layer was extracted with ethyl acetate (2 × 20 mL). The organic layers were combined, washed with water (1 × 10 mL) and brine (1 × 10 mL), and dried (MgSO$_4$). The solvent was evaporated, leaving Boc-L-Cys(Meb)-OH as an oil to which was added *N*-hydroxysuccinimide (1.5 g, 13 mmol) in 25 mL of tetrahydrofuran. The solution was cooled and dicyclohexylcarbodiimide (2.68 g; 13 mmol) was added, with 2 mL of tetrahydrofuran as a rinse. The reaction was stirred at 0 °C for 2 h. The solutions was filtered, and the filtrate was evaporated. The residue was crystallized from hot 2-propanol, yielding 4.2 g (74%) of white crystals: mp 80–86 °C. The crystals were used as such in subsequent transformations. A sample was recrystallized: mp 82–84 °C; $[\alpha]^{27}_{D}$ −48.0° (*c* 0.99, EtOAc).

Boc-L-Cys(Meb)-LL-Acp-OEt. Boc-L-Cys(Meb)-OSu (4.91 g, 11.2 mmol) was added to an ice-cold solution of H-LL-Acp-OEt (**8**, 2.08 g, 11.2 mmol) in 22 mL of dichloromethane, and the solution was stirred at 5 °C for 18 h. After evaporation, the residue was dissolved in 100 mL of ethyl acetate and washed with water (2 × 25 mL) and brine (1 × 25 mL). The washes were pooled and extracted with ethyl acetate (1 × 20 mL). The organic layers were pooled, dried (MgSO$_4$), and evaporated, leaving the product as a foam. Crystallization from chloroform–petroleum ether yielded 4.85 g (85%) of white crystals: mp 109–111 °C; TLC R_f 0.56 (A), 0.79 (B); ^{1}H NMR (Me$_2$SO-d_6) δ 1.20 (3 H, t, 7.1 Hz), 1.39 (9 H, s), 1.86–2.18 (4 H, m), 2.71–2.81 (2 H, m), 3.71 (5 H), 4.00–4.26 (5 H, m), 6.84 (2 H, d, 8.4 Hz), 6.92 (1 H, d, 8.4 Hz), 7.23 (2 H, d, 8.4 Hz), 7.78 (1 H, s), 8.09 (1 H, d, 7.5 Hz).

Anal. Calcd for C$_{24}$H$_{35}$O$_7$N$_3$S: C, 56.56; H, 6.92; N, 8.24; S, 6.29. Found: C, 56.49; H, 6.75; N, 8.24; S, 6.36.

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Registry No. **3**, 89959-25-1; **4**, 89959-26-2; **5**, 89959-27-3; **6**, 89959-28-4; **7**, 90025-86-8; **8**, 84245-61-4; **9**, 66413-65-8; Boc-Cys(Meb)-OH·DCHA, 31025-14-6; Boc-L-Cys(Meb)-OH, 18942-46-6; Boc-L-Cys(Meb)-LL-Acp-OEt, 89975-16-6; L-homoserine lactone hydrochloride, 2185-03-7; carbobenzoxyglycine hydroysuccinimide ester, 2899-60-7; *N*-(benzyloxycarboyl)glycyl-L-homoserine lactone, 89959-29-5.

A Palladium-Catalyzed Synthesis of Ketones from Acid Chlorides and Organozinc Compounds

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The reaction of acid halides and organometallic compounds (i.e., Zn, Cd, Mg) has historically been frequently used for ketone synthesis. Although organozinc compounds were generally employed prior to the 1930s, organocadmium reagents were subsequently demonstrated to be more satisfactory.[1] Recently, several transition-metal-catalyzed coupling reactions of acid chlorides and organometallic reagents to form ketones have been reported.[2–11] Of these, the most selective and general route appears to be the palladium-catalyzed reaction between acid chlorides and organotin compounds.[5]

We have found that the reaction between acid chlorides and organozinc compounds is catalyzed by palladium complexes to produce ketones in higher yields, selectivities, and rates than the uncatalyzed reaction. The reaction proceeds under mild conditions (0–23 °C) and is general in scope (see Table I). Ketones can be prepared by the reactions between primary and secondary alkylzinc reagents and alkyl acid chlorides (i.e., 4-octanone and 2-methyl-3-hexanone, respectively), arylzincs and alkyl acid chlorides (i.e., acetophenone), and alkylzincs and aryl acid chlorides (i.e., valerophenone). Thus, the reaction of di-*n*-butylzinc (prepared in situ by the reaction of *n*-butylmagnesium chloride with a slight excess of zinc chloride) with butanoyl chloride in the presence of benzylchlorobis(triphenylphosphine)palladium[12] (**1**) in THF/Et$_2$O gave 4-octanone in nearly quantitative yield (GC analysis, see Table I).[13] Under the same conditions, the uncatalyzed reaction gave a 5% yield of 4-octanone (~7% conversion, 60% selectivity). A 92% isolated yield of 4-octanone (greater than 99% pure) was obtained by using the palladium-catalyzed method on a large scale (see Experimental Section).

Reactions involving aryl acid chlorides differed from those using alkyl acid chlorides in that the corresponding aryl aldehyde was formed as a significant byproduct. Thus the reaction between benzoyl chloride and di-*n*-butylzinc in the presence of **1** in THF/Et$_2$O solution gave benzaldehyde (40%) in addition to the desired product, valerophenone (53%). We suggest the byproduct is formed by the β-hydrogen elimination of a palladium alkyl intermediate and the resulting palladium aroylhydrido species undergoing reductive elimination to yield benzaldehyde. The selectivity to benzaldehyde was affected both by the nature of the catalyst and solvent as shown in Table I. In general, the byproduct benzaldehyde was minimized by either using diethyl ether as the sole solvent or (dppf)PdCl$_2$[14] (**2**) as the catalyst. The best yield to valerophenone (97%) was obtained by using the combination of **2** and diethyl ether. This trend was also seen for the reaction between di-*n*-butylzinc and terephthaloyl chloride (see Table I).

Another example of the dependency of the solvent on selectivity was observed in the synthesis of 2-methyl-3-hexanone from butanoyl chloride and diisopropylzinc. Although in THF/Et$_2$O solutions of **1**, 2-methyl-3-hexanone was formed in 95% yield, surprisingly, 4-heptanone (4%) was the byproduct. The formation of 4-heptanone requires the isomerization of the isopropyl to an *n*-propyl group before reaction with acid chloride. In solutions of **1** in diethyl ether as the sole solvent, the yield of the byproduct 4-heptanone decreased to ~0.5%. In contrast to the aryl acid chloride results, changing the catalyst from **1** to **2** did not affect the yield of 4-heptanone.

Tetrakis(triphenylphosphine)palladium (**3**), although less active than **1**, is also an effective catalyst for this ketone synthesis. Under the same conditions shown in

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† ARCO Chemical Co. is a division of Atlantic Richfield Co.

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[13] The addition of the acid chloride to the alkylzinc solution containing catalyst was done at 0 °C to control the exotherm of the reaction.

[14] Dppf = 1,1′-(diphenylphosphino)ferrocene. Bidentate phosphines on palladium complexes have been observed to minimize β-hydrogen elimination as a side reaction in palladium-catalyzed Grignard and zinc aryl dihalide coupling reactions. Minato, A.; Tamao, K.; Hayashi, T.; Suzudi, K.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 845–848.

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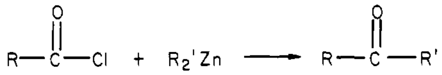
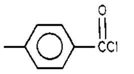
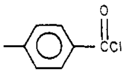
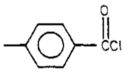
Table I. Palladium-Catalyzed Ketone Synthesis[a]



$$R-C(O)-Cl + R'_2Zn \longrightarrow R-C(O)-R'$$

R	R′	product	cat.	solvent	% yield[b]
n-C_3H_7	n-C_4H_9	4-octanone	1	THF/Et_2O	98
n-C_7H_{15}	n-C_3H_7	4-undecanone	1	THF/Et_2O	97
n-C_3H_7	i-C_3H_7	2-methyl-3-hexanone	1	THF/Et_2O	95
n-C_3H_7	i-C_3H_7	2-methyl-3-hexanone	1	Et_2O	98
n-C_3H_7	Ph	butyrophenone	1	THF/Et_2O	95
CH_3	Ph	acetophenone	1	THF/Et_2O	97
Ph	n-C_4H_9	valerophenone	1	THF/Et_2O	53[c]
Ph	n-C_4H_9	valerophenone	2	THF/Et_2O	87
Ph	n-C_4H_9	valerophenone	1	Et_2O	91
Ph	n-C_4H_9	valerophenone	2	Et_2O	97
	n-C_4H_9	1,4-bis(1-oxopentyl)benzene	1	THF/Et_2O	33[d]
	n-C_4H_9	1,4-bis(1-oxopentyl)benzene	1	Et_2O	75[e]
	n-C_4H_9	1,4-bis(1-oxopentyl)benzene	2	THF/Et_2O	82

[a] Conditions: acid chloride = 11 mmol, Grignard = 10 mmol (in Et_2O), $ZnCl_2$ = 5.4 mmol, solvent = 16 mL for the $ZnCl_2$ and 4 mL for the acid chloride, cat. = 0.027 mmol, reaction time = 0 °C for 1/2 h and 23 °C for 1 h. [b] GC yields based on millimoles of Grignard used to prepare zinc reagents (internal standard = hexadecane). [c] Reaction time for aryl acid chlorides = 14 h. [d] 11 mmol of $ZnCl_2$ and 20 mmol of Grignard were used for the terephthaloyl chloride reactions (internal standard = dodecane). [e] 25 mL of Et_2O was used to completely dissolve the terephthaloyl chloride.

Table I, but with the zinc reagent in 10 mL of THF and a reaction time of 1 h, **1** gave complete conversion to 4-octanone while **3** gave a 70% conversion. For aryl acid chlorides, **3** exhibited selectivity patterns (i.e., aldehyde formation) similar to **1**.

In summary, the reaction between acid chlorides and organozinc compounds catalyzed by palladium metal complexes gives high yields of a variety of ketones under mild conditions.[15,16] In certain cases, the selectivities to ketones are affected both by the nature of the solvent and catalyst. We have also demonstrated that the reaction is practical for large-scale laboratory synthesis. This method gives better yields and selectivities than the uncatalyzed route using zinc reagents and offers an attractive alternative to other known routes to ketones.

Experimental Section

The preparation of ketones were carried out in an argon atmosphere with anhydrous reagents with use of standard inert gas techniques. Water was removed from zinc chloride by heating at 150 °C under vacuum (0.5 mmHg). Tetrahydrofuran (THF) was dried by distillation under argon from lithium aluminum hydride. n-Butylmagnesium chloride (2 M in Et_2O) and n-butanoyl chloride were purchased from Aldrich Chemical Co. and used without further purification. The catalyst, benzylchlorobis(triphenylphosphine)palladium was prepared according to the literature procedure[12] by the reaction of benzyl chloride and tetrakis(triphenylphosphine)palladium (as purchased from Strem Chemical). The isolated metal complex was not recrystallized. Di-n-butylzinc was prepared in situ from zinc chloride and n-butylmagnesium chloride as described below. GC analyses were done on a Varian 3700 gas chromatograph using an 8 ft. glass column packed with 5% SP 2100. A temperature program from 80 to 300 °C at 10 °C/min was used.

Preparation of 4-Octanone. A 5-L, four-neck, fluted flask equipped with a mechanical stirrer was charged with zinc chloride (118 g, 0.86 mol) and 1.2 L of THF. This solution was cooled to 0 °C and 800 mL (1.6 mol) of n-butylmagnesium chloride was added via an additional funnel over a 2-h period. The reaction mixture was stirred at room temperature for 2 h to insure complete conversion to di-n-butylzinc.

The above slurry containing a white precipitate was cooled to 0 °C and benzylchlorobis(triphenylphosphine)palladium (1.1 g, 0.0014 mol) was added as a solid. To this mixture, butanoyl chloride (182 g, 1.7 mol) in 200 mL of THF was added over a 1-h period. The reaction mixture was then stirred in the ice bath for 2 h and at 23 °C for 2 h to insure complete reaction. The reaction mixture was cooled to 0 °C and a 3 N HCl solution added at a rate to maintain the temperature below 16 °C until all of the white precipitate dissolved (~800 mL of acid solution is required). The aqueous layer was separated and the organic layer washed with 100-mL portions of water, brine, saturated aqueous bicarbonate (two times), water, and brine. The combined aqueous layers were extracted with 500 mL of Et_2O, which was then washed with water, brine, and bicarbonate as described above. The combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. The volatiles were flashed distilled from the catalyst residue and other solids at 60 °C (0.5 mmHg). The resulting clear distillate was fractionally distilled with use of a 20-cm Vigreux column at 10 cm of Hg. The fraction boiling between 96 and 98 °C (189 g, 1.48 mol) was greater than 99% 4-octanone by GC analysis. This represents a 92% yield based on the Grignard reagent.

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Registry No. **1**, 86633-24-1; **2**, 72287-26-4; **3**, 14221-01-3; $CH_3(CH_2)_2C(O)Cl$, 141-75-3; $CH_3(CH_2)_6C(O)Cl$, 111-64-8; $CH_3C(O)Cl$, 75-36-5; $PhC(O)Cl$, 98-88-4; p-$ClC(O)C_6H_4C(O)Cl$, 100-20-9; Bu_2Zn, 1119-90-0; Pr_2Zn, 628-91-1; i-Pr_2Zn, 625-81-0; Ph_2Zn, 1078-58-6; 4-octanone, 589-63-9; 4-undecanone, 14476-37-0; 2-methyl-3-hexanone, 7379-12-6; butyrophenone, 495-40-9; acetophenone, 98-86-2; valerophenone, 1009-14-9; 1,4-bis(1-oxopentyl)benzene, 79784-58-0.

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(15) I thank Dr. Charles Polley, Jr., for GC/MS confirmation of all the products discussed herein.

(16) After submission of this manuscript, independent researchers reported the synthesis of ketones by the reaction of organozincs with acyl chlorides catalyzed by palladium-phosphine complexes. Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181-5184.