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Communications

A Cobalt–Phosphine Complex as Mediator in the Formation of Carbon–Carbon Bonds

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Summary: The tetrakis(trimethylphosphine)cobalt(0) complex, $[Co\{P(CH_3)_3\}_4]$, in either stoichiometric or catalytic amounts, was shown to be an efficient mediator for a one-pot Reformatsky-type reaction between activated halogen derivatives (esters, amides, lactones) and carbonyl compounds (aldehydes, ketones) to produce a variety of alcohols.

We have investigated the reaction of activated halogen derivatives (esters, amides, lactones, nitriles) with carbonyl compounds (aldehydes, ketones), in the presence of tetrakis(trimethylphosphine)cobalt(0), $[Co\{P(CH_3)_3\}_4]$, in order to explore the potential of Co–phosphine complexes as mediators in the formation of carbon–carbon bonds. The $[Co\{P(CH_3)_3\}_4]$ complex was selected because it may be expected, by analogy with other low-valent metal complexes,[1] to undergo oxidative addition reactions with halogen derivatives, yielding intermediate species capable of functioning as nucleophiles. Furthermore, $[Co\{P(CH_3)_3\}_4]$ is a well-identified complex that can be conveniently obtained[2] by reducing a mixture of anhydrous cobalt(II) chloride and trimethylphosphine (1:4 mole ratio) with magnesium metal in tetrahydrofuran.

We found that activated halogen derivatives react with carbonyl compounds, in the presence of $[Co\{P(CH_3)_3\}_4]$, to give addition products as shown in Scheme 1.

Scheme 1

$$CoL_4 + R_1R_2CO + XC(R_3)(R_4)COR_5 \rightarrow R_1R_2C(OH)C(R_3)(R_4)COR_5$$

$L = (CH_3)_3P$; R_1 = alkyl, alkenyl, aryl; R_2, R_3, R_4 = H, alkyl; X = Cl, Br; $R_5 = OCH_3, OC_2H_5, OC(CH_3)_3, N(C_2H_5)_2$; $R_4, R_5 = -CH_2CH_2O-$

Two series of experiments were carried out. In one, a variety of electrophiles was reacted with the same activated halogen derivative, *tert*-butyl α-bromoacetate;[3] in the other, a variety of activated halogen derivatives was reacted with the same electrophile, benzaldehyde. The results obtained, as well as the experimental conditions, are summarized in Table 1. In each case, the chief product was the 1,2-addition compound to the carbonyl; yields depended on both the electrophile and the halogen derivative, as well as on the ratio of the organic substrates to the $[Co\{P(CH_3)_3\}_4]$ complex. Alkyl succinates, formed by the α-coupling of two α-haloester moieties, and alcohols resulting from the reduction of the carbonyl reagents were often present in variable quantities as byproducts.[4]

For most systems, the stoichiometry of the reaction was investigated using both a 1.0:1.0:1.0 and a 1.0:1.0:2.0 mole

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[◆] Abstract published in *Advance ACS Abstracts*, December 15, 1993.

[1] Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principle and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 742–748.

[2] (a) Klein, H. F. *Angew. Chem.* **1971**, *83*, 363. (b) Klein, H. F.; Karsch, H. H. *Chem. Ber.* **1975**, *108*, 944–955.

[3] A *tert*-butyl ester was used because it was considered to be most likely to yield an isolable organometallic compound (Orsini F.; Pellizzoni, F.; Ricca, G. *Tetrahedron Lett.* **1982**, *23*, 3945–3948).

[4] The reduction of the carbonyl group may be attributed to the presence of a cobalt hydride complex formed as byproduct in the reduction of the $CoCl_2$–trimethylphosphine system.

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Table 1. Cobalt-Mediated Nucleophilic Addition of Halocompounds to Carbonyl Electrophiles, R^1COR^2

halo compd	R^1COR^2		addition product yield[a,c] (%)	reduction product yield[a] (%)	di-*tert*-butyl succinate yield[b] (%)	exptl procedure[j]
	R^2	R^1				
tert-butyl α-bromoacetate	H	$C_{10}H_7$	66.7 [22.2][e]			A
tert-butyl α-bromoacetate			51.0[d]	49.0	11.2	C
tert-butyl α-bromoacetate			85.0[e]			A
tert-butyl α-bromoacetate	H	$C_6H_5CH_2$	85.0[e,f]			B
tert-butyl α-bromoacetate			75.5[d]	23.0	12.0	C
tert-butyl α-bromoacetate			34.0 [25.7][e]			A
tert-butyl α-bromoacetate	H	$C_6H_5CH{=}CH$	91.0[e,f]			B
tert-butyl α-bromoacetate			55.0[d]			C
tert-butyl α-bromoacetate	CH_3	C_6H_5	85.0[e,f]			B
tert-butyl α-bromoacetate			62.3[d]	5.2	6.9	C
tert-butyl α-bromoacetate	$-(CH_2)_3CH{=}CH-$		86.0[e]			B
tert-butyl α-bromoacetate			31.7[d]		22.9	C
tert-butyl α-bromoacetate			71.0[d]			A
tert-butyl α-bromoacetate	$-(CH_2)_5-$		82.0[d]			B
tert-butyl α-bromoacetate			67.1[e]		5.0	C
tert-butyl α-bromoacetate			73.4 [15.0][d]			A
tert-butyl α-bromoacetate	H	C_6H_5	92.0[d]			B
tert-butyl α-bromoacetate			73.9[d]	6.5	9.3	C
ethyl α-bromoacetate			98.0[e]			B
ethyl α-bromobutyrate			75.0 [23.0][e]			A
			81.0[d,f]			B
methyl α-bromoisobutyrate			65.0[d]			B
methyl γ-bromocrotonate			75.0[d,h]	13.0		B
α-bromobutyrolactone			50.0 [38.0][d]			A
			75.0[d,i]			B
α-bromoacetonitrile			36.0[d]	5.0		B
methyl α-chloroacetate			90.0[d]	8.0		B
N,N′-diethyl-α-chloroacetamide			20.0 [7.3][e]	4.0		A
			46.0[d]	6.0		B

[a] Relative to the carbonyl electrophile. [b] Relative to the halo compound. [c] Yields in brackets refer to the product formed by water elimination from the hydroxilic function; such product was observed in significant amounts when procedure A was used. [d] Yields of isolated products. [e] Yields determined by ^1H-NMR and GLC. [f] The reaction was performed by adding the bromo compound and benzaldehyde to the Co(0) complex at −50 °C, over a 2-h period. The reaction mixture was allowed to reach room temperature before workup. [g] The diastereoisomeric ratio was 1/1. [h] The diastereoisomeric threo/erythro ratio was 1.25/1. [i] The diastereoisomeric threo/erythro ratio was 1.5/1. [j] Procedure A (stoichiometric in Co(0), described in the text): the halo compound and the carbonyl compound were added to the Co(0) complex in a 1/1/1 molar ratio at room temperature, unless stated otherwise. Procedure B (described in the text): the halo compound/carbonyl compound/Co(0) complex molar ratio was 10/10/1 (substoichiometric in Co(0)). Procedure C: similar to procedure A except that the halo compound/carbonyl compound/Co(0) complex molar ratio was 2/1/1.

ratio of activated halogen derivative, electrophile, and Co(0) complex. For one model system (*tert*-butyl α-bromoacetate and benzaldehyde), the reaction was also carried out with 2.0:2.0:1.0 and 1.5:1:5:1.0 mole ratios (not reported in Table 1).[5] In each case equimolar amounts of the three reagents gave the highest yields of addition product, with complete reaction of the organic components. The order of addition of the halogen derivative and electrophile to the Co(0) complex also affected the outcome of the reaction. Highest yields of addition product, and minimized formation of both succinate and alcohol, were achieved with a "one-pot" procedure in which the two organic reagents were added simultaneously to the Co(0) complex. We also found that the addition product was formed very cleanly when the reaction was carried out with a 10:1 mole ratio of the organic reagents to cobalt, provided that a sufficient quantity of magnesium metal was present. The reaction, however, did not take place in the absence of cobalt.[6]

The data summarized in Table 1 illustrate some general features of this cobalt-mediated addition reaction. No β-elimination[7] occurred with halogen substrates containing β-hydrogen atoms, such as α-bromobutyrate and α-methyl-α-bromopropionate. The addition to γ-bromocrotonate, which took place exclusively at the α-carbon, occurred with regioselectivity; no significant diastereoselection was instead observed with either α-bromobutyrolactone or α-bromobutyrate. The addition reaction also proceeded with α-bromo nitriles and α-bromoamides, provided the latter were N,N-dialkylated. Finally, substitution of bromine by chlorine in a halo ester was found to lower the reaction rate without significantly changing the yields.[8]

The results obtained in this work, and especially the 1:1:1 stoichiometry of the reaction, suggest a mechanism

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(5) The excess of aldehyde with respect to Co(0) complex was recovered unchanged.

(6) To investigate whether an organomagnesium compound might be involved in the carbon–carbon bond formation, two parallel experiments were performed. *tert*-Butyl α-bromoacetate and benzaldehyde were added at room temperature to two reaction flasks, one containing a substoichiometric amount of Co(0) complex and magnesium in tetrahydrofuran, according to procedure B reported in the text, and the other containing only magnesium in tetrahydrofuran. The amount of bromo ester, carbonyl compound, and magnesium were the same in both experiments and so were the other experimental conditions (speed of addition of the reagents, speed of stirring, time of reaction). No reaction was observed in the magnesium-only experiment from which 90% of the α-bromoacetate and benzaldehyde were recovered unchanged.

(7) Orsini, F.; Pelizzoni, F.; Vallarino, L. M. *J. Organomet. Chem.* **1989**, *367*, 375–382 and references cited therein; (b) *Tetrahedron Lett.* **1988**, *29*, 6037–6038.

(8) Two model experiments were performed, under the same experimental conditions, to compare the reactivities of chloro and bromo esters. In each case the progress of the reaction was monitored at intervals by gas chromatographic analysis. In one experiment, ethyl α-bromoacetate and benzaldehyde were slowly added (2 h) to the Co(0) complex in tetrahydrofuran at room temperature, according to procedure B described in the text. The mixture was stirred for an additional 15 min, after which time no residual benzaldehyde was detected. Workup of the mixture yielded 98% of addition product. In the parallel experiment with methyl α-chloroacetate, most of the initial benzaldehyde was still unreacted after 2 h and 15 min. The molar ratio of product to benzaldehyde increased to 0.6/1 after 2 more h of stirring and to 9/1 after an additional 5 h. After this time, no further significant increase in addition product was observed. The reaction mixture was worked up after 7 h and gave a 90% yield of addition product.

involving the oxidative addition of the activated halogen compound to the cobalt(0) complex to give a cobalt(II) species,[9] as well as the substitution of a phosphine ligand by a carbonyl donor group. Reaction between the two organic moieties bound to the same cobalt center would then yield the 1,2-addition product, together with a Co(II)–phosphine complex from which the active Co(0) species can be regenerated by reduction with magnesium metal. Thus, the addition of the halo derivative to the electrophile can also proceed under conditions that are catalytic with respect to the cobalt–phosphine complex, as long as sufficient magnesium is present to carry on the Co(0)–Co(II)–Co(0) cyclic conversion.

The Co(0)-mediated addition of activated halogen compounds, and in particular of halo esters, to carbonyl compounds offers two important advantages compared to the similar Reformatsky reaction. First, the reaction can be carried out under milder conditions (e.g., at a temperature as low as −50 °C).[10] Second, the yields of addition product are much higher (e.g., 92% versus 60–65% when the substrates are *tert*-butyl α-bromoacetate and benzaldehyde).[3] The exclusive formation of the 1,2-addition product with α,β-unsaturated ketones represents an added advantage,[11] as does the formation of the α-adduct with γ-bromocrotonate.[12] Finally, the fact that the reaction can be carried out with a catalytic amount of the Co–phosphine complex offsets the disadvantage inherent in the use of trimethylphosphine.

High selectivity in the addition of carbon nucleophiles to aldehydes and ketones has been achieved in recent years by the use of organometallic reagents involving early transition metals or f-block elements.[13] Neutral complexes of the late transition metals have seldom been used in addition reactions of this type.[14] Thus, to our knowledge the reaction described in this paper represents the first example of a carbon–carbon bond formation by nucleophilic attack to a carbonyl group, mediated by a Co–phosphine complex. Work is in progress to explore further the mechanism and scope of this reaction.

In a typical procedure for the stoichiometric reaction (procedure A), a 1 M solution of trimethylphosphine in tetrahydrofuran (8 mL) was added to a mixture of activated magnesium turnings (700 mg) and anhydrous $CoCl_2$ (260 mg, 2 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere until a dark-brown color developed (2–3 h). The excess of magnesium was filtered off, and to the resulting solution were added *tert*-butyl α-bromoacetate (2 mmol) and benzaldehyde (2 mmol) in tetrahydrofuran (4 mL) dropwise over a 2-h period.[15] The reaction mixture was stirred for an additional 15 min, diluted with diethyl ether, poured into crushed ice/aqueous HCl, and extracted with ethyl acetate (3 × 15 mL). The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The crude material was flash chromatographed over silica gel (ethyl acetate/*n*-hexane (15/85)) and yielded 73.4% of *tert*-butyl 3-hydroxy-3-phenylpropionate and 15.0% of *trans-tert*-butyl cinnamate.

In a typical procedure for the substoichiometric reaction (procedure B), a 1 M solution of trimethylphosphine in tetrahydrofuran (2 mL) was added to a mixture of activated magnesium turnings (700 mg) and anhydrous $CoCl_2$ (65 mg, 0.5 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere until a dark brown color developed (2–3 h). A tetrahydrofuran solution (6 mL) of *tert*-butyl bromoacetate (5 mmol) and benzaldehyde (5 mmol) was added dropwise over a 2-h period. The reaction mixture was stirred for an additional 15 min, diluted with diethyl ether, poured into crushed ice/aqueous KCl, and extracted with ethyl acetate (3 × 15 mL). The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The crude material did not require further purification (92% of the theoretical amount was obtained).

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Supplementary Material Available: Characterization data (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[9] This intermediate could not be isolated under the conditions of our reaction. Therefore, it remains undetermined whether the complex is a C-metallated species or an enolate. A similar question has long been debated for the Reformatsky reagent: (a) Orsini, F.; Pelizzoni, F.; Ricca, G. *Tetrahedron* **1984**, *40*, 2781–2787. (b) Vaughan, W. R.; Bernstein, S. C.; Lorber, M. E. *J. Org. Chem.* **1965**, *30*, 1790–1793. (c) Dekker, J.; Boersma, J.; van der Kerk, G. J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 553–555.

[10] In a typical procedure for the reaction performed at −50 °C *tert*-butyl α-bromoacetate and benzaldehyde were added to the Co(0) complex over a 2-h period, according to procedure B described in the text. Gas chromatographic analysis of the reaction mixture at intervals of 3, 25, 40, and 50 h showed the addition product/benzaldehyde molar ratios to be 0.2/1, 0.6/1, 1.2/1, and 1.5/1, respectively. The reaction mixture was worked up after 70 hours and yielded 70% of the addition product. The same reaction performed at 0 °C required 3 h to be completed and yielded 75% of the addition product and 12% of the reduction product.

[11] With unhindered esters such as haloacetates, the 1,2-addition compound is usually the isolated product also in the case of the Reformatsky reagent. It has been speculated, however, that this result might reflect the outcome of the product isolation rather than the true profile of the reaction (Rathke, Michael W. *Org. React.* **1975**, *22*, 423–460). This could be particularly true when the yields of the reaction are low, as found for cyclohexenone (Cure, J.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1969**, 2471–2476).

[12] In the Reformatsky reaction of ethyl γ-bromocrotonate with benzaldehyde, an exclusive γ-addition mode was observed in tetrahydrofuran (Rice, E. L.; Boston, M. C.; Frazier, J. O.; Hudlicky, T. *J. Org. Chem.* **1984**, *49*, 1845).

[13] See, for instance: Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; John Wiley and Sons: New York, Chichester, Brisbane, Toronto, Singapore, 1988; Chapter 14.

[14] For a somewhat similar reaction involving a nickel derivative see: Inaba, S. I.; Rieke, R. D. *Tetrahedron Lett.* **1985**, *26*, 155–157.

[15] This addition time was chosen to avoid a local excess of substrates.