Alkylative 1,2-Carbonyl Transposition of 2-Methoxy-2-cyclohexenones

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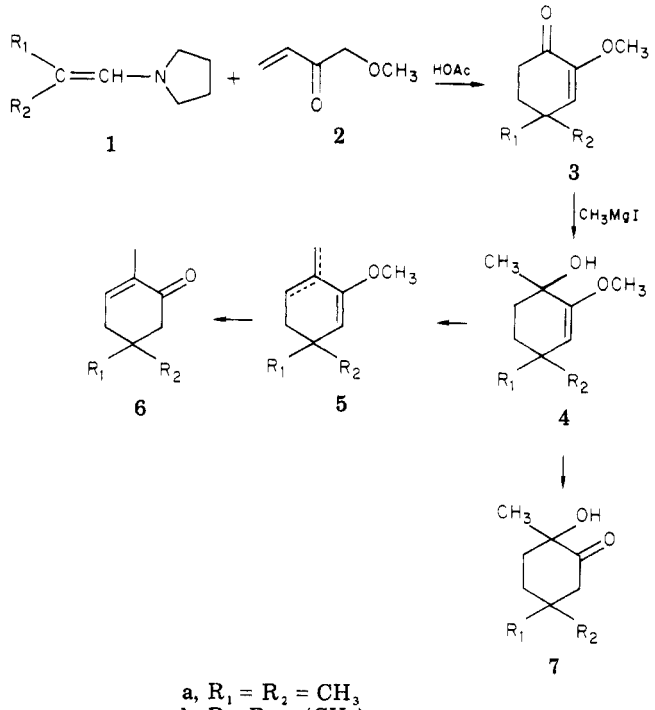
A new alkylative 1,2-carbonyl transposition sequence is described for the conversion of a number of substituted 2-methoxy-2-cyclohexenones (**3**) to substituted 2-methyl-2-cyclohexenones (**6**). The sequence involves reaction of **3** with methylmagnesium iodide to yield alcohol **4** which is then converted to **6** by either of two possible dehydration–hydrolysis procedures. The monoterpene carvotanacetone (**6c**) is one of the compounds prepared by this method. When this sequence was performed on the bicyclic substrate **9a**, enone **11** was the major product formed. Attempts to induce a related 1,2-methyl shift upon acid treatment of alcohol **10b** were not successful but simply led to the "normal" enone **12b**. A simpler and more effective procedure for the preparation of the starting methoxy enones **3** and **9** is also described.

The necessity of transposing a carbonyl group from one carbon to a neighboring position, sometimes with concomitant alkylation, is often encountered in the synthesis of natural products or other complex organic molecules.[1,2] In this report we outline an alkylative 1,2-carbonyl transposition of 2-methoxy-2-cyclohexenones which may be applied to cyclohexyl, bicyclo[4.4.0]decyl, or spiro[4.5]decyl systems.[3,4] Also, an improved procedure for the preparation of the methoxy enone precursors is described.

The 2-methoxy-2-cyclohexenones were prepared by using a variation of the annelation method described by Wenkert.[5] We have found that simply by reacting enamine **1a** and an excess of 1-methoxy-3-buten-2-one (**2**)[6] with 1 equiv of acetic acid in the absence of solvent at room temperature for 2.5 h, enone **3a** (Scheme I) may be obtained in 71% yield.[7] Similarly, a spiroannelation reaction[8] of enamine **1b** with **2** in the presence of acetic acid gave the new spiro[4.5] enone **3b** in good yield (Table I). The best yield of **3c** was obtained by stirring disubstituted enamine **1c** with **2** for several hours prior to the addition of acetic acid but the yield was only moderate. Reaction of the ketone enamine **8a** with **2** and acetic acid gave **9a** in good yield.[9] Substituted 2-methoxy-2-cyclohexenones may also be prepared by treatment of 2,3-epoxycyclohexanones with sodium methoxide in methanol.[2a]

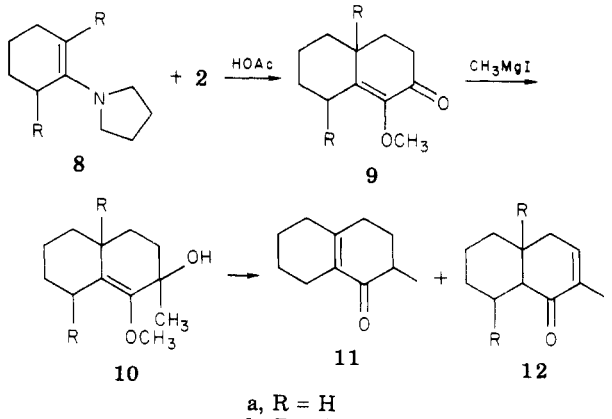
With this selection of methoxy enones in hand we investigated next the alkylative carbonyl transposition sequence. Reaction of **3** or **9** with methylmagnesium iodide accomplished the alkylation step and gave in high yield alcohol **4** or **10**, respectively, which was used without purification in the second step of the sequence. In a previous report we showed that treatment of Grignard

Scheme I



a, $R_1 = R_2 = CH_3$
b, $R_1, R_2 = (CH_2)_4$
c, $R_1 = (CH_3)_2CH$, $R_2 = H$

Scheme II



a, R = H
b, R = CH_3

(1) For an extensive list off carbonyl transpositions and related transformations see ref 1 in B. M. Trost, K. Hiroi, and S. Kurozumi, *J. Am. Chem. Soc.*, **97**, 438 (1975).

(2) See the following for examples of more recent carbonyl transposition sequences: (a) K. M. Patel and W. Reusch, *Synth. Commun.*, **5**, 27 (1975); (b) B. M. Trost and J. L. Stanton, *J. Am. Chem. Soc.*, **97**, 4018 (1975); (c) B. M. Trost, K. Hiroi, and N. Holy, *ibid.*, **97**, 5873 (1975); (d) W. Oppolzer, T. Sarkar, and K. K. Mahalanabis, *Helv. Chim. Acta*, **59**, 2012 (1976); (e) W. E. Fristad, T. R. Bailey, and L. A. Paquette, *J. Org. Chem.*, **43**, 1620 (1978); (f) S. Kano, T. Yokomatsu, T. Ono, S. Hibino, and S. Shibuya, *J. Chem. Soc., Chem. Commun.*, 414 (1978).

(3) We first reported the use of this sequence in the synthesis of the sesquiterpene (−)-acorenone.[4]

(4) G. L. Lange, W. J. Orrom, and D. J. Wallace, *Tetrahedron Lett.*, 4479 (1977); G. L. Lange, E. E. Neidert, W. J. Orrom, and D. J. Wallace, *Can. J. Chem.*, **56**, 1628 (1978).

(5) E. Wenkert, N. F. Golob, S. S. Sathe, and R. A. J. Smith, *Synth. Commun.*, **3**, 205 (1973).

(6) This vinyl ketone is readily prepared by heating 1,4-dimethoxy-2-butanone with *p*-toluenesulfonic acid.[5]

(7) A similar solvent-free reaction mixture was found to be essential in the successful preparation of an (−)-acorenone synthon.[4]

(8) Spiroannelations of enamines and methyl vinyl ketone have been reported but the reaction times were long and the yields only moderate: V. V. Kane, *Synth. Commun.*, **6**, 237 (1976); S. F. Martin, *J. Org. Chem.*, **41**, 3337 (1976).

(9) Related bicyclic systems have been prepared in low yield by reaction of 1,4-dimethoxy-2-butanone and a substituted cyclohexanone in the presence of base.[5]

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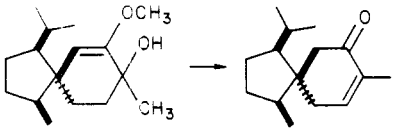
Table I. Summary of Synthetic Results

enamine	annelation: reacn time,[a] h	annelation: product (% yield)	Grignard product	dehydration-hydrolysis method of Grignard product[b]	substituted 2-methyl-2-cyclohexenone (% yield)[c]
1a	2.5	3a (71)	4a	A	6a (62)[d]
				B	6a (59)
1b	6.0	3b (69)	4b	A	6b (55)[e]
				B	6b (64)
1c	5.5 + 12[f]	3c (32)	4c	A	6c (55)[g]
				B	6c (43)
8a	16	9a (75)	10a	A	11 (73) + 12a (9)
8b	24[h]	9b (22)[i]	10b	A	12b (25)[i]

[a] Enamine with excess 2 and 1 equiv of acetic acid. [b] See Experimental Section for details of the two methods. [c] Distilled yield calculated from the annelation product 3 or 9. Percentage of ketol determined by GC analysis of distillate. [d] Plus 31% of ketol 7a. [e] Plus 14% of ketol 7b. [f] 1c and 2 stirred for 5.5 h, acetic acid added, and stirring continued an additional 16 h. [g] Plus 35% of ketol 7c. [h] See Experimental Section for additional base treatment which was required to complete the cyclization. [i] Yield was not optimized.

product 13 with *p*-toluenesulfonic acid in refluxing benzene gave the transposition product (−)-acorenone (14) in high

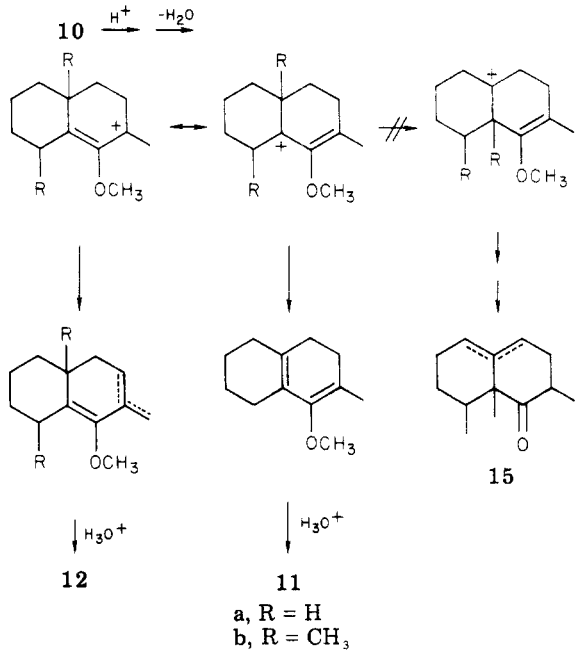


13 14

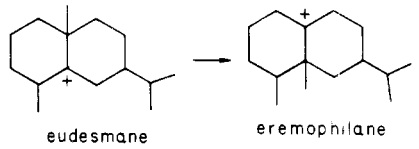
yield.[4] Presumably, the water formed in the dehydration of the tertiary alcohol then effected hydrolysis of the enol ether. When this same dehydration-hydrolysis procedure (method A) was performed on **4a**, a 2:1 mixture of enone **6a** and ketol **7a** was obtained (Table I). With alcohol **4a**, it would appear the rate of dehydration to diene **5** was only slightly faster than the rate of hydrolysis of the enol ether while with **13** the rate of hydrolysis was much slower (i.e., no ketol was formed), probably for reasons of steric hindrance. Ketol **7a** does not undergo dehydration under the reaction conditions of method A, so another procedure to convert **4a** to **6a** was investigated. In method B, the Grignard product **4a** was first dehydrated with phosphorus oxychloride in pyridine to diene **5a**,[10] which was hydrolyzed with aqueous acid to give a purer sample of **6a** (see Table I). Similarly, when method A was used for the conversion of **4b** to the spiro enone **6b** a significant proportion of ketol **7b** was formed, so method B was preferred here also. Treatment of alcohol **4c** by either method gave as the major product the monoterpene carvotanacetone (**6c**), which was identical (except for optical activity) with a sample prepared by hydrogenation of (−)-carvone.[11] If any of the ketols **7** were desired, they could readily be obtained by stirring overnight an ether solution of **4** with aqueous acid in a two-phase system.

Treatment of **10a** under the conditions of method A gave as the major product enone **11** along with a small amount of **12a**. As **12a** was not converted to **11** under the reaction conditions, the isomerization must have taken place prior to the hydrolysis of the enol ether. Scheme III outlines

Scheme III



possible intermediates to account for the conversion of **10a** → **11** + **12a**. This isomerization suggested the possibility of inducing, in an appropriately substituted system, a 1,2-methyl shift similar to that postulated in the biogenetic conversion of the eudesmane to the eremophilane classes

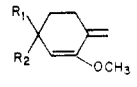


eudesmane eremophilane

of sesquiterpenes.[12] Alcohol **10b** was prepared as outlined in Scheme II starting with the enamine of 2,6-dimethylcyclohexanone (8). Treatment of **10b** under the conditions of method A gave the "normal" product **12b** but none of the rearranged compound **15** (Scheme III). The rearrangement would have resulted in loss of the stable allylic cation and this may explain why the transformation did not take place.

In conclusion, we have reported a procedure for the facile preparation of a number of substituted 2-methoxy-2-

(10) In all instances examined the major isomer of diene 5 had the new double bond in the exocyclic position



The dienes would typically exhibit the following spectroscopic data: UV (EtOH) λ_{max} 245 nm; NMR (CCl_4) vinyl protons δ 4.6–4.7 (2 H, m) and 5.2 (1 H, m). On hydrolysis of the enol ether this exocyclic double bond must have isomerized into the more substituted endocyclic position.

(11) P. Bey and R. E. Ireland, *Org. Synth.*, **53**, 63 (1973).

(12) J. R. Hanson, "Terpenoids and Steroids", Vol. 7, The Chemical Society, London, 1977, p 101.

Table II. Physical Data of Products[a]

compd	bp, °C (P, torr)	IR ν (neat), cm⁻¹	UV (EtOH) λmax, nm	NMR (CCl_4) δ	mass spectra m/e (rel int)
3a	50–55 (0.2)[e]	1690, 1630, 1380, 1135	259	as reported[b]	154 (M^+, 48), 139 (83), 111 (100)
3b	91–95 (0.3)	1695, 1625, 1220, 1150	264	1.6–2.0 (10 H, m), 2.2–2.5 (2 H, m), 3.42 (3 H, s), 5.54 (1 H, s)	180 (M^+, 100), 165 (32), 151 (79), 138 (89)
3c	76–80 (0.6)	1695, 1130, 1225, 1160	259	0.90 (6 H, d, J = 6 Hz), 1.5–2.5 (6 H, m), 3.47 (3 H, s), 5.60 (1 H, s)	168 (M^+, 4), 125 (100), 97 (41)
9a	76–80 (0.1)	1690, 1625, 1460, 1110	251	1.0–2.5 (13 H, m), 3.5 (3 H, s)	180 (M^+, 100), 165 (30), 151 (46), 138 (62)
9b	82–88 (0.1)	1690, 1610, 1220, 1110		1.16 (3 H, d, J = 8 Hz), 1.32 (3 H, s), 1.3–2.0 (9 H, m), 2.4 (2 H, m), 3.58 (3 H, s)	
6a	60–80 (8.0)[c]	1685, 1630, 1380	235	1.0 (6 H, s), 1.75 (3 H, br s), 2.18 (4 H, br s), 6.50 (1 H, m)	138 (M^+, 100), 123 (13), 110 (9), 96 (8)
6b	80–95 (3.0)[c]	1680, 1645, 1370	238	1.4–1.8 (11 H, m), 2.28 (4 H, s), 6.60 (1 H, m)	164 (M^+, 100), 121 (67), 109 (51), 88 (95)
6c	identical with sample of carvotanacetone prepared by hydrogenation of carvone[d]				
11	60–80 (2.5)[c]	1670, 1645, 1395, 1225	242	1.1 (3 H, d, J = 7 Hz), 1.3–1.8, (6 H, m), 1.9–2.3 (7 H, m)	164 (M^+, 28), 135 (7), 122 (100), 91 (7)
12b	purified by prep TLC	1675, 1460, 1390, 1370	236	1.0 (3 H, s), 1.0 (6 H, d, J = 7 Hz), 1.7 (3 H, br s), 1.2–1.7 (5 H, m), 2.0–2.2 (2 H, m), 6.5 (1 H, m)	192 (M^+, 95), 177 (74), 123 (100), 121 (58)

[a] All new compounds gave satisfactory absolute mass determinations (see supplementary data). [b] See ref 5. [c] Temperature of oven for distillation using Kugelrohr apparatus. [d] See ref 11. [e] mp 30–32 °C.

cyclohexenones, which may then be converted to 2-methyl-2-cyclohexenones via a new alkylative carbonyl transposition sequence. These transformations have been used in the syntheses of the monoterpene carvotanacetone (**6c**) and the sesquiterpene (−)-acorenone (**14**),[4] and it is anticipated they may find general use in organic synthesis.

Experimental Section

Infrared spectra were recorded on a Beckman AccuLab 6 spectrophotometer, proton magnetic resonance spectra on a Varian A-60A spectrometer, using Me_4Si (δ = 0) as an internal standard, ultraviolet spectra on a Cary 118 spectrophotometer, mass spectra on a Varian MAT CH7 spectrometer operating at 70 eV, and accurate mass determinations on a VG Micromass 7070F instrument. Gas chromatographic (GC) analyses and collections were performed on an Aerograph Autoprep Model A-700 with a 9 ft × 0.25 in. column of 20% Carbowax 20M on HP 80/100 mesh Chromosorb W. Thin-layer chromatographic (TLC) analyses and separations were accomplished on silica gel GF 254 with thicknesses of 0.25 and 0.50 mm, respectively. Enamines **1** and **8a** were prepared by using standard procedures[13] while **8b** was prepared by using a $TiCl_4$ catalyst.[14]

Preparation of 2-Methoxy-2-cyclohexenones 3 and 9a. General Procedure. A 25-mmol sample of enamine **1** or **8a** was stirred under nitrogen and then cooled in an ice bath while 3.0 g (30 mmol) of freshly distilled 1-methoxy-3-buten-2-one (**2**)[5] was added dropwise over 5 min through a serum cap. To this yellow solution was added dropwise over 5 min 1.5 g (25 mmol) of glacial acetic acid, and after an additional 10 min the ice bath was removed. The stirring was continued at room temperature for the time indicated in Table I to give a viscous, dark, reddish brown liquid. (Note that in the preparation of **3c**, **1c** and **2** were stirred for 5.5 h before the addition of acetic acid and stirring was then continued for a further 12 h.) The product was then dissolved in 75 mL of chloroform, and the solution was extracted three times with water, once with 5% HCl, once with saturated Na_2CO_3 solution, and once with brine. After the organic phase was dried with anhydrous $MgSO_4$, the solvent was removed and the residue was distilled under vacuum with a micro or a short-path apparatus to give the yields and physical data for **3** and **9a** reported in Tables I and II.

Preparation of 9b. Enamine **8b** and **2** were stirred with acetic acid for 24 h and the reaction mixture was worked up as described in the general procedure above. TLC analysis of the crude product indicated a significant amount of a compound which was more polar than the desired product **9b**. It was concluded that the two methyl groups in **8b** had retarded the cyclization step of the annelation procedure and so the crude product was treated with 0.3 M sodium ethoxide in ethanol for 1 h at 50 °C. After workup, TLC analysis of the product indicated the more polar spot was no longer present and distillation gave the results reported in Tables I and II.

Preparation of Grignard Products 4 and 10. General Procedure. A solution of 20 mmol of **3** or **9** in 15 mL of anhydrous ether was added dropwise over 10 min to a 15% excess of 0.5 M methylmagnesium iodide in ether under a nitrogen atmosphere. The reaction mixture was heated to reflux for an additional hour and then cooled, and 15 mL of saturated NH_4Cl solution was added. The aqueous phase was separated and extracted three times with ether, and the combined organic phases were extracted with brine and dried with anhydrous $MgSO_4$. Removal of the solvent yielded a 95–100% yield of alcohols **4** and **10**, which were analyzed by TLC (30% ether/petroleum ether). Compounds **4a,b** revealed essentially one spot on TLC analysis with only trace amounts of impurities while **4c** and **10a,b** showed two spots for the epimeric alcohols of about equal intensity. IR and NMR spectra of the Grignard products were consistent with the structures proposed; in particular, the NMR spectra of all five compounds showed methyl singlets at δ 1.3 and 3.5 for the carbinol methyl group and the methyl ether, respectively. The Grignard products were used in the next step without purification.

Dehydration–Hydrolysis Procedures for Preparation of 6, 11, and 12b. Method A. A solution of 2 mmol of alcohol **4** or **10** and 20 mg of *p*-toluenesulfonic acid in 10 mL of benzene was refluxed under nitrogen for 2.5 h. The reaction mixture was cooled, 60 mL of benzene was added, and the solution was extracted once with saturated $NaHCO_3$ solution and once with brine and then dried with anhydrous $MgSO_4$. After removal of the solvent, the residue was distilled by using a short-path Kugelrohr

(13) G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963); Y. Chan and W. W. Epstein, *Org. Synth.*, **53**, 48 (1973).

(14) F. Johnson, L. G. Duquette, A. Whitehead, and L. C. Dorman, *Tetrahedron*, **30**, 3241 (1974).

apparatus and the distillate was examined by analytical GC (175–220 °C depending on sample) and TLC (30% ether/petroleum ether). Ketol **7**, when present, appeared at a longer retention time and a smaller R_f than enone **6**. The product yields and physical data are recorded in Tables I and II. In some instances analytical samples were obtained by preparative GC or TLC.

Method B. To a solution of 4 mmol of alcohol **4** in 6 mL of dry pyridine was added 2 mmol of phosphorus oxychloride, and the solution was refluxed under nitrogen for 2.5 h. The reaction mixture was cooled, 15 mL of water was added, and the cloudy mixture was extracted three times with ether (total volume ~100 mL). The combined organic phases were extracted with cold 6 N HCl until all the pyridine was removed. The ether solution was transferred to a round-bottomed flask, 20 mL of 2 N HCl was added, and the two-phase system was vigorously stirred at room temperature for 18 h to effect hydrolysis of the enol ether moiety. The aqueous phase was separated and extracted three times with ether, and the combined organic phases were extracted once with saturated $NaHCO_3$ solution and once with brine and then dried. After removal of the solvent, the residue was distilled with a Kugelrohr apparatus and analyzed by GC and TLC. Generally a small amount of unhydrolyzed diene **5** was detected and was found to have a shorter retention time and a larger R_f than those for enone **6**.[10] The yields of enone **6** for this procedure are reported in Table I.

Conversion of 4 to Ketol 7. A solution of 4–5 mmol of crude Grignard product **4** in 100 mL of ether was stirred vigorously for 18 h with 25 mL of 5% H_2SO_4. After the aqueous phase was extracted three times with ether, the combined organic phases were extracted once with a saturated $NaHCO_3$ solution and once with brine and then dried with anhydrous $MgSO_4$. Removal of the solvent yielded ketol **7** which exhibited carbonyl absorption at 1720 cm^{-1} in its IR spectrum and a singlet methyl carbinol resonance at δ 1.3 in its NMR spectrum.

Acknowledgments. The authors acknowledge the financial assistance of the National Research Council of Canada.

Registry No. **1a**, 2403-57-8; **1b**, 4134-23-0; **1c**, 55023-48-8; **2**, 43042-58-6; **3a**, 42117-32-8; **3b**, 70702-97-5; **3c**, 70702-98-6; **4a**, 70702-99-7; **4b**, 70703-00-3; **4c**, 70703-01-4; **5a**, 70703-02-5; **5b**, 70703-03-6; **5c**, 70703-04-7; **6a**, 42747-41-1; **6b**, 70703-05-8; **6c**, 2244-15-7; **7a**, 70703-06-9; **7b**, 70703-07-0; **7c**, 6756-92-9; **8a**, 1125-99-1; **8b**, 56021-68-2; **9a**, 70703-08-1; **9b**, 70703-09-2; **10a**, 70703-10-5; **10b**, 70703-11-6; **11**, 64889-15-2; **12a**, 70703-12-7; **12b**, 70703-13-8; methyl iodide, 74-88-4.

Supplementary Material Available: A table listing the absolute mass determinations of all new compounds reported (1 page). Ordering information is given on any current masthead page.

Preparation of Highly Reactive Metal Powders. Preparation and Reactions of Highly Reactive Palladium and Platinum Metal Slurries

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Reduction of compounds of the type $[P(C_2H_5)_3]_2MX_2$ of palladium and platinum with 2 equiv of potassium in ethereal solvents results in highly reactive metal slurries containing insoluble metal and low valent metal phosphine compounds which readily react with a variety of aryl halides to yield the organometallic complexes, *trans*-$[P(C_2H_5)_3]_2M(R)X$ (M = Pd, Pt; R = C_6H_5, C_6F_5; X = I, Br, Cl, CN). Such a palladium slurry reacts with allyl bromide to yield $P(C_2H_5)_3Pd(C_3H_5)Br$. Reduction of PdI_2 with lithium and naphthalene and in the absence of phosphine results in a palladium powder which reacts with C_6F_5I to yield C_6F_5PdI, which was isolated as its triethylphosphine adduct.

In 1972, we reported a general procedure for the preparation of highly reactive metal powders.[1] The basic procedure involved the reduction of a metal salt in a hydrocarbon or ethereal solvent.[1-9] We have noted that the reactivities and in some cases products are highly dependent on the reduction conditions, i.e., anion, reducing agent, solvent, temperature, and presence of added alkali salts, Lewis acids, or Lewis bases.[3-9]

In a previous communication,[8] we reported the preparation of highly reactive metal slurries of nickel, palladium, and platinum and the oxidative insertion of these metals into aryl halide bonds to yield the complexes *trans*-$[P(C_2H_5)_3]_2M(R)X$. Organometallic compounds of this type are well known and have been prepared in a variety of ways, most often by alkylating agents such as Grignard and lithium reagents[10,11] and more recently from the zerovalent triethylphosphine complexes of these metals[12] as well as from metals obtained by the metal vaporization technique.[13]

In this paper we describe in detail the preparation of metal slurries of palladium and platinum by alkali metal reduction of the compounds $[P(C_2H_5)_3]_2MX_2$ and the reaction of the resulting metal slurries with a variety of organic halides.

Experimental Section

Starting Materials. Triethylphosphine (Orgmet, Inc.) and the organic halides were used as received. Tetrahydrofuran (THF)

(1) R. D. Rieke and P. M. Hudnall, *J. Am. Chem. Soc.*, **94**, 7178 (1972).
(2) R. D. Rieke, P. M. Hudnall, and S. Uhm, *J. Chem. Soc., Chem. Commun.*, 269 (1973).
(3) R. D. Rieke and S. E. Bales, *J. Am. Chem. Soc.*, **96**, 1775 (1974).
(4) R. D. Rieke and L. Chao, *Synth. React. Inorg. Met.-Org. Chem.*, **4**, 101 (1974).
(5) R. D. Rieke, K. Öfele, and E. O. Fischer, *J. Organomet. Chem.*, **76**, C19 (1974).
(6) R. D. Rieke, *Top Curr. Chem.*, **59**, 1 (1975).
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(9) S. Uhm, Ph.D. Thesis, Unversity of North Carolina—Chapel Hill, 1974.
(10) M. L. H. Green, "Organometallic Compounds", Vol. 2, Methuen, London, 1968, p 224.
(11) G. W. Parshall and J. J. Mrowca, *Adv. Organomet. Chem.*, **7**, 157 (1968).
(12) R. A. Schunn, *Inorg. Chem.*, **15**, 208 (1976).
(13) K. J. Klabunde and J. Y. F. Low, *J. Am. Chem. Soc.*, **96**, 7674 (1974).

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