Palladium-Catalyzed Formylation of Aryl, Heterocyclic, and Vinylic Halides

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Abstract: Aryl, heterocyclic, and vinylic halides react under about 1200 psi of 1:1 carbon monoxide–hydrogen in the presence of a basic tertiary amine and a dihalobis(triphenylphosphine)palladium(II) catalyst at 80–150° to form aldehydes in good yields. Acid chlorides also react under similar conditions to form aldehydes.

The oxidative addition reaction of organic halides with palladium(0) complexes has proved to be a very convenient and practical way to produce palladium–carbon bonded compounds. Catalytic reactions of these compounds prepared in the above manner, with olefins,[1] with carbon monoxide and alcohols,[2] and with amines[3] have been reported previously. We have now found that a combination of carbon monoxide and hydrogen will convert the organopalladium complexes into aldehydes and that the reaction may be used to produce aldehydes from aryl, heterocyclic, and vinylic halides catalytically.

We have used as catalysts dihalobis(triphenylphosphine)palladium(II) complexes which presumably are reduced by the hydrogen in the reaction mixture to a palladium(0) complex, perhaps the bis(triphenylphosphine)carbonyl derivative. The palladium(0) complex then probably undergoes oxidative addition with the organic halide, inserts carbon monoxide, and finally is reduced by hydrogen. The hydridohalobis(triphenylphosphine)palladium(II) product either directly loses HX, or it reacts with a tertiary amine also present in the reaction mixture, the palladium(0) complex is re-formed, and the cycle can begin again. A possible formulation is shown in Scheme I.

Scheme I

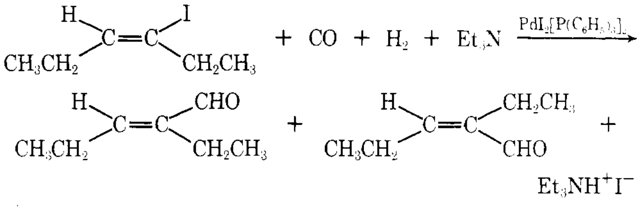
$$
\begin{aligned}
&[PdX_2[P(C_6H_5)_3]_2 + H_2 + CO \longrightarrow \\
&\qquad\qquad Pd(CO)[P(C_6H_5)_3]_2 + 2HX] \\
&Pd(CO)[P(C_6H_5)_3]_2 + RX \rightleftharpoons \\
&\qquad\qquad RPd(X)(CO)[P(C_6H_5)_3] + P(C_6H_5)_3 \\
&RPd(X)(CO)[P(C_6H_5)_3] \xrightleftharpoons{P(C_6H_5)_3} RCOPd(X)[P(C_6H_5)_3]_2 \\
&RCOPd(X)[P(C_6H_5)_3]_2 + H_2 \longrightarrow \\
&\qquad\qquad RCHO + HPd(X)[P(C_6H_5)_3]_2 \\
&HPd(X)[P(C_6H_5)_3]_2 + R'_3N + CO \longrightarrow \\
&\qquad\qquad R'_3NH^+X^- + Pd(CO)[P(C_6H_5)_3]_2
\end{aligned}
$$

$$RX + CO + H_2 \xrightarrow[R'_3N]{PdX_2[P(C_6H_5)_3]_2} RCHO + HX$$

Results and Discussion

Numerous aryl, heterocyclic, and vinylic halides have been successfully formylated. The reaction is limited to organic halides which do not easily undergo β-hydride elimination. Some *o*-dihalobenzenes, also, do not react normally. Alkyl halides with β hydrogens undergo elimination in preference to formylation. Formylation of *o*-dibromobenzene yields only benzaldehyde, the second bromine group being reduced rather than formylated. Reaction conditions vary depending upon the halide used. Generally iodides are more reactive than bromides. We find that temperatures between about 80 and 150° are usually required for reasonable reaction rates. When higher temperatures are employed, decomposition reactions sometimes become significant. Better yields are usually obtained if some inert solvent is added to the reaction mixture, such as benzene, toluene, or xylene. Pressures of about 1200–1500 psi initially were used, and they generally decreased several hundred pounds during the reactions. Reactions did occur at atmosphere pressure, but yields were poor. The ratios of carbon monoxide to hydrogen could be varied, but 1:1 was used for most of the experiments. The tertiary amine employed was not critical. We used either triethyl- or tri-*n*-butylamine in amounts in small excess of the halide present. The reactions carried out are listed in Table I. The nmr spectra of the new products are given in Table II.

The formylation reaction appears to be widely applicable judging from the examples studied. The palladium catalyst apparently does not catalyze the reduction of nitriles or double bonds since these groups are present in examples which reacted normally. The nitro group in 4-nitrobromobenzene apparently is readily reduced, however, since only polymeric products were obtained from it. *o*-Dibromobenzene also reacted abnormally as noted above. In addition to iodo- and bromobenzene derivatives, 1-bromonaphthalene, 3-bromopyridine, and 2-bromothiophene were also found to give the expected aldehydes in good yields. The three examples of vinylic halides tried, (*E*)-2-bromostyrene, (*E*)-3-iodo-3-hexene, and 2-iodo-1-hexene, gave the predicted aldehyde products in reasonable yields. In the second example both the *E* and *Z* aldehydes were found. In the third example, some double bond isomerization was also observed from the terminal to an internal position. This isomerization could be suppressed by carrying out the reaction at 80 rather than 100°, but this slowed the reaction considerably. The total yield of aldehydes remained about the same, but the relative amount of 2-methyl-2-hexenal compared with the expected product 2-formyl-1-hexene changed from 24:76 at 100° to 17:83 at 80°, while the reaction rate decreased by a factor of about 10.



From the mechanism proposed for the formylation, it would be expected that acylpalladium complexes prepared by the oxidative addition of acid halides to palladium(0) compounds should also be reducible with hydrogen to aldehydes. Indeed this can be done catalytically in the pres-

Table I. Formylation Reactions of Organic Halides

Organic halide (mmol)	Base, (mmol)	Catalyst, (mmol)	CO:H_2	Initial press., psi	Temp, °C	Reaction time, hr	Product (% yield)	Mp or bp (mm), °C	Reported mp or bp (mm), °C	Mol wt Found	Mol wt Calcd
$C_6H_5Br^a$ (6.9)	n-Bu_3N (7.6)	$(PPh_3)_2PdBr_2$ (0.2)	1:1	1350	125	24	C_6H_5CHO (94)^b				
$C_6H_5I^a$ (6.9)	n-Bu_3N (7.7)	$(PPh_3)_2PdI_2$ (0.2)	1:1	1500	125	9	C_6H_5CHO (95)^b				
4-$CH_3OC_6H_5Br$ (17.2)	n-Bu_3N (19)	$(PPh_3)_2PdBr_2$ (0.25)	1:2	1450	150	10	4-$CH_3OC_6H_4CHO$ (84)	73–75 (0.7)	245–248^c	135.0482	135.0524
4-$NCC_6H_4Br^d$ (25)	Et_3N (30)	$(PPh_3)_2PdBr_2$ (0.375)	1:1	1510	150	24	4-NCC_6H_4CHO (76)	99–100	92–93^e	131.0427	131.0371
3,4-$(CH_3O)_2C_6H_3Br^f$ (25)	n-Bu_3N (30)	$(PPh_3)_2PdBr_2$ (0.375)	1:1	1475	140	72	3,4-$(CH_3O)_2C_6H_3CHO$ (69)^g	107–112 (1)	42.5–43.5^h	166.0652	166.0630
3,4-$(CH_3O)(AcO)C_6H_3Br^i$ (25)	n-Bu_3N (30)	$(PPh_2)_2PdBr_2$ (0.375)	1:1	1520	145	26	3,4-$(CH_3O)(AcO)C_6H_3CHO$ (78)	67–69	77–78^j	194.0457	194.057
1,4-$C_6H_4Br_2{}^d$ (25)	n-Bu_3N (60)	$(PPh_3)_2PdBr_2$ (0.5)	1:1	1375	140	24	1,4-$C_6H_4(CHO)_2$ (83)^k	112–114	115–116^l	134.0347	134.0368
1,2-$C_6H_4Br_2{}^d$ (25)	Et_3N (60)	$(PPh_3)_2PdBr_2$ (0.5)	1:1	1190	140	41	C_6H_5CHO (66)	65–66 (15)			
1-$C_{10}H_7Br$ (17.2)	n-Bu_3N (19)	$(PPh_3)_2PdBr_2$ (0.25)	1:1	1225	125	24	1-$C_{10}H_7CHO$ (82), $C_{10}H_8$	147–149 (12)	158–159 (14)^m	156.0697	156.0575
3-Bromopyridine^f (25)	Et_3N (10 ml)	$(PPh_3)_2PdBr_2$ (0.375)	1:1	1350	145	26	3-Pyridinecarboxaldehyde (80)	79–81 (12)	97–99 (26)^n	107.0319	107.0371
2-Bromothiophene (17.2)	n-Bu_3N (19)	$(PPh_3)_2PdBr_2$ (0.25)	1:1	1230	130	20	2-Thiophenecarboxaldehyde (76)	78–79 (12)	97–100 (27)^o	111.9940	111.9938
(E)-$C_6H_5CH{=}CHBr^f$ (25)	Et_3N (30)	$(PPh_3)_2PdBr_2$ (0.25)	1:1	1430	80	26	(E)-$C_6H_5CH{=}CHCHO$ (65)^b				
(E)-$CH_3CH_2CH{=}C(I)CH_2CH_3{}^d$ (25)	Et_3N (30)	$(PPh_3)_2PdI_2$ (0.25)	1:1	1250	80	20	($E + Z$)-$CH_3CH_2CH{=}C(CHO)CH_2CH_3$ (75)	45–47 (12)	148^p	112.0877	112.0888
$CH_3(CH_2)_3C(I){=}CH_2{}^{d,q}$ (25)	Et_3N (30)	$(PPh_3)_2PdI_2$ (0.25)	1:1	1380	100	3	$CH_3(CH_2)_3C(CHO){=}CH_2$ (53) $CH_3(CH_2)_2CH{=}C(CHO)CH_3$ (20)	38–44 (14)		112^s 112.0865	112.0888 112.0888
$CH_3(CH_2)_3C(I){=}CH_2{}^d$ (25)	Et_3N (30)	$(PPh_3)_2PdI_2$ (0.25)	1:1	1225	80	24	$CH_3(CH_2)_3C(CHO){=}CH_2$ (75)^{b,r} $CH_3(CH_2)_2CH{=}C(CHO)CH_3$ (15)^{b,r}				

[a] p-Xylene, 1.5 ml was used as solvent. [b] Yield determined by gas chromatography. [c] E. L. Niedzielski and F. F. Nord, *J. Amer. Chem. Soc.*, **63**, 1462 (1941). [d] Benzene, 15 ml used as solvent. [e] H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **80**, 5377 (1958). [f] Benzene, 10 ml used as solvent. [g] 15% of the 4-bromoveratrol was unreacted after 72 hr. [h] J. R. Johnson, Ed., *Org. Syn.*, **16**, 91 (1936). [i] Benzene, 5 ml was used as solvent. [j] A. Russell, *J. Amer. Chem. Soc.*, **70**, 1060 (1948). [k] Yield base on 1,4-$C_6H_4Br_2$ reacted; 11.2% was recovered. [l] E. C. Horning, Ed., "Organic Syntheses," Collect. Vol. III, Wiley, New York, N.Y., 1955, p 788. [m] H. Rupe and W. Brentano, *Helv. Chim. Acta*, **19**, 581 (1936). [n] C. Niemann, R. N. Lewis, and J. T. Hays, *J. Amer. Chem. Soc.*, **64**, 1680 (1942). [o] N. Rabjohn, Ed., "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 915. [p] H. Sutter and N. Wijkman, *Justus Liebigs Ann. Chem.*, **505**, 252 (1933). [q] Yield based on 91% purity of starting iodide. The other 9% was 1-iodo-1-hexene. [r] Yield based upon reacted iodide. About 68% of the iodide reacted in 24 hr. [s] Parent ion observed, but it was too weak for determination of a more accurate value.

Table II. Proton Nmr Data for the Formylation Products

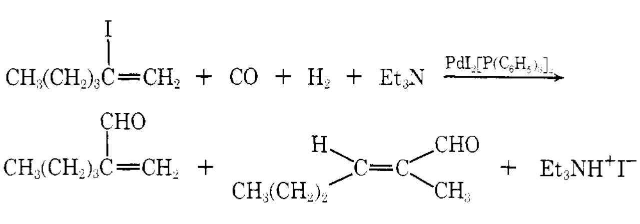
Compd	Nmr absorptions, τ values[a,b] Vinylic	Aliphatic	Aldehyde
$(E + Z)$-$CH_3CH_2CH{=}C(CHO)CH_2CH_3$	(t) 3.66 (1 H) J = 8 Hz	(m) 6.90–9.30 (10 H)	(s) 0.68, 0.10 (1 H)[c]
$CH_2{=}C(CHO)(CH_2)_3CH_3$	(s) 3.75 (1 H) (s) 3.98 (1 H)	(t) 7.75 (2 H) (m) 8.25–9.35 (7 h)	(s) 0.43 (1 H)
(E)-$CH_3(CH_2)_2CH{=}C(CHO)CH_3$	(t) 3.45 (1 H) J = 7 Hz	(q) 7.65 (2 H) (s) 8.25 (3 H) (m) 8.50 (2 H) (m) 9.00 (3 H)	(s) 0.57 (1 H)

[a] Recorded in $CDCl_3$ at 60 MHz using TMS as an internal standard. [b] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. [c] Isomer ratio 2:1.

Table III. Hydrogenolysis of Acid Chlorides

Acid chloride, (mmol)	Amine, (mmol)	Catalyst, (mmol)	Initial hydrogen press., psi	Temp, °C	Reaction time, hr	Product (% yield)[a]
C_6H_5COCl[b] (25)	n-Bu_3N (30)	$(PPh_3)_2PdCl_2$ (0.375)	1380[c]	125	20	C_6H_5CHO (81)
C_6H_5COCl[d] (25)	n-Bu_3N (30)	$(PPh_3)_2PdBr_2$ (0.375)	725	125	20	C_6H_5CHO (84)
2-$CH_3OC_6H_4COCl$[d] (50)	Et_3N (60)	$(PPh_3)_2PdCl_2$ (0.75)	1150	140	12	2-$CH_3OC_6H_4CHO$ (34)[e]
4-ClC_6H_4COCl[d] (25)	Et_3N (30)	$(PPh_3)_2PdCl_2$ (0.375)	1205	145	15	4-ClC_6H_4CHO (64)

[a] Yields were determined by vpc. [b] Benzene, 10 ml was used as solvent. [c] A 1:1 mixture of CO and H_2 was used. [d] Benzene, 15 ml was used as solvent. [e] About 16% anisole and unidentified higher boiling products were also formed.



ence of a tertiary amine as can be seen from the three examples listed in Table III. This reduction of acid halides to aldehydes is undoubtedly closely related mechanistically to the heterogeneous Rosenmund reduction. One significant difference from the Rosenmund reduction, however, is that aliphatic acid halides do not give useful yields of aldehydes under our reaction conditions, while they apparently do in the Rosenmund reduction.[4] The different ligands present in the Rosenmund catalyst apparently favor the hydrogen reduction, while the phosphine ligands allow decarbonylation and elimination to become seriously competing reactions in the present case. We have also attempted to use the Rosenmund catalyst for the formylation of bromobenzene at 100° under our reaction conditions, but no reaction occurred.

Nickel-Catalyzed Formylations. A few attempts were made to use halobis(triphenylphosphine)phenylnickel(II) complexes as catalysts for the formylation of bromo- and iodobenzene, but results were not encouraging. While we did find a turnover of four to five times of the catalyst in the formylation of iodobenzene with triethylamine at 100°, the yield based upon iodobenzene was only about 20%. Considerable reduction to benzene probably accompanied the reaction. Bromobenzene did not react under the usual conditions, and a stoichiometric reaction with chlorobis(triphenylphosphine)phenylnickel(II) with 1:1 CO and H_2 gave only benzene and biphenyl at 100°.

Experimental Section

Reagents. Tri-n-butylamine (Eastman) and triethylamine (Eastman) were distilled from potassium hydroxide and stored over Linde 4A molecular sieves. 4-Bromo-2-methoxyphenyl acetate was prepared by bromination of o-methoxyphenol as described by Riegel.[5] The 4-bromo-2-methoxyphenol (mp 35–36°; 10 g) was then allowed to react with 10 ml of acetic anhydride and 1 ml of pyridine at 100° for 1 hr. Ice and water were added, and the solid was separated by filtration. Recrystallization twice from hexane yielded colorless crystals of the acetate, mp 57–58°.

Chloro-, bromo-, and iodobis(triphenylphosphine)phenylnickel(II) were prepared by published procedures.[6] The vinylic halides and palladium catalysts were prepared as described earlier.[2] All other organic halides and chlorides were commercial products used without further purification. The carbon monoxide (CP grade, Matheson) and hydrogen (prepurified grade, Matheson) were also used without additional purification.

Analysis. Samples were analyzed by gas chromatography on a 15-ft 20% SE-30 on Chromosorb W column. If known samples were available, sensitivity coefficients were obtained with diphenyl ether. The diphenyl ether was then added as an internal standard after the reaction was complete. High resolution mass spectra were obtained by peak matching using a Du Pont (CED) 21-110B double focus mass spectrometer. Proton nuclear magnetic resonance spectra were measured with a Varian Associates Model A60A spectrometer or a Perkin-Elmer R12B spectrometer using TMS as an internal standard. In all examples, formation of an aldehyde was confirmed by testing with a 2,4-dinitrophenylhydrazine reagent.

General Procedure for the Formylation of Organic Halides. A 45-ml or 75-ml Parr bomb equipped with a 3000-psi inconel rupture disk, a 3000-psi pressure gauge, and a magnetic stirring bar was charged with 25.0 mmol of the organic halide, 0.375 mmol of dihalobis(triphenylphosphine)palladium(II), 30.0 mmol of either tri-n-butylamine or triethylamine and benzene (usually 10 ml in the 45-ml bomb and 15 ml in the 75-ml bomb). The bomb was flushed with argon, sealed, and pressurized to 600 psi with carbon monoxide. After the pressure was released, the bomb was repressurized to 600 psi with carbon monoxide and finally pressurized to 1200 psi with hydrogen. The reaction vessel was then heated with magnetic stirring in an oil bath, and the time, pressure, and temperatures were periodically recorded until gas absorption stopped. The reaction vessel was then cooled, the gas pressure slowly released, and the bomb opened. A precipitate of palladium metal was generally present if all of the organic halide had reacted. The reaction mixture was then dissolved in ether and washed with several portions of 20% hydrochloric acid solution to remove salts and excess amine. The ether layer was then washed with distilled water, dried with anhydrous magnesium sulfate, concentrated under reduced pressure, and distilled *in vacuo*. Reaction conditions, yields, melting ranges or boiling ranges, and mass spectral analysis of all compounds studied are shown in Tables I and III. Proton nmr data of the new products are shown in Table II.

3-Pyridinecarboxaldehyde. To the 45 ml-Parr bomb were added 3.95 g (25.0 mmol) of 3-bromopyridine, 10 ml of triethylamine, 10 ml of benzene, and 0.30 g (0.375 mmol) of dibromobis(triphenylphosphine)palladium(II). The bomb was then flushed with argon, sealed, and pressurized to 1200 psi with equal amounts of carbon monoxide and hydrogen as described in the general procedure. The reaction vessel was heated in an oil bath with stirring at 145°. After 20 min, the pressure reached a maximum of 1350 psi. Times and pressures were periodically recorded until gas absorption stopped (26 hr), and the pressure in the reaction vessel had decreased to 1025 psi. The reaction vessel was cooled, and the gases were slowly released. After addition of anhydrous ether, the reaction mixture was filtered to remove the triethylamine hydrobromide, concentrated *in vacuo* to remove ether, benzene, and triethylamine, and finally distilled to give 2.15 g (80% yield) of product, bp 79-81° (12 mm). The nmr spectrum of the product is given in Table II.

1,4-Benzenedicarboxaldehyde. The 75-ml reaction bomb was charged with 5.9 g (25.0 mmol) of 1,4-dibromobenzene, 11.2 g (60.0 mmol) of tri-*n*-butylamine, 15 ml of benzene, and 0.40 g (0.5 mmol) of dibromobis(triphenylphosphine)palladium(II). The reaction vessel was then flushed and pressurized to 1200 psi with carbon monoxide and hydrogen as described above. After 15 min, the presure reached 1375 psi at 140° and decreased to 600 psi after 24 hr of reaction. The vessel was then cooled to room temperature and the pressure released. The reaction mixture was treated as in the above example. After evaporation of the ether, the resulting solids were sublimed (100° (8 mm)) to give 3.79 g of a mixture of the terephthalaldehyde and 1,4-dibromobenzene. The mixture was separated by chromatography on silica gel. There were obtained 0.66 g (2.8 mmol) of 1,4-dibromobenzene and 2.47 g (18.4 mmol) of 1,4-benzenedicarboxaldehyde, mp 112-114°, 83%. Recrystallization from hexane yielded 2.21 g of pure dialdehyde, mp 115-116°.

Formylation of 2-Iodo-1-hexene. To the 75-ml reaction bomb were added 5.23 g (25.0 mmol) of 2-iodo-1-hexene (containing 9% 1-iodo-1-hexene), 3.04 g (30.0 mmol) of triethylamine, 15 ml of benzene, and 0.221 g (0.25 mmol) of diiodobis(triphenylphosphine)palladium(II). Carbon monoxide and hydrogen were added as described in the general procedure. During the reaction, carried out at 100°, the pressure decreased from 1380 to 1050 psi over a period of 3 hr. The reaction mixture was treated as described in the general procedure to give 1.85 g (73% yield based on the 2-iodo-1-hexene) of a mixture of 2-formyl-1-hexene (53%) and (*E*)-2-formyl-2-hexene (20%). The boiling point of the mixture was 38-44° (14 mm). The mixture could easily be separated for analysis by preparative gas chromatography on a 15-ft 20% SE-30 on Chromosorb W column at 165°; retention time for 2-formyl-1-hexene was 350 sec and for (*E*)-2-methyl-2-pentenal was 465 sec.

Stoichiometric Reaction of CO and H_2 with Chlorobis(triphenylphosphine)phenylnickel(II). To the 75-ml Parr bomb were added 6.96 g (10.0 mmol) of chlorobis(triphenylphosphine)phenylnickel(II), 5.56 g (30.0 mmol) of tri-*n*-butylamine, 1.70 g (10.0 mmol) of diphenyl ether, and 10 ml of *o*-xylene. Carbon monoxide and hydrogen were added as described above, and the mixture was reacted at 100° with magnetic stirring. The gas pressure decreased from 1360 to 1240 psi over a period of 1 hr. Analysis of the reaction mixture by glc on a 15-ft 20% SE-30 on Chromosorb W column at 100° indicated that only benzene and biphenyl were produced.

Nickel-Catalyzed Formylation. To the 75-ml Parr bomb were added 3.94 g (5.0 mmol) of iodobis(triphenylphosphine)phenylnickel(II), 10 ml of iodobenzene (~90 mmol), 10 ml of triethylamine, and 10 ml of benzene. The reaction vessel was sealed, pressurized to 1200 psi with 1:1 CO:H_2 as described above, and reacted at 100°. The pressure decreased from 1375 to 500 psi in 75 hr. Analysis by vpc indicated all the iodobenzene had reacted, producing ca. 25.0 mmol of benzaldehyde.

A reaction similar to the above but with 3.70 g (5.0 mmol) of bromobis(triphenylphosphine)phenylnickel(II), 15.72 g (100.0 mmol) of bromobenzene, 11.13 g (110.0 mmol) of triethylamine, and 10 ml of benzene at 115-120° was attempted. After 12 hr, the pressure had decreased only from 1380 to 1350 psi and then apparently stopped. No benzaldehyde was found in the reaction mixture.

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References and Notes

(1) H. A. Dieck and R. F. Heck, *J. Amer. Chem. Soc.*, **96**, 1133 (1974).
(2) A. Schoenberg, J. Bartoletti, and R. F. Heck, *J. Org. Chem.*, **39**, 3318 (1974).
(3) A. Schoenberg and R. F. Heck, *J. Org. Chem.*, **39**, 3327 (1974).
(4) E. Mosettig and R. Mozingo, *Org. React.*, **4**, 362 (1948).
(5) B. Riegel and H. Wittcoff, *J. Amer. Chem. Soc.*, **68**, 1913 (1946).
(6) M. Hidai, T. Kashuwagi, T. Ikeuchi, and Y. Uchida, *J. Organometal. Chem.*, **30**, 279 (1971).