn] system.[21]

The bidentate ligands dppb, dppp (1,3-bis(diphenylphosphino)propane), dppe (1,3-bis(diphenylphosphino)ethane), and (*Z*)-bis(diphenylphosphino)ethylene were also tested in order to determine the effect of chelation. The first two, dppb and dppp, showed very high yields, whereas their shorter chain congener, dppe, was less effective as a ligand in terms of reaction yield, though it produced the highest regioselectivity (entries 4–6). The last ligand, which has the smallest "bite", resulted in a very low yield (entry 7).

Having determined that the nature of the phosphine ligand is a very important factor in the $Pd(OAc)_2$-catalyzed hydrocarboxylation of alkynes, and that PPh_3 and dppb

(20) (a) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2953. (b) *Ibid.* 2956.
(21) Tsuji, Y.; Kondo, T.; Watanabe, Y. *J. Mol. Catal.* **1987**, *40*, 295.

Table IV. Effects of Pd:PPh_3:dppb Ratio on the Catalytic Hydrocarboxylation of Terminal Alkynes

entry	alkyne R	Pd:PPh_3:dppb	yield (%)	turnover no.	1:2
1	Ph	1:0:0	0		
2		1:4:0	88	89	92:8
3		1:0:2.3	77	60	89:11
4		1:3.9:1.8	96	89	93:7
5	*n*-C_6H_{13}	1:4:0	49	49	93:7
6		1:8:0	83	93	87:13
7		1:12:0	72	71	89:11
8		1:0:4	87	86	87:13
9		1:0:6	78	77	90:10
10		1:4:1.9	79	84	87:13
11	*sec*-Bu	1:8:0	54	53	86:14
12		1:4:2.2	70	67	87:13
13	*t*-Bu	1:4:0	39	41	57:43
14		1:3.9:2	70	76	21:79

are suitable choices,[22] further experiments were performed to establish the optimal ratio of the metal catalyst to these ligands. The results of these experiments are summarized in Table IV; these results established the following two points:

I. In general, the presence of suitable phosphine ligands in this system is crucial for effective hydrocarboxylation of alkynes; otherwise, the starting materials are consumed in competing side reactions. One possible explanation for this observation is that suitable phosphine ligands help maximize the concentration of the active catalyst by preventing the loss of palladium metal. It is well-known that, in catalytic processes using a palladium compound as catalyst precursor, loss of the palladium catalyst due to deposition of palladium metal is a distinct possibility.[23]

II. The optimal Pd(OAc):PPh_3 ratios for phenylacetylene and 1-octyne are 1:4 and 1:8, respectively (entries 2 and 5–7); the bidentate ligand dppb, in corresponding ratios, was slightly better than PPh_3 for 1-octyne but somewhat less effective for phenylacetylene (entries 3, 8, and 9; note that since dppb is a bidentate ligand, $^n/_2$ equiv of it is required to give the same ratio of metal to phosphorus atoms as would result with *n* equiv of PPh_3.)

Some preliminary results from our laboratories[24] had indicated that using a *mixture* of PPh_3 and dppb in the hydrocarboxylation of alkenes is sometimes superior to using either one alone; this prompted us to carry out a number of experiments using a mixture of these two phosphines. Although this approach was not advantageous with 1-octyne (entry 10) and was only slightly better for phenylacetylene (entry 4), it gave much better results with other terminal alkynes such as 3-methyl-1-pentyne and 3,3-dimethyl-1-butyne (entries 11–14). In addition, the effectiveness of using a mixture of PPh_3 and dppb was much more evident in the hydrocarboxylation of internal alkynes. As seen in Table V, 2-heptyne did not undergo hydrocarboxylation with a 1:4 ratio of $Pd(OAc)_2$:PPh_3, and even with a 1:8 ratio only 9% yield was obtained (entries 1, 2). In contrast, the same substrate gave 56% and 82% yields with dppb and a mixture of dppb plus PPh_3, respectively (entries 3, 4). With 1-phenyl-1-propyne and 1-phenyl-1-butyne, a 1:8 ratio of $Pd(OAc)_2$:PPh_3 gave only 32% yield, whereas using dppb either alone or in a mixture with PPh_3 greatly increased the reaction yields to 91–96% (entries 6, 7, 9, 10). The strong influence of

(22) In the actual chronology of the experiments, dppp was tested long after the other ligands; therefore, although in hindsight dppp appears to be a better ligand than both PPh_3 and dppb, its effectiveness was not examined further.

(23) (a) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49. (b) James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810.

(24) El-Ali, B.; Vasapollo, G.; Alper, H. Unpublished results.

Table V. Influence of the Ratio of Pd:PPh_3:dppb on the Catalytic Hydrocarboxylation of Internal Alkynes

	alkyne					
entry	R	R′	Pd:PPh_3:dppb	yield (%)	turnover no.	3:4
1	Bu	Me	1:4:0	0		
2			1:8:0	9	9	
3			1:0:2.2	56	57	35:65
4			1:4:2	82	82	38:62
5	Ph	Me	1:8:0	32	32	43:57
6			1:0:4	94	93	36:64
7			1:4.3:2	96	93	42:58
8			1:4.3:0.44	82	79	40:60
9	Ph	Et	1:8:0	32	33	68:32
10			1:4:2	91	91	64:36

dppb on the reaction yield is even more dramatically apparent in entry 8 of Table V, which demonstrates that the presence of small amounts of dppb in the reactions using PPh_3 as the main ligand results in a 50% yield increase. An additional observation which is not reflected in the data tabulated in Table V but which is very important nonetheless is that hydrocarboxylation of internal alkynes is much more consistently reproducible with dppb or a mixture of PPh_3 and dppb than with PPh_3 alone.

The observation that a mixture of two phosphine ligands is more effective in promoting the catalytic hydrocarboxylation of alkynes than using either of the two ligands alone is very interesting. Such "ligand synergism" has important mechanistic implications; for instance, it suggests the possible involvement of two or more metal centers (each of which may contain one or more of the monodentate ligands) bridged to each other by the bidentate ligands. A search of the literature of homogeneous catalysis has revealed a related example in the report by Hughes and co-workers.[25] These authors observed a "mixed ligand effect" in the Rh-catalyzed hydroformylation of 1-hexene, whereby the course of the reaction was influenced by the presence of monophosphine *and* diphosphine ligands in the catalytic system. On the basis of ^{31}P NMR studies, they postulated that three phosphorus atoms must be coordinated to the rhodium center in the active catalyst.

In summary, the best choice of ligands, and the one which is generally effective in the hydrocarboxylation of terminal and internal alkynes, is a mixture of PPh_3 and dppb. A $Pd(OAc)_2$:PPh_3:dppb ratio of 1:4:2 was commonly used in most reactions; as indicated above, however, the use of slightly less dppb or PPh_3 does not seem to affect the reaction yield appreciably.

B. Activities of Various Metal Catalysts. The activities of a number of catalyst precursors in the hydrocarboxylation of phenylacetylene are shown in Table VI. The activity observed with $Pd(OCOF_3)_2$ is comparable to that of $Pd(OAc)_2$, whereas $PdCl_2$ was much less active. Many reports have indicated[26] that chloride ions can strongly influence the catalytic activity of Pd catalysts, and it seemed reasonable that these might be responsible for the low reactivity of $PdCl_2$ in the present system. We set out to verify this possibility by examining the effect of removing the chloride ions from the reaction medium on the reaction yield. It was reasoned that adding some

(25) (a) Hughes, O. R.; Unruh, J. D. *J. Mol. Catal.* **1981**, *12*, 71. (b) Hughes, O. R.; Young, D. A. *J. Am. Chem. Soc.* **1981**, *103*, 6636.

(26) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (c) Backvall, J. E.; Bystrom, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619. (d) Waegell, B. *Organometallics in Organic Synthesis*; de Meijere, A., tom Dieck, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 1987; p 203. (e) Milstein, D. *Organometallics*, **1982**, *1*, 888.

Table VI. Activities of Various Catalysts in the Catalytic Hydrocarboxylation of Phenylacetylene

entry	catalyst	yield (%)	1a:2a
1	$Pd(OAc)_2/PPh_3$	88	92:8
2	$Pd(OCOF_3)_2/PPh_3$	87	92:8
3	$PdCl_2/PPh_3$	15[a]	
4	$PdCl_2/NaOAc/PPh_3/dppb$	77	96:4
5	$Pd(PPh_3)_4$	77	92:8
6	10% Pd/C	0	
7	10% $Pd/C/PPh_3/dppb$	85	86:14

[a] Small amounts of the dicarbonylation products, anhydride and (*Z*)-diacid, as well as some unidentified species, were also present.

NaOAc to the reaction mixture would bring about a ligand-exchange equilibrium, trapping the chloride ions as insoluble NaCl and removing them from the catalytic cycle. Thus, an experiment was conducted in which a mixture of $PdCl_2$ and NaOAc was used in an otherwise standard catalytic reaction. Entry 4 in Table VI shows that the presence of NaOAc dramatically improved the activity of $PdCl_2$ to approximately the same level as $Pd(OAc)_2$. Similarly, Milstein has shown[26e] that the $PdCl_2$-catalyzed allylic carbonylation (carbomethoxylation) of (+)-carvone occurs much more readily in the presence of carboxylic acid anions. Therefore, any one of $Pd(OAc)_2$, $Pd(OCOCF_3)_2$, or a mixture of $PdCl_2$ and NaOAc can efficiently catalyze the hydrocarboxylation of alkynes.

In all three of the catalyst precursors discussed above the Pd center is in the +2 oxidation state; to examine the activity of a Pd(0) catalyst precursor, $Pd(PPh_3)_4$ was used in an otherwise standard catalytic reaction (entry 5). Although this compound is somewhat less effective than $Pd(OAc)_2$, it is nevertheless a good precatalyst; therefore, starting with a Pd(0) species does not hinder the catalysis significantly. This outcome is not at all surprising in view of the fact that Pd(II) compounds often undergo in-situ reduction to Pd(0) when heated in a CO atmosphere.[27]

A heterogeneous catalyst precursor such as palladium on carbon (Pd/C) does not, on its own, catalyze alkyne hydrocarboxylation (entry 6). Interestingly, in the presence of suitable phosphine ligands, Pd/C becomes quite an effective catalyst (entry 7). This effect was previously observed in the case of allylic substitution by Bergbreiter and Chen.[28a] It is not known what the key species is in such heterogeneous processes.[28b]

C. Effects of CO Gas Pressure, P_{CO}. The data plotted in Figure 1 show that the presence of CO gas is essential for alkyne hydrocarboxylation: virtually no reaction occurs in its absence. The reaction yield is 57% with a pressure of 32 psi (ca. 2.2 atm) and increases gradually with increasing P_{CO} up to a pressure of 120 psi (ca. 8.3 atm) at which point the yield seems to reach a plateau at 83%. Since the solubility of CO gas in solvents is proportional to (among other factors) P_{CO}, these results imply that sufficient concentrations of CO gas dissolved in the reaction medium are vital for the catalysis. Another possible inference is that the carbonyl moiety of the product acid probably originates from the CO gas rather than formic acid. Additional support for the latter assertion comes from a similar study carried out in our laboratories on alkene hydrocarboxylation with HCOOH.[24] Complementary experiments using ^{13}C-labeled starting materials (^{13}CO gas and $H^{13}COOH$) found that only in traces of the acid product did the carbonyl moiety originate

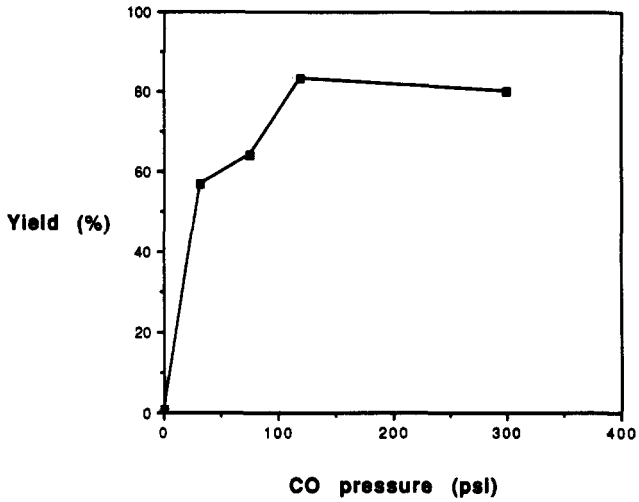


Figure 1. Effect of CO pressure on the catalytic hydrocarboxylation of alkynes.

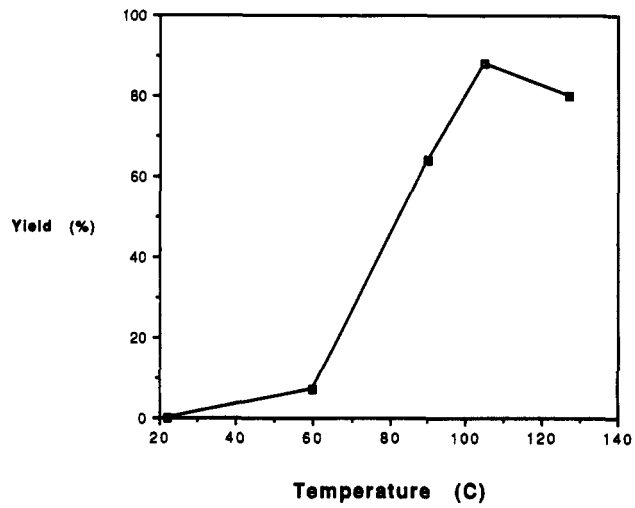


Figure 2. Effect of temperature on the catalytic hydrocarboxylation of alkynes.

from formic acid. It seems reasonable to conclude, therefore, that, in the hydrocarboxylation of alkynes with formic acid, the carbonyl moiety of the product acid originates from the CO gas and that each molecule of formic acid serves as a net source of one molecule of water (i.e., "H" and "OH" moieties). Indeed, water on its own has been shown to induce the catalytic hydrocarboxylation of alkynes, albeit in a much more sluggish manner than formic acid (vide infra). Some of the possible ways in which formic acid might provide a net molecule of water will be discussed later along with other mechanistic considerations.

D. Effects of Temperature, Reaction Time, and Solvents. The data plotted in Figure 2 indicate that a temperature of about 105 °C is optimal for alkyne hydrocarboxylation: lower temperatures decrease the yield drastically and higher temperatures do not offer any advantages. As a result, for most experiments the temperature was maintained between 100 and 110 °C.

Figure 3 shows that catalytic hydrocarboxylation of alkynes in the present system proceeds at about 1 turnover/min and a typical reaction is over in about 1.5 h. For the purpose of ensuring optimal results, however, in most experiments the reaction was allowed to proceed for 15–24 h. It is noteworthy that at least over the time range of 1.5–22 h, and the temperature range of 60–127 °C, the regioselectivity of the catalytic reaction remains unchanged within a rather narrow margin of experimental error. These

(27) Moiseev, I. I. *Pure Appl. Chem.* **1989**, *61*, 1755.
(28) (a) Bergbreiter, D. E.; Chen, B. *J. Chem. Soc.* **1983**, *1238*. (b) Bergbreiter, D. E.; Chen, B.; Weatherford, D. *J. Mol. Catal.* **1992**, *74*, 409.

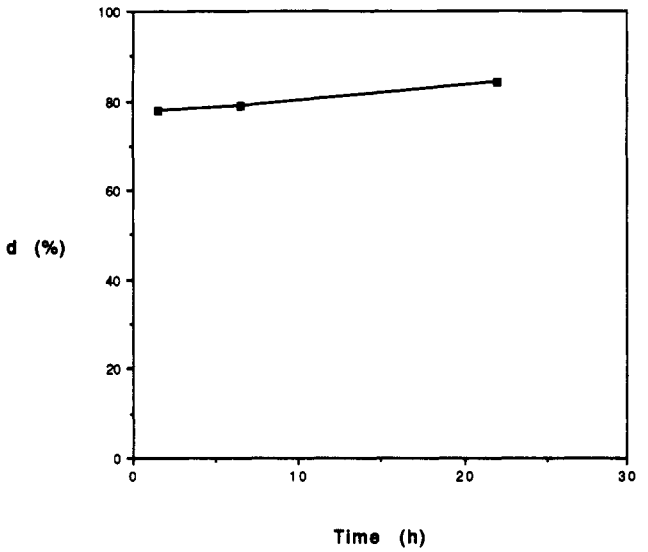


Figure 3. Influence of reaction time on the catalytic hydrocarboxylation of phenylacetylene.

Table VII. Effects of Various Acids on the Catalytic Hydrocarboxylation of Alkynes Using $Pd(OAc)_2$, PPh_3, and dppb[a]

entry	alkyne	acid	Al:W:Ac[b]	yield (%)	1:2
1	1-octyne			0	
2	Ph≡Ph	H_2O	100:218:0	0	
3	Ph≡H	H_2O	106:100:0	35	88:12
4	1-octyne	HCl(aq)	104:102:30	30[c]	
5		CF_3CO_2H(aq)	104:183:23	16	96:4
6		HCO_2H(aq)	98:137:10	10	90:10
7		$(-CO_2H)_2$(aq)	100:164:11	12	99:1
8		99% CF_3CO_2H	103:0:222	28	91:9
9		98% HCO_2H	112:8:160	83	87:13
10		99% $(-CO_2H)_2$	111:0:125	66	99:1

[a] Reaction conditions: $Pd(OAc)_2$ (0.027 mmol), PPh_3 (0.108 mmol), dppb (0.054 mmol), alkyne (2.70 mmol), water and/or acid (as indicated in the table), DME (5 mL), CO gas (120 psi), 100–110 °C, 18–24 h. [b] Molar ratio of alkyne:water:acid. [c] Other, unidentified products were also present in the product mixture.

observations indicate that the regioselectivity of the reaction is most probably determined *during* the main catalytic cycle and depends on steric and other factors influencing the reaction mechanism. In other words, the possibility of an independent isomerization process occurring parallel to the main catalytic process is slim. This point will be further elaborated later (vide infra).

Among the solvents tested, DME, acetone, and THF are the suitable choices in that order; acetonitrile and chloroform are poor solvents for this reaction.

E. Effect of Various Acids. As implied by its name, hydrocarboxylation requires a source of "H" and "COOH" moieties in addition to the substrate, the alkyne in this case. A number of experimental observations (vide supra) have led us to the conclusion that the "CO" of the "COOH" moiety is supplied by the CO gas. Therefore, the only additional reagent necessary for this reaction is one which can serve as a net source of "H" and "OH". The most obvious reagent for this purpose, and the one most widely used in hydrocarboxylation of alkenes and alkynes, is water. As seen from Table VII, however, water is not a satisfactory reagent in the present system, since it gives either no reaction (entry 2) or only a low yield (entry 3). Note that no reaction takes place without an added source of "H" and "OH" (entry 1); this is in contrast to the dicarbonylation of alkynes with $PdCl_2/CuCl_2/CO/O_2$, where the residual moisture is sufficient for the reaction.[3]

Table VIII. Catalytic Hydrocarboxylation of Alkynes Using Oxalic Acid

entry	alkyne R	alkyne R′	Pd:PPh_3:dppb	O:A[a]	yield (%)	turnover no.	ratio[b]
1	Ph	H	1:4:0	0.57	6	6	92:8
2			1:0:2.1	0.49	58	58	97:3
3			1:4:2.1	0.50	56	59	93:7
4			1:0:2.1	1.09	77	79	97:3
5	n-C_6H_{13}	H	1:0:2.1	1.13	66	73	99:1
6			1:4:2	1.20	78	78	96:4
7			1:4:2.3	2.06	76	73	91:9
8	$(CH_2)_3CN$	H	1:4.2:2.2	2.15	65	63	97:3
9	$Ph(CH_2)_2$	H	1:4:2.1	2.16	90	86	91:9
10	Ph	Me	1:4.2:2.1	2.10	96	95	48:52
11	Ph	Ph	1:4.2:2.1	2.03	88	90	

[a] Molar ratio of oxalic acid to alkyne used in the reaction. [b] This column represents the ratios of 1:2, when R′ = H, and 3:4, when R′ = Me or Ph.

The poor reactivity of water prompted an examination of the effects of adding acids to the water reactions. Hydrochloric acid was tested first, since it is the most commonly used acid in the hydrocarboxylation of alkenes and alkynes. The use of this acid in the present system resulted in a low yield and the formation of byproducts (entry 4). Low yields were also obtained with aqueous solutions of the organic acids CF_3COOH, HCOOH, and $(-COOH)_2$ (entries 5–7). A closer examination of these results reveals that the reaction yield is more or less proportional to the amount of acid used; in other words, the reaction seems to require stoichiometric, rather than catalytic, amounts of H^+. Accordingly, reactions in which formic and oxalic acids were present in stoichiometric or excess amounts gave good yields (entries 9, 10), but the yield was still quite poor with stoichiometric amounts of CF_3COOH (entry 8).

In contrast to the results discussed above, Whiting et al.[29] have reported that, in the stoichiometric hydrocarboxylation of phenylacetylene and 1-hexyne with $Ni(CO)_4$, HCl gave the best results whereas oxalic and trichloroacetic acids were unreactive. The same authors also showed that phenylacetylene can be hydrocarboxylated in alkaline media. Similar observations have been made by others. Recently, Alper and Amer[6a] have reported a much milder process for the catalytic hydrocarboxylation of terminal alkynes under phase-transfer conditions.

How does hydrocarboxylation proceed in both basic and acidic media? In basic media, the nucleophilic attack by the hydroxyl anion on coordinated CO is thought to form metal hydroxycarbonyl species, which insert into the metal–alkyne bond. The alkenyl ligand thus formed and a hydride ligand, formed by the decarboxylation of a second hydroxycarbonyl ligand, reductively eliminate to give the products. In acidic media, the metal is probably protonated first, and the hydride ligand thus formed inserts into the metal–alkyne bond to give a metal alkenyl intermediate. Insertion of CO into the metal–alkenyl bond and hydrolysis furnish the products.

F. Alkyne Hydrocarboxylation with Oxalic Acid. Although formic acid was selected as the best choice of acid for alkyne hydrocarboxylation in the present system, the use of oxalic acid was also explored briefly (Table VIII). Like formic acid, oxalic acid does not promote hydrocarboxylation in the absence of CO gas, which is to say that the CO moiety in the product originates from CO gas and not from oxalic acid. In comparison to formic acid

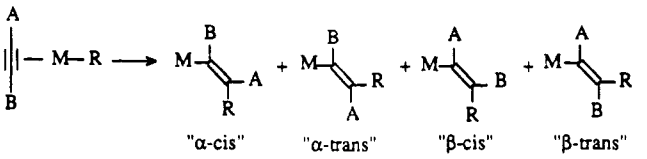
(29) (a) Jones, E. R.; Shen, T. Y.; Whiting, M. C. *J. Chem. Soc.* **1951**, 766122. (b) Jones, E. R. H.; Shen, T. Y.; Whiting, M. C. *J. Chem. Soc.* **1950**, 230. (c) *Ibid.* **1951**, 48. (d) Jones, E. R. H.; Whitham, G. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 1865.

Table IX. Effect of Catalyst to Alkyne Ratio on the Catalytic Hydrocarboxylation of Phenylacetylene

entry	Ph–CC–H/Pd	yield (%)	turnover no.	**1a**:**2a**
1	24	75	18	92:8
2	94	96	90	93:7
3	509	36	183	89:11
4	502[a]	33	165	95:5

[a] Twice as much dppb was used in this experiment compared to the previous entry.

Scheme I



reactions, the oxalic acid reactions are much more sensitive to the choice of phosphine ligands. For example, dppb is much better than PPh_3 in promoting the reaction of phenylacetylene with oxalic acid (entries 1, 2). This reaction is also quite sensitive to the ratio of oxalic acid to alkyne; a ratio of 1–2:1 seems to be optimal (entries 2, 3). The yields of the oxalic acid reactions are somewhat variable for different alkynes. In comparison to the corresponding reactions with formic acid, oxalic acid gives matching or higher yields for some alkynes (entries 8–10) and lower ones with others (entries 5–7).

G. Effects of Metal Catalyst to Alkyne Ratio. Table IX contains the results of four reactions with varying ratios of phenylacetylene to $Pd(OAc)_2$. On the basis of these results, 1% $Pd(OAc)_2$ was used in most of the reactions reported in the present study. Higher than 100 turnover numbers can be obtained by using less catalyst, but in these cases the reaction yield decreases significantly even with additional amounts of phosphine ligands (entries 3, 4).

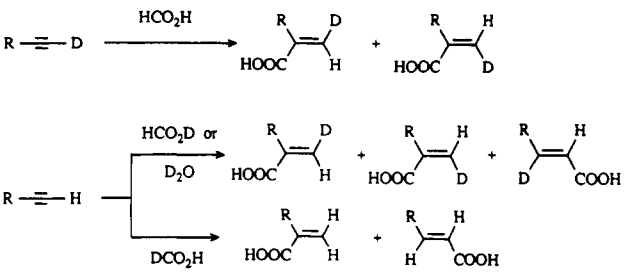
Discussion

Having discussed the experimental findings which led to the optimization of reaction conditions for the catalytic hydrocarboxylation of alkynes, it is necessary now to deal with the implications of these and other findings for the mechanism of this reaction. The remainder of this paper will discuss some mechanistic considerations, beginning with the alkyne insertion step which is central to the mechanism of alkyne hydrocarboxylation.

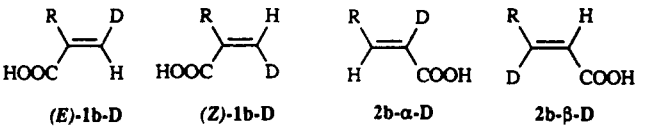
Alkyne Insertion Reaction. The insertion of π-coordinated alkynes into M–R (R = H, alkyl, alkenyl, or aryl) bonds has been known for over 30 years, and numerous examples of this reaction can be found in the literature of organometallic chemistry. Two main features of such insertions are the stereochemistry ("cis" vs "trans") and the regiochemistry (α vs β) of the addition step. The possible products of an alkyne insertion reaction are shown in Scheme I. The stereo- and regiochemistry of the alkyne insertion step in the present catalytic reactions are discussed below in terms of the products of these reactions.

A. Stereochemistry of Addition. Hydrocarboxylation of internal alkynes in the present system leads to products in which the stereochemistry of addition was determined to be "cis" for both regioisomers (vide supra). With the products of terminal alkyne reactions, however, the situation is somewhat more complicated. The 1,1-disubstituted product, for instance, is symmetrical at one end and yields no information about the stereochemistry

Scheme II



of addition. If a terminal alkyne labeled at the C-1 position were used, the stereochemistry of this product would be distinguishable by ^1H NMR spectroscopy. Thus, the labeled alkyne 1-deuterio-4-phenyl-1-butyne was prepared and used in an otherwise standard catalytic experiment. The possible products of this reaction are shown as follows (R = $PhCH_2CH_2$):



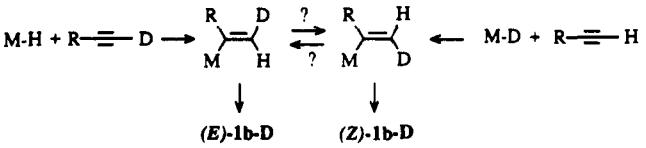
The GC/MS spectra of the reaction products confirmed the incorporation of one deuterium: $M^{\bullet+}$ = 249. The ^1H NMR spectrum of the product mixture consisted of two broad singlet resonances in the vinylic region. By comparison to the results of previous experiments with unlabeled 4-phenyl-1-butyne, these resonances were assigned to (*E*)- and (*Z*)-**1b**-D; neither **2b**-α-D nor **2b**-β-D was detected in the reaction mixture. In accord with literature reports,[19] the more downfield vinylic resonance (6.32 ppm) was assigned to the (*E*) stereoisomer in which the vinylic H is cis to the carbonyl moiety. The integration of this resonance was 1.28 times more intense than that of the other vinylic resonance, indicating a 56:44 ratio for the (*E*) and (*Z*) products, respectively.

Three other experiments, complementary to the labeling experiment described above, were conducted by using *un*deuterated 4-phenyl-1-butyne with HCOOD, DCOOH, and D_2O. The experiment with HCOOD resulted in a 43:40:17 mixture of (*E*)- and (*Z*)-**1b**-D and **2b**-β-D, respectively. The experiment using DCOOH resulted in a 91:9 mixture of **1b** and **2b**, respectively, *with no deuterium incorporation.* When D_2O was used as the source of D^+, the reaction yield was much less than that of the HCOOD reaction (7% vs 63%), but the product distribution was not significantly different, consisting of (*E*)- and (*Z*)-**1b**-D and **2b**-β-D in a 33:45:22 ratio. These results have been summarized in Scheme II; the following conclusions can be drawn from the above results:

I. The retention of deuterium in the reaction of the labeled alkyne implies that during the course of the hydrocarboxylation reaction terminal alkynes do not undergo oxidative addition of the sp C–H(D) bond. Oxidative addition of the sp C–H bond in terminal alkynes gives hydrido alkynyl or vinylidene complexes with some metal compounds.[30] If this were the case in the present system, any palladium deuteride species formed as a result of the oxidative addition of the deuterioalkyne to the metal catalyst would be expected to undergo rapid D/H exchange with the large excess of H^+ ions present in the reaction

(30) (a) Zargarian, D. Synthesis and Characterization of A Series of Rhodium Alkynyl Compounds. M.Sc. Thesis, University of Waterloo, 1987. (b) Marder, T. B.; Zargarian, D.; Calabrese, J. C.; Herskovitz, T. H.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1484.

Scheme III



medium. Such an exchange process would reduce the concentration of the Pd–D species and diminish the likelihood of D-incorporation into the final product. Hence, the presence of the deuterium label in the final product rules out the oxidative addition of terminal alkynes. Moreover, assuming that the hydrocarboxylation of both terminal and internal alkynes proceeds via two very similar mechanisms, oxidative addition of the sp C–H bond may not be considered because it is not available to internal alkynes.

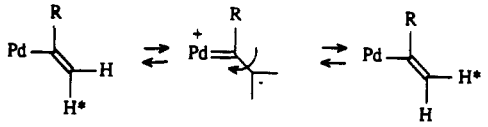
II. That none of the above experiments lead to a product in which the incoming "H" (or "D") and "COOH" moieties end up being *gem* to each other supports the exclusion of a metal vinylidene intermediate from the reaction mechanism. Indeed, the involvement of metal vinylidines in alkyne hydrocarboxylation reactions was initially suggested by Reppe in 1953;[4] this idea was discarded as soon as the hydrocarboxylation of internal alkynes was discovered. Therefore, the most probable mode of bonding for alkynes in the present system is that in which the alkyne is coordinated to the metal in a π-fashion.

III. That deuterium incorporation into a vinylic position in the product occurs with HCOOD but not with DCOOH demonstrates that formic acid reacts by protonating the metal center, i.e., by O–H(D) rather than sp^2 C–H(D) bond activation. This point will be further elaborated later (vide infra).

IV. The 1,1-disubstituted product, **1**, results from a combination of "cis" *and* "trans" additions of the "H" and "COOH" moieties, whereas the 1,2-disubstituted product, **2**, originates from a "cis" addition to give the (*E*) stereoisomer. Whereas the observed "cis" additions can be attributed to a concerted insertion of the coordinated alkyne into the Pd–H bond, the formation of a mixture of stereoisomers ((*E*)- and (*Z*)-1-D) in the reaction of the labeled terminal alkyne implies an overall "trans" addition. The two stereoisomers in this case originate via either a concerted "cis" addition process followed by isomerization at the C=C bond of the coordinated alkenyl ligand (Scheme III) or a "trans" addition of the coordinated alkyne into the Pd–H bond.

The literature of organometallic chemistry contains several reports of such net "trans" additions of alkynes into M–H or M–R bonds.[31-45] For instance, Goldman[31] has also used deuterium labeling experiments to show that the 1,1-disubstituted alkenes formed by the insertion of terminal alkynes into a Rh–Ph bond have two stereoisomers arising from "cis" and "trans" additions. Jones[32] has isolated and characterized (X-ray) *cis*- and *trans*-rhodium alkenyl complexes arising from the insertion of electron-poor alkynes into a Rh–H bond. Also, Tanke and Crabtree[33] have shown that hydrosilylation of terminal alkynes can occur by either "cis" or "trans" additions of the alkyne into the M–H or M–SiR_3 bond. In some cases, "trans" insertion is the preferred mode of addition. For instance, very recently Berke[34] and co-workers have shown that the tungsten hydride complex (*trans,trans*)-[WH(NO)(CO)$_2$(PMe$_3$)$_2$] reacts with the activated alkynes R–CC–COOR′ (R = H, Me, Ph, COOR′; R′ = Me, Et) to give selectively the "trans" addition product when R = H, Me, and COOR′. When R = Ph, the "trans" insertion product, which forms preferentially under kinetically controlled conditions, undergoes a thermal isomerization process and is converted to the "cis" product. In a relevant study, Herberich and Barlage[35] have shown that the hydride complexes Cp_2MH_2 (M = Mo, W) and Cp_2ReH promote a "cis" insertion of the hydride into activated alkynes; the resultant (*Z*)-alkenyl ligands then undergo thermal or photochemical isomerization to provide a *Z* and *E* mixture. In contrast, the metallocene hydrides Cp_2ZrHCl[36] and $Cp^*_2MH_2$[37] (M = Zr, Hf) give stereospecific "cis" insertion.

Scheme IV



A theoretical study[46] has shown that a "cis" addition can occur by a more or less concerted process whereby the M–R bond approaches the alkyne in a coplanar, end-on manner to give the resultant *cis*-metal alkenyl species. The occurrence of "trans" additions, however, is not very well understood. Through their sustained studies of alkyne insertions into Pt–H bonds, Clark and co-workers[47] have provided strong evidence for either radical or electron-transfer mechanisms for the "trans" mode of addition. An alternative proposal involves bipolar cis–trans isomerization mechanisms.[33,37-40] One version of a bipolar mechanism can be envisaged here (Scheme IV) as an explanation for the observation of the "trans" addition products observed in the present study. The bipolar species shown in Scheme IV can be thought of as a metastable intermediate or simply as an extreme case of resonance delocalization. The main thrust of this mechanism is the notion that the C=C bond weakens enough to allow a rotation which results in the "trans" insertion product.

Evidently, the phenomenon of "trans" insertion can be explained by invoking a number of different mechanisms,

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(33) Tanke, R.; Crabtree, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 7984.
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none of which can be completely ruled out for all cases. The major difficulty in developing one generally acceptable and unifying mechanism is that the nature of these reactions and their stereochemical outcomes are strongly influenced by such variables as solvent polarity, the presence of minute impurities like oxygen in the reaction media, the alkyne substituents, and the metal complex itself.

B. Regiochemistry of Addition. As discussed earlier, alkyne hydrocarboxylation in the present system produces two regioisomers in varying degrees of regioselectivity. With terminal alkynes, the regioselectivity is better than 80:20 in favor of the 1,1-disubstituted product with most substrates; the 1,2-disubstituted isomer is the main product with 3,3-dimethyl-1-butyne and the only one with (trimethylsilyl)acetylene (Table I). With unsymmetrically substituted internal alkynes, on the other hand, the regioselectivity (ratio of 3:4) is generally lower, in the range of 35 (±5):65 (±5); with 4-methyl-2-pentyne, the regioselectivity is about 80:20 (Table II).

Assuming that the alkyne inserts into a Pd–H rather than a Pd–COOH bond, the following question arises: What factors govern the regiochemistry of this reaction? More specifically, how do the steric and electronic properties of the alkyne control the regioselectivity?

A survey of the reported cases of alkyne insertions into metal hydride bonds indicates that, like the stereochemistry of this reaction, the regiochemistry is also variable, and factors like the solvent and the reaction temperature exert a strong influence over the regioselectivity. Heck[48] showed that the steric factors are predominant in determining the regioselectivity of alkene insertions into Pd–R bonds. Generally, these reactions lead to the addition of R to the *least* substituted carbon of the double bond. Similarly, Bergman and co-workers[37] have found that alkyne insertion into Ni–Me and Ni–Ph bonds occurs at the less crowded carbon atom, thereby resulting in the formation of metal alkenyl ligands wherein the *more* bulky substituent is *gem* to the metal. These authors also demonstrated that electronic effects of the alkyne substituents are not crucial; instead, the regioselectivity is sensitive to only steric crowding. Curiously, however, "... it is the metal end of the Ni–CH_3 bond rather than the CH_3 group which behaves as the sterically *less* active substituent in the insertion transition state."[37a]

The regioselectivity of the present system can also be attributed mainly to steric effects. Thus, with most of the terminal alkynes tested, the Pd–H bond tends to add preferentially to the *less* crowded carbon, i.e., to the terminus. This is evident for terminal alkynes with small- or medium-sized substituents like $(CH_2)_5CH_3$, $(CH_2)_3Cl$, and *sec*-Bu (Table I). For alkynes with large substituents like *t*-Bu and $SiMe_3$, however, the opposite is true. These two cases can be rationalized by arguing that addition of Pd–H to the terminal carbon of these alkynes would place the sterically very demanding substituent closer to the metal and its other ligands. In other words, the energetics of the addition reaction are quite sensitive to the size of the substituent. Perhaps one exception to the above trend is phenylacetylene for which addition to the terminal carbon is highly preferred (about 90–95%). This result is contrary to our expectations if the phenyl group is regarded to be at least as bulky as $SiMe_3$.[18] Since phenylacetylene reacts like a terminal alkyne bearing a small substituent, we are forced to conclude that the electronic effects of the phenyl group effectively counteract its steric influence, thereby leading to the predominance of the 1,1-disubstituted products.

Steric effects also seem to be the main factor in determining the regioselectivity of internal alkyne reactions. The difference is that here the hydride adds to the *more* crowded carbon atom. One exception is in the hydrocarboxylation of 1-phenyl-1-butyne, where the hydride adds preferentially to the carbon bearing the *less* bulky Et group (68:32; Table II). It is as if in this case the effective steric bulk of the Et group is more than that of the Ph group! To complicate the matter further, the regioselectivities observed for the other three unsymmetrical alkynes (R = Bu, Ph, *i*-Pr; R′ = Me) increases in the order *i*-Pr > Ph ≈ *n*-Bu, implying once again that the effective bulk of the Ph group is comparable to that of a small, straight chain alkyl group. It is noteworthy that regioselectivities of these reactions have been shown to be highly reproducible within a very narrow range of experimental error (<±5) by repeating each experiment at least three times.

In summary, the regioselectivity of alkyne hydrocarboxylation in the present system seems to be affected mainly by steric bulk of the alkyne substituents. On the basis of the assumption that the alkyne inserts into the Pd–H bond of an intermediate in the catalytic cycle, with terminal alkynes the hydride tends to add to the less crowded, terminal carbon atom except for alkynes bearing very bulky substituents. With internal alkynes, the opposite was observed; however, the small number of the substrates tested do not allow any firm conclusions at this stage.

Hydrocarboxylation Mechanism. Some of the first mechanisms proposed for the $Ni(CO)_4$-catalyzed hydrocarboxylation of acetylene by Reppe and other pioneers in this field had little basis in established mechanistic knowledge but are historically significant. These mechanisms have been presented in Pino's review[2] and shall not be discussed here. Owing partly to the complex nature of alkyne hydrocarboxylation, and to a lack of detailed mechanistic studies in this field, the mechanism of this reaction is poorly understood. The analogous hydrocarboalkoxylation of alkynes (ROH instead of H_2O) and both the hydrocarboxylation and hydrocarboalkoxylation of alkenes have been studied more carefully and are better understood, although even the mechanisms of these reactions remain elusive. The main theme arising from the latter studies is that transition metal-catalyzed hydrocarboalkoxylation of alkynes and alkenes can, in principle, proceed through either a M–H or a M–COOR intermediate. The mechanism involving M–COOH or M–COOR addition to alkynes or alkenes has been endorsed by Fenton,[49] Norton,[19] and Milstein;[50] the mechanism involving hydride addition to alkynes or alkenes has been supported by Knifton,[51] Tsuji,[52] and Toniolo.[53]

On the basis of the above literature precedents and the experimental observations made during this study, the following tentative mechanism has been proposed for the $Pd(OAc)_2$-catalyzed hydrocarboxylation of alkynes with formic acid (Scheme V). Beginning with step A, it is reasonable to assume that the trimeric, solid-state structure

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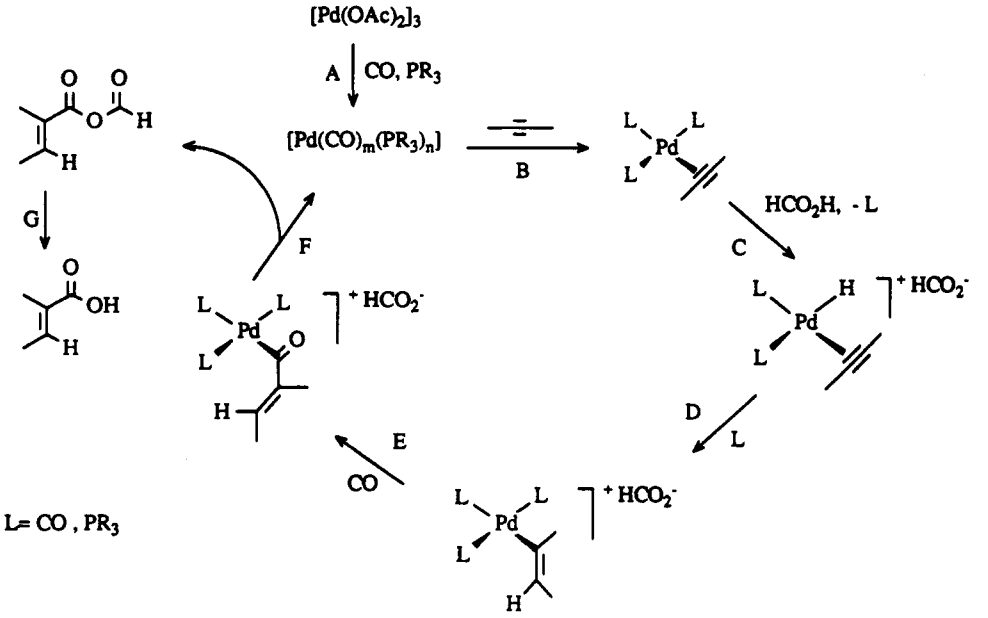
Scheme V



of $Pd(OAc)_2$ breaks down and the starting Pd(II) center gets reduced to Pd(0) in the CO atmosphere. These assertions find support in the findings of Moiseev,[27] summarized in the following reaction:

$$Pd(OAc)_2 + CO \longrightarrow Pd + (Ac)_2O + CO_2$$

By drawing an analogy to these finding, we have supposed that in the present system the species $[Pd(CO)_m(PR_3)_n]_x$ is formed in the presence of phosphine ligands and CO. The structure of this species will be assumed to be monomeric in order to simplify the arguments and the illustrations; in principle, however, other structures containing two, three, or more nuclei can also be considered.

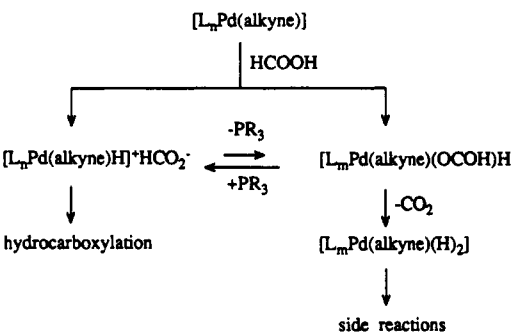
The complex $[Pd(CO)_m(PR_3)_n]$ can then undergo ligand substitution (step B) and coordinate a molecule of alkyne. The central question is how this alkyne complex reacts with formic acid. We propose that formic acid reacts by forming a metal hydride species, in essence protonating the electron-rich metal centre to form, initially, a cationic hydrido species (step C). Pd(0) species are electron-rich and are known[54] to form Pd–H bonds in the presence of strong acids. The stability of the formate ligand is variable and depends on many factors. In general, bases and higher temperatures accelerate its decomposition to give metal hydrides and CO_2.[55] Formate decarboxylation is not always facile, however, and a few well characterized complexes containing stable formate ligands are known.[56-60]

The formate anion can either coordinate to the metal to give a neutral compound or act as a counteranion to the cationic species. The latter is more plausible in the present system for two reasons. First, the coordination of the formate anion would render it prone to decarboxylation, leading to a dihydride complex that would be incapable of inducing hydrocarboxylation and would probably cause alkyne hydrogenation to alkenes or alkanes. Second, unambiguous precedents exist[61] for the displacement of weakly coordinating, labile anions (e.g., chloride, acetate, triflate, formate) from the coordination sphere of metals by less labile ligands. In a relevant case, Yamamoto[60] has shown that a formate ligand can be displaced from the coordination sphere of Pd by phosphine ligands, as follows:

$$[(\eta^3\text{-allyl})PdL(OCOH)] + L \xrightarrow[L = PR_3]{-20^\circ C} [(\eta^3\text{-allyl})PdL_2]^+HCOO^-$$

Therefore, it is conceivable that during the course of the catalysis in the present system, an equilibrium exists between two species in which the formate is either a noncoordinating counteranion or a ligand attached to the metal center (Scheme VI). In the presence of suitable phosphine ligands, the formate will be displaced from the coordination sphere of the metal nucleus and the catalysis will proceed. The absence of suitable phosphine ligands, on the other hand, would drive the equilibrium in the direction of the species with the coordinated formate. This, in turn, will facilitate formate decarboxylation and will lead to side reactions such as alkyne hydrogenation or polymerization.

Scheme VI



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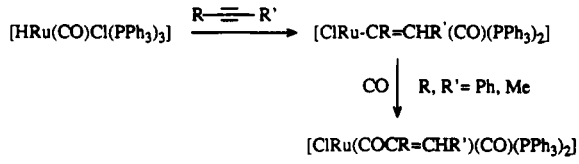
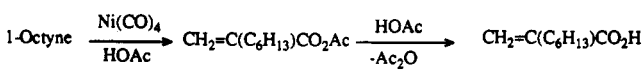
The hydrido alkyne intermediate, generated in step C (Scheme V) from the protonation of the alkyne complex, would then undergo a 1,2-addition (insertion) of the alkyne triple bond to the Pd–H bond (step D). Regardless of the mode of hydride addition ("cis" vs "trans", concerted vs stepwise), an alkenyl ligand forms which can then undergo a migratory insertion into a metal carbonyl bond to give a metal acyl compound (step E). Ros and co-workers have recently reported[62] excactly this sequence of reactions:



The final step in the catalytic cycle is the cleavage of the palladium acyl intermediate, which leads to the formation of the products and the regeneration of the catalyst (Scheme V, step F). The most probable candidate for inducing such a cleavage is the formate counteranion, which would give a mixed anhydride. Although our experimental results provide no direct evidence for the formation of a mixed anhydride, this idea seems feasible in light of a few relevant observations made by others. For instance, in palladium-catalyzed carboxylation of vinyl triflates,[63] aryl halides,[64] and optically active 1-arylethyl formates,[65] the products have been presumed to form by a formate anion mediated cleavage of metal acyls to give mixed formic anhydrides as unstable intermediates. Moreover, Matsuda and co-workers[66] have shown that the $Pd(OAc)_2$/NaOAc catalyzed carboxylation of arenediazonium salts gives mixed aromatic acetic anhydrides, ArCOOAc, which are converted to aromatic acids upon workup. Finally, Chiusoli and Cameroni[67] have reported that 1-octyne reacts with $Ni(CO)_4$ in acetic acid to produce a mixed anhydride which can be detected by infrared spectroscopy; reaction with acetic acid converts the mixed anhydride to 2-methyleneoctanoic acid and acetic anhydride:



An important point in the above reaction is that the same mixed anhydride and acid form even in the presence of methanol, indicating that cleavage by acetate anion is favored over the nucleophilic attack by methanol to give the corresponding methyl ester. Of course, no competing nucleophiles are present in our system, making the formate anion-induced cleavage even more plausible. Such a cleavage would result in a mixed formic acid anhydride, which is very unstable at higher than ambient temperatures[65] and decomposes readily to give the corresponding acid (Scheme V, step G). In addition, this decomposition is autocatalytic in the presence of acids, bases, or water.[68]

Alkyne hydrocarboxylation with oxalic acid probably follows a mechanism similar to that of the formic acid reaction. Thus, an analogous acyl intermediate would form in which oxalate is the counteranion; the cleavage of the metal acyl bond by the oxalate anion can then give a mixed oxalic anhydride, which would decompose to give the product acids.

The mechanism illustrated in Scheme V belongs to the class of "hydride" mechanisms mentioned earlier. It is, of course, one possibility among several other sequence of reactions which can be envisaged for the hydrocarboxylation of alkynes. An obvious alternative would be the "carboalkoxy" mechanism, which has been favored by Norton[19] to involve a nucleophilic attack on a M–CO species to form M–COOR (or M–COOH in the present case); this species then undergoes insertion by the coordinated alkyne to give alkenyl intermediates. This mechanism was judged unlikely for the present system, because this type of nucleophilic attack generally occurs in basic, rather than acidic, reaction media.[50] Although in principle both water and the formate anion can act as nucleophiles in our reactions, the likelihood of this is not great because both species are weak nucleophiles. In fact, the catalysis proceeds *less* efficiently with the *more* nucleophilic of these two reagents, i.e., water.

Conclusion

This study has shown that terminal and internal alkynes can be hydrocarboxylated in high yields and turnover numbers in a system consisting of CO gas, formic acid, and catalytic quantities of $Pd(OAc)_2$ and phosphine ligands. Although our original goal of eliminating the requirement of CO gas in alkyne hydrocarboxylation through the use of formic acid has not been accomplished yet, the results presented above have led to a more optimized set of reaction conditions, as well as a better understanding of the mechanism of this reaction.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and British Petroleum for financial support. We thank Prof. B. R. James for helpful discussions and for providing us with a copy of an unpublished manuscript.

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