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Low-valent complexes of cobalt and phosphorus donor ligands as mediators in Reformatsky-type reactions

Fulvia Orsini [a,*], Maurizio Pulici [b], Lidia M. Vallarino [c]

[a] *Dipartimento di Chimica Organica e Industriale dell'Universita' degli Studi-Centro di Studio delle Sostanze Organiche Naturali del CNR, Via Venezian 21, 20133 Milano, Italy*

[b] *Institute of Physical and Chemical Research, 2-1 Hirosawa, Wako, Saitama, 351-01, Japan*

[c] *Department of Chemistry, Virginia Commonwealth University, Richmond, VA 23284, USA*

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Abstract

A series of low-valent cobalt complexes of mono- and poly-dentate phosphorus donors (phosphines and phosphinites) was screened for effectiveness as mediators of the Reformatsky-type addition of benzaldehyde and *tert*-butyl α-bromoacetate in tetrahydrofuran at room temperature. The results are discussed in terms of the donor properties of the ligands and reactant ratios. With the triphenylphosphine–cobalt 2:1 system, the reaction gave addition product in high yields and excellent purity, providing a convenient alternative to the classical Reformatsky reaction.

Keywords: Cobalt; Reformatsky reaction; Phosphine complexes

1. Introduction

We previously reported that a cobalt(0)-trimethylphosphine complex is an efficient mediator for the one-pot Reformatsky-type reaction of activated halogen derivatives with carbonyl compounds, producing secondary and tertiary alcohols [1] (Scheme 1). This system offered several advantages over the classical zinc-mediated Reformatsky reaction [2], the most notable being the milder conditions [3] and the higher yields of addition products. Furthermore, the reaction which could be carried out under either stoichiometric or non-stoichiometric conditions with respect to cobalt, was regioselective with α,β-unsaturated carbonyl derivatives, giving almost exclusively the 1,2-addition products.

As an extension of the previous study, we have investigated the reaction of benzaldehyde with *tert*-butyl α-bromoacetate, in the presence of low-oxidation-state cobalt complexes containing the phosphorus donors shown in Fig. 1. A general objective of this work was to explore how the properties of each ligand (electronic character and bulk of the substituents on the phosphorus atom, denticity, size and flexibility of chelate rings) could influence the effectiveness of the respective cobalt complex as mediator in the Reformatsky-type addition reaction. A more specific objective was to identify a ligand with the effectiveness of trimethylphosphine, but less toxic and easier to handle. We were also interested in gaining some insight into the reaction mechanism, and in exploring the possibility that appropriate chiral ligands might give rise to enantioselectivity [4].

2. Experimental section

2.1. Starting materials and procedures

Trimethylphosphine (**1**), tributylphosphine (**2**), tribenzylphosphine (**3**), tricyclohexylphosphine (**4**), tri-*tert*-butylphosphine (**5**), triphenylphosphine (**6**), methyldiphenylphosphinite (**7**), 1,2-bis(diphenylphosphino) ethane (DIPHOS) (**8**), (R)-(+)-1,2-bis(diphenylphosphino)propane [(R)-PROPHOS] (**9**), (R)-(+)-2,2'-bis (diphenylphosphino)-1,1'-binaphthyl [(R)-(+)-BINAP] (**10**), (−)2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [(R,R)-DIOP] (**12**),

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[*] Corresponding author.

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

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

Scheme 1.

(2S,4S)-*tert*-butyl 4-(diphenylphosphino)-2-(diphenylphosphinomethyl)-1-pyrrolidine carboxylate (**13**) and 1,1,1-tris(diphenylphosphinomethyl)ethane (TRIPHOS) (**15**) were purchased from Aldrich and were used as received. (−)-2,3-Bis(diphenylphosphino)bicyclo [2.2.1]hept-5-ene [(R,R)(−)-NORPHOS] (**11**) was purchased from Merck and used as received. Compound **14** was prepared according to the literature [5]. Anhydrous

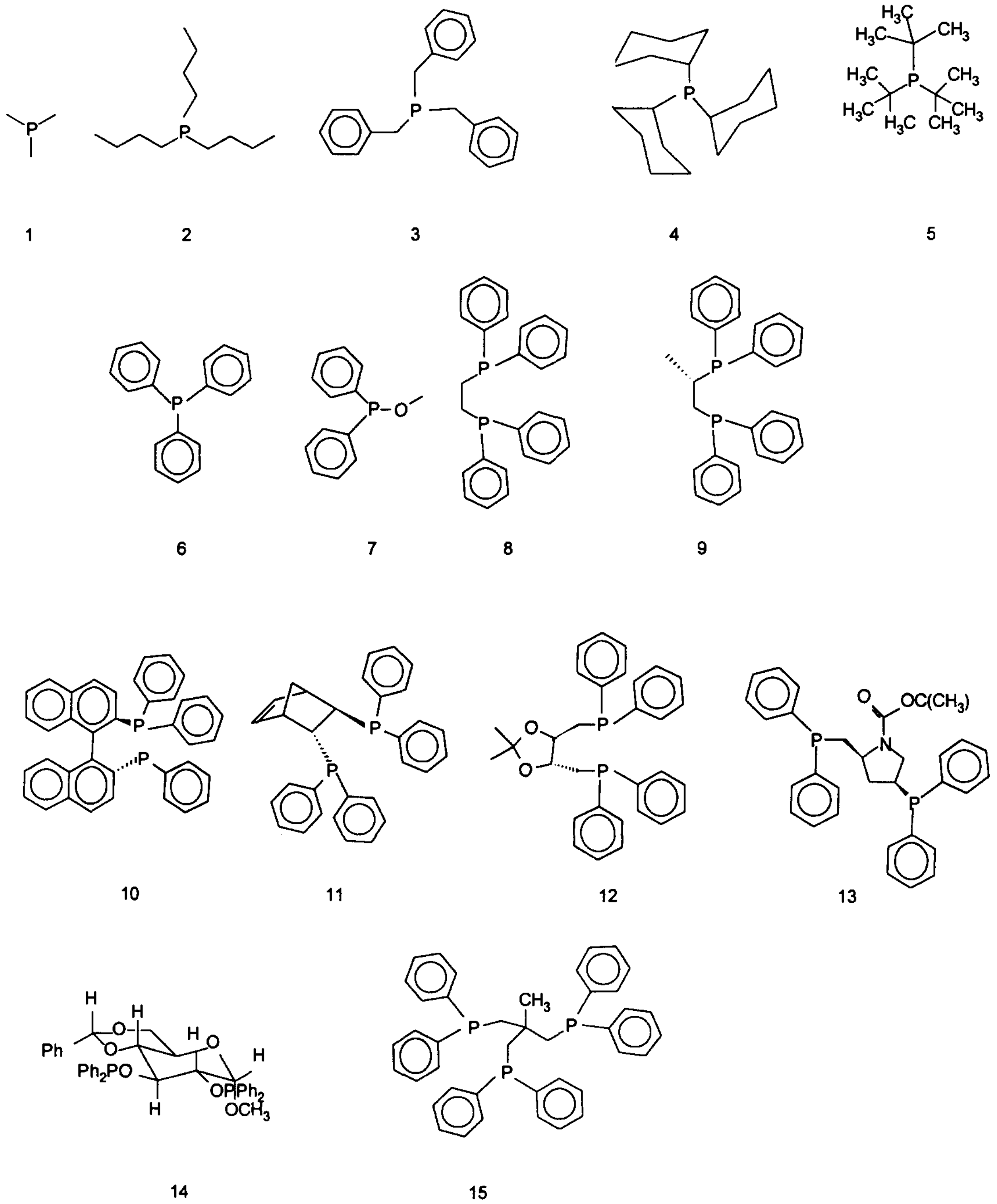

Fig. 1. Schematic formulae of phosphorus donors used in this work.

cobalt(II) chloride was heated at 120–150°C for 2 h prior to use. Reagent grade tetrahydrofuran (THF) was refluxed over $LiAlH_4$ and distilled. Magnesium metal (as turnings) was activated by treatment with a solution of 1,2-dichloroethane in THF, followed by washing with THF. Reagent grade benzaldehyde and *tert*-butyl α-bromoacetate (Fluka) were used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained with Varian XL-200 and Bruker AC-300 instruments. Gas chromatographic (GS) analyses were performed using a DANI 86.10 instrument connected to a Hewlett-Packard HP 3396A integrating recorder and equipped with a WCOT Fused Silica capillary column (CP-Sil-5 CB stationary phase, 25 m × 0.32 mm i.d., film thickness 0.12 μm, carrier hydrogen 0.4 kg cm^{-2}, injector temperature 180°C, detector temperature 250°C, program: 50°C for 4 min at start, 10°C min^{-1} to 200°C, followed by 2 min at 200°C.) Thin layer chromatography (TLC) was carried out on silica gel plates (60 F254, Merk); zones were detected visually by ultraviolet irradiation (254 nm) or by spraying with methanol/H_2SO_4 9 : 1, followed by heating at 100°C.

Enantiomers were detected and determined quantitatively from the ^1H NMR spectra taken in the presence of a chiral europium(III) shift reagent (tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium-(III), Fluka).

2.2. *Preparation of the cobalt-(phosphorus-donor ligand) mediators*

All reactions were carried out at 25°C under dry dinitrogen using glassware dried by flaming in a stream of dry dinitrogen.

2.2.1. *Monodentate ligands*

Activated magnesium turnings (500 mg, 20.6 mmol), anhydrous cobalt(II) chloride (65 mg, 0.5 mmol), and the phosphine or phosphinite (1.0 or 2.0 mmol) were added to THF (2.0–4.0 ml) [6]. The mixture was stirred until the original purple-blue turned to yellow-brown, with the hue depending on the ligand. (The colour change was usually complete after 2–3 h.) The heterogeneous mixture thus obtained was used as such for the substoichiometric reactions. For the stoichiometric reactions, the clear supernatant liquid was transferred by syringe to another flask immediately before use.

2.2.2. *Bidentate and tridentate ligands*

Anydrous cobalt(II) chloride (65 mg, 0.50 mmol) dissolved in anhydrous ethanol (ca. 5 ml) was mixed with the ligand (0.55 or 1.1 mmol) dissolved in anhydrous ethanol or benzene (ca. 5 ml). The solution was evaporated to dryness under reduced pressure, and the resulting blue or green-blue solid was dissolved in THF (2 ml) immediately before use. This solution was added to the activated magnesium as described for monodentate ligands, to produce the low-covalent Co-(phosphorus donor) complex.

2.3. *Reaction of benzaldehyde with tert-butyl α-bromoacetate in the presence of the cobalt-(phosphorus donor) mediators*

All reaction were carried out at 25°C under dry dinitrogen atmosphere, using glassware dried by flaming in a stream of dry dinitrogen.

2.3.1. *Stoichiometric reactions*

The filtered solution of the Co-(phosphorus donor) (0.5 mmol) was treated dropwise with a solution containing benzaldehyde (0.053 g, 0.5 mmol) and *tert*-butyl α-bromoacetate (0.1 ml, 0.5 mmol) in THF (3 ml). The progress of the reaction was monitored by GC or TLC; when benzaldehyde was no longer present, the solution was diluted with ethyl acetate (20 ml) and poured over crushed ice/0.1N HCl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 ml). The combined organic solutions were washed with water (2 ml), dried, and evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane and purified by filtration over silica gel until complete removal of Co-containing species (TLC analysis). The solution was evaporated to dryness under reduced pressure and the residue was dissolved in deuterochloroform for ^1H NMR analysis. The products *tert*-butyl 3-phenyl-3-hydroxypropionate, benzyl alcohol and hydrobenzoin (*meso* and racemic)] were identified and determined quantitatively from ^1H-NMR spectra, by comparison with authentic samples.

2.3.2. *Substoichiometric reactions*

These were carried similarly to the stoichiometric reactions, except that the Co:benzaldehyde:*tert*-butyl α-bromoacetate mole ratio was 0.1 : 1 : 1, and the solution containing the reactants was added directly to the magnesium metal/Co-(phosphorus donor) mixture. The rate of addition was regulated so as to preserve the original yellow-brown of the Co-(phosphorus donor) mediator. The time for complete reaction was usually 2 h. If the reactants were added too fast, the the reaction mixture turned blue. The solution returned to yellow-brown after some time if the addition of the reactants was interrupted.

3. Results and discussion

The reaction of *tert*-butyl α-bromoacetate with benzaldehyde, when carried out in the presence of a low-oxidation-state cobalt complex containing one of the

$[CoL_4] + C_6H_5CHO + BrCH_2COO^tBu$
$\rightarrow C_6H_5CH(OH)COO^tBu$
L = Phosphorus donors listed in Table 1.

Scheme 2.

phosphorus donors shown in Fig. 1 resulted in each case in complete conversion of the reactants and formation of the addition compound (Scheme 2) as the major or sole product [7]. Benzylalcohol and hydrobenzoin [8] (*meso* as and racemic) were the only byproducts formed in significant yields. Traces of di(*tert*-butyl) succinate, formed by α-coupling of two *tert*-butyl α-bromoacetates, were occasionally detected. The results of the various reactions are summarized in Table 1. The yields of the byproducts are relative to the yield of the addition product, taken as unity [9]. The reactions with trimethylphosphine (**1**) and tri-*n*-butylphosphine (**2**) were carried out both under stoichiometric conditions (1 : 1 mole ratio of cobalt to addition substrates) and under sub-stoichiometric conditions (1 : 10 Co/substrate ratio). Since no significative difference was found, the reactions with all other donors were performed using the easier procedure (the sub-stoichiometric).

Several trends are evident from the data collected in Table 1. First, all reactions involving monodentate donors gave essentially the same results — excellent yields of addition product, little or no byproducts — even though compounds **1–7** differ considerably in the electronic character and steric requirements of the organic groups attached to the phosphorus donor atom. In these reactions the phosphorus-to-cobalt mole ratio could be reduced from 4 : 1 to 2 : 1 without loss of effectiveness. Indeed, addition compounds obtained using 2 : 1 phosphorus-to-cobalt ratios contained negligible or no byproducts (see examples 2 and 4). This effect was even more marked for bidentate ligands. For example, with **8** and **9** in a 2 : 1 donor-to-cobalt ratio (that is, 4 : 1 P-to-Co ratio) the total yield of byproducts approached or outweighed that of the addition product. For this reason, the bidentate ligands **10–15** were studied only with 1 : 1 donor-to-cobalt ratios. Second, reactions involving bidentate chelating donors gave consistently greater quantities of byproducts than reactions with monodentate donors under parallel conditions. (However, when bidentate **9** was used in a 1 : 1 donor-to-cobalt ratio with two added equivalents of the monodentate $P(CH_3)_3$, the results mirrored those obtained with $P(CH_3)_3$ alone). A final comment concerns the influence of the chelate rings of the bidentate ligands **8–14** and of the tridentate ligand **15**. With the latter, which forms relatively unstrained and flexible six-membered chelate rings, the addition compound was obtained in high yields, approaching those obtained with monodentate ligands. The yields of addition product were generally lower with ligands that form five-membered chelate rings (**8**, **9** and **11**). Slightly better results were obtained with ligands that form seven-membered chelate rings

Table 1
Summary data for the addition of *tert*-butyl α-bromoacetate to benzaldehyde in the presence of Co-(phosphorus donor) mediators

Phosphorus Donor Ligand	Ligand/Co Mole Ratio	Experimental Procedure [a]	Addition Product [b]	Benzyl Alcohol [b]	Dihydro-benzoin [b] (meso)	Dihydro-benzoin [b] (racemate)	Dialkyl-succinate [b]
1	4	A	1	–	0.06	–	–
	4	B	1	–	–	–	–
2	4	B	1	0.06	traces	0.04	traces
	2	A	1	–		traces	traces
3	4	B	1	0.1	–	–	–
4	4	B	1	–	–	0.05	–
	2	B	1	traces	traces	traces	–
5	4	B	1	–	–	traces	–
6	4	B	1	–	traces	traces	–
7	4	B	1	0.06	0.08	–	–
8	2	B	1	0.32	0.19	0.32	–
	1	B	1	0.23	traces	0.17	–
9	2	B	1	1.24	0.09	1	–
	1 [c]	B	1	–	–	–	–
10	1	B	1	0.33	traces	0.33	traces
11	1	B	1	0.21	traces	0.21	traces
12	1	B	1	–	–	–	–
13	1	B	1	0.2	traces	traces	traces
14	1	B	1	0.22	traces	0.31	traces
15	1	B	1	traces	traces	traces	traces

[a] Procedure A (stoichiometric in Co^0): the halocompound and the carbonyl compound were added to the Co^0 complex in a 1/1/1 molar ratio at room temperature in tetrahydrofuran solution. Procedure B: the halocompound/carbonyl compound/Co^0 complex molar ratio was 10/10/1 (substoichiometric in Co^0).

[b] Determined by GLC and ^1H-NMR. [c] Reaction in the presence of 2 equivalents of PMe_3.

(**12–13**), except when the backbone is rigid (**10** and **14**). No enantioselectivity in the formation of the addition product was observed using ligands with one or more stereo-centres in the backbone (**9–14**). In each case, the racemate was obtained.

These results, when considered in conjunction with those previously reported [1], provide considerable information on the "key species" (intermediate or transition-state complex) involved in this Reformatsky-type reaction. This "key species" must contain cobalt, since the reaction does not take place unless a cobalt(II) salt is present among the initial reactants [1]. In each case the cobalt must be present in a low oxidation state (most likely zero), since the reaction takes place in the presence of a stoichiometric amount of the isolated complex $[Co\{P(CH_3)_3\}_4]$ [1], and equally well in the presence of a catalytic amount of this or any of the other cobalt-(phosphorus-donor) systems investigated in this work, provided a sufficient amount of magnesium metal is also present as reductant. In the "key species", the phosphorus donor must be coordinated to the cobalt, since they affect the outcome of the reaction [10]. It is also reasonable to conclude that the "key species" generally does not contain more than two phosphorus donor atoms, since the Reformatsky-type reaction gives poorer results when the system contains two bidentate chelating phosphines per cobalt. (A bidentate chelating ligand would be displaced from a precursor complex with much greater difficulty than two monodentate ligands, thus hindering concomitant access of the benzaldehyde and *tert*-butyl α-bromoacetate reactants). Finally, it is reasonable to conclude that the *tert*-butyl α-bromoacetate binds to the cobalt of the "key species" by oxidative addition [1], since the typical blue colour of tetrahedral Co^{II}-(phosphorus donor) complexes appears in the solutions of sub-stoichiometric reactions when the rate of addition of the benzaldehyde/*tert*-butyl α-bromoacetate reactants exceeds that of the $Co^{II} \rightarrow Co^0$ reduction by magnesium metal.

4. Conclusions

This work has shown that the Reformatsky-type addition of an activated halogen-derivative to a carbonyl compound proceeds with excellent yields in tetrahydrofuran at room temperature, in the presence of a sub-stoichiometric amount of cobalt(II) chloride and a wide variety of phosphorus-donors (optimal P : Co ratio, 2 : 1), together with an excess of magnesium metal. When the phosphorus donor is the solid, air-stable triphenylphosphine, this reaction provides an effective synthetic route to secondary and tertiary alcohols, under conditions much milder and more convenient than those required for the classical Reformatsky reaction.

This work has also provided a substantial body of evidence in support of a reaction mechanism involving the formation of a "key species" by oxidative addition of the activated halogeno-derivative to the Co^0-(phosphorus donor) precursor, accompanied by coordination of the carbonyl compound. Reaction of the two organic moieties bound to the same cobalt would then yield the 1,2-addition product, together with a Co^{II} complex from which the original Co^0-(phosphorus donor) precursor can be regenerated by reduction with magnesium metal. Such a mechanism offers a single, unifying interpretation for this type of reaction, whether performed with stoichiometric or substoichiometric (catalytic) cobalt reagent ratios. The suggested mechanism also accounts for the observed lack of enantio-selectivity in reactions involving chiral phosphine ligands. If the "key species" is indeed a high-spin Co^{II} complex, it will be labile and will rapidly interconvert among its stereoisomeric forms; therefore, the two Co-bound reacting moieties can not be held in the unique relative positions required for the formation of a single enantiomer.

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[7] An exception was the reaction with **9**, where benzyl alcohol and hydrobenzoin were the predominant products.

[8] Benzaldehyde was converted quantitatively to benzyl alcohol (40%) and hydrobenzoin (60%, *meso* and racemic) when the reaction was carried out under stoichiometric conditions, using a 1 : 1 mole ratio of benzaldehyde to $[Co(tri\text{-}n\text{-}butylphosphine)_4]$, in the absence of both magnesium metal and *tert* butyl α-bromoacetate.

[9] The yield of addition product is in each case close to 100% (based on reactants).

[10] In the absence of phosphorus donors the reaction is very sluggish and produces a complex mixture of products.