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# FORMATION OF (C-C)BONDS CATALYZED BY VITAMIN $B_{12}$

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Abstract - Under reducing reaction conditions vitamin $B_{12}$ and related cobalt complexes are powerful catalysts for the 1,4 addition of alkyl-, vinyl - and acyl derivatives to activated olefins. Several examples illustrate the intra- and intermolecular (C-C)bond formation. The reaction mechanism involves the formation and cleavage of a (Co-C)bond.

## INTRODUCTION

Vitamin $B_{12a}$ and a number of related cobalt complexes have been shown to act as catalysts in non-enzymatic reactions such as autoxydation, hydrogenation of olefins, reduction of functional groups, reductive elimination and reductive (C-C)bond formation (Ref. 1). Of special interest in organic synthesis is the selective formation of (C-C)bonds under mild reaction conditions using nontoxic, naturally occurring catalysts, such as vitamin $B_{12a}$.

1,4 additions of organic halides to activated olefins by means of organometallic intermediates are well-known. The most important version is the so-called conjugate addition of organocuprates (Ref. 2). Generally these reactions involve several steps, the protection of base-sensitive functional groups is necessary and a stoichiometric amount of copper reagent is used.

Based on the known organometallic chemistry of vitamin $B_{12}$ (Ref. 3 & 4) and related cobalt complexes (Ref. 5) a new version of the addition of alkyl-, vinyl- and acyl-derivatives to activated olefins has been developed, which offers several advantages: the reaction is carried out in one step, the protection of base-sensitive functional groups is not necessary, the cobalt complexes (vitamin $B_{12}$) are used only in catalytic amounts.

## BASIC PRINCIPLES

Cobalt complexes, suitable as catalysts in (C-C)bond forming reactions under reducing conditions should exhibit the following properties:

- they should easily and reversibly be reduced to the corresponding Co(I) complexes.
- the Co(I) complexes should exhibit high nucleophilicity at Co and form readily organometallic intermediates containing a (Co-C)bond with alkyl-, vinyl- and acyl-derivatives in fast reactions.
- the (Co-C)bond of the organometallic intermediates should be cleaved in a fast reaction with the formation of an active carbon species and a cobalt complex, which has to be recycled to the active Co(I) complex at the same reaction conditions.
- the cobalt complex should exhibit appropriate solubility and stability under the reaction conditions.

Hydroxycobalamin-hydrochloride (vitamin $B_{12a}$) **1**, and the synthetic Co(HDP) complex **2*** (for the five-step synthesis ex acetone see Ref. 6 & 7) have been found to be excellent catalysts. Other cobalt complexes as e.g. cobalt(II)phthalocyanine, cobalt tetraphenylporphyrin or cobaloximes might also act as catalysts under suitable reaction conditions.

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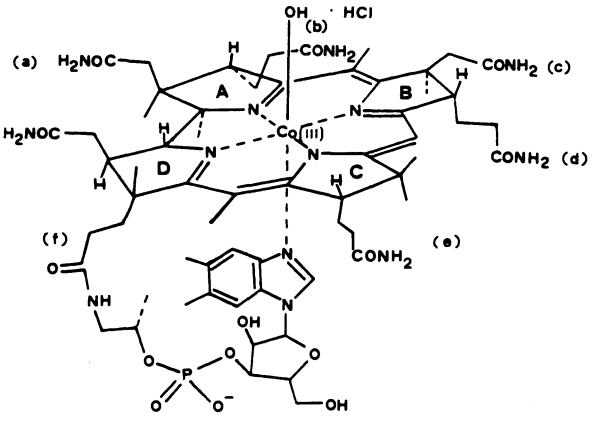
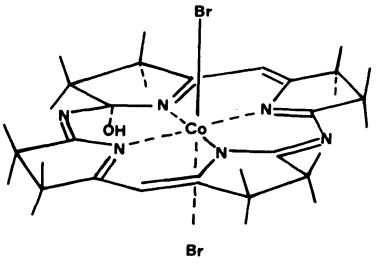
* Co(HDP) stands for [1-Hydroxy-2,2,3,3,7,7,8,8,12,12,13,13,17,17,18,18-hexadecamethyl-10,20-diaza-octahydro-porphinato]cobalt(III)-dikation.




1




2

Reduction of Co(III) complexes. - In macrocyclic tetradentate cobalt complexes like 1 and 2 Co(III) is generally ligated by two axial ligands (X, Y), Co(II) by one (Y) and Co(I) by none. This trend of decreasing coordination number has been qualitatively described by the X-Co-Y three center 4 → 5 → 6 electron bonding model, which combines axial ligand σ-orbitals with metal orbitals of substantial $d_{z^2}$ character (Ref. 8). The macrocyclic ligand L represents by itself a subunit of the cobalt chelates, which may undergo reduction.

Figure 1 shows the thermodynamic stabilities of 1 and 2 in their different oxidation states. The ranges of stability of Co(IV), Co(III), Co(II), Co(I) and the ligand (L) are separated by white zones, their width being due to the variation of $E^{o'}$ caused by different axial ligands X, Y and solvent.

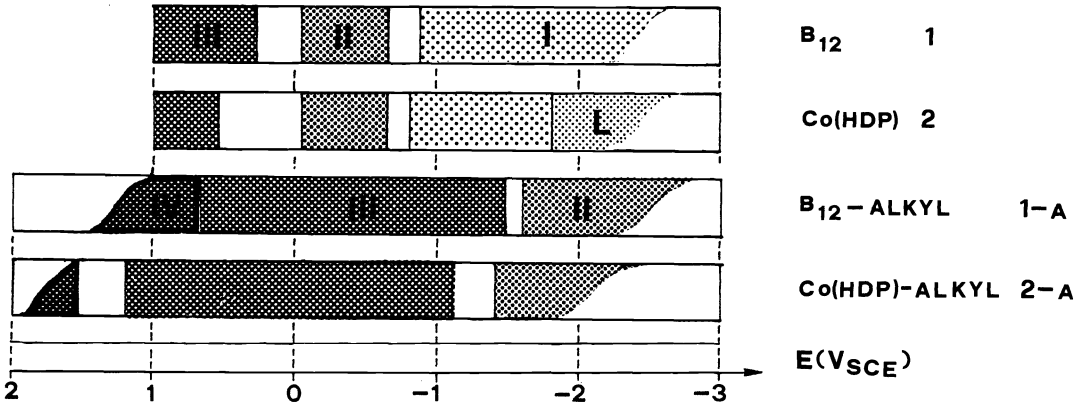



Fig. 1: Potential ranges of thermodynamic stability of non-alkylated and alkylated Co-complexes 1 and 2 at variable electrode potentials (potential values for 1 are taken from Ref. 9-11, for 2 from Ref. 12).

Formation of the (Co-C)bond. - Co(I) complexes of 1 and 2 are very powerful nucleophiles and react rapidly with alkylhalides in an oxydative addition to form alkyl-Co derivatives of 1 and 2. Second order rate law has been determined for alkylations of Co(I) in 1 (Ref. 13). The stereochemistry of the substitution at carbon is not uniform; primary halides and tosylates show predominantly inversion, secondary halides e.g. cyclohexyl derivatives yield the thermodynamically more stable product. (For a discussion see Ref. 1.) The reactivity pattern of alkyl derivatives RX follows generally the sequence X: J > Br > Cl and R: prim > sec. Vinylhalides are much less reactive than alkylhalides; vinyliodides react with Co(I) complexes, the corresponding chlorides behave virtually inert.

Cleavage of the (Co-C)bond. - The dissociation energy of the (Co(III)-C)bond in compounds of type 1 and 2 span the range of 20 to 30 kcal/mol (Ref. 14). Homolytic cleavage of the (Co(III)-C)bond is observed in photolysis or thermolysis (Ref. 15). The one-electron reduced alkyl-cobalt complexes, which formally contain a (Co(II)-C)bond, have been shown to exist, although they are much less stable than the corresponding Co(III) compounds. The 1st order rate constant for decomposition of the (Co(II)-C)bond in case of methyl-cobalamin has been estimated to be 1200 $s^{-1}$ at -30° (Ref. 16).

Catalytic cycle. - Since in a catalytic cycle the (Co-C)bond has to be formed and cleaved in fast reactions and under the same reaction conditions, two main procedures can be envisaged:

- If the catalytic reaction is carried out in the dark, a reduction potential has to be chosen at which the alkyl-cobalt(III) complex is reduced. This potential is limited on the negative side by the direct reduction of the electrophile R-X the activated olefin or the solvent (cf. Fig. 2).
- If on the other hand, upon exposure to visible light ($\lambda$ = 400 - 500 nm) the (Co(III)-C)-bond cleavage is achieved photochemically, a sufficiently negative reduction potential has to be chosen to ensure the reformation of Co(I). This potential is much less negative than in the dark-reaction and lies at $\sim$ -0,9 V (SCE). (cf. Fig. 2).

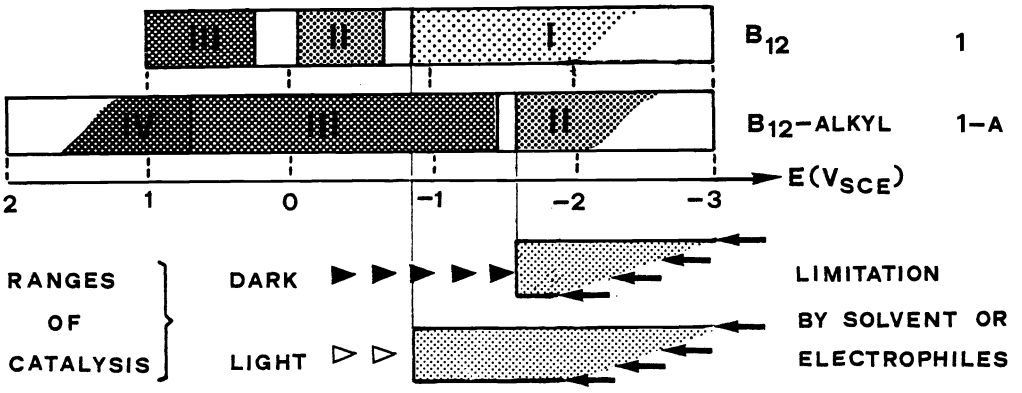



Fig. 2: Potential range for the vitamin $B_{12}$-catalyzed conversion of organic electrophiles undergoing oxidative addition with Co(I).

As a result of the reductive or photochemically induced cleavage of the (Co-C)bond, a reactive carbon species is split off and undergoes further reactions according to the reaction conditions. In case of reductive cleavage in the dark in presence of protons and absence of activated olefins the corresponding protonated species were isolated. Since the protonation occurs with retention of configuration, it may be concluded that neither a free radical nor a free carbanion is involved (Ref. 17 & 18). In presence of activated olefins the products of conjugate addition are formed even in protic solvents.

## VITAMIN $B_{12}$-CATALYZED CONJUGATE ADDITION

The electrolysis of alkylhalides R-X in presence of activated olefins at -1,5 to -1,6 V (SCE) in the dark and in presence of catalytic amounts (1 to 10 mol%) of 1 or 2 leads to coupling products (equation 1). As by-products the corresponding alkanes R-H might be formed (equation 2).

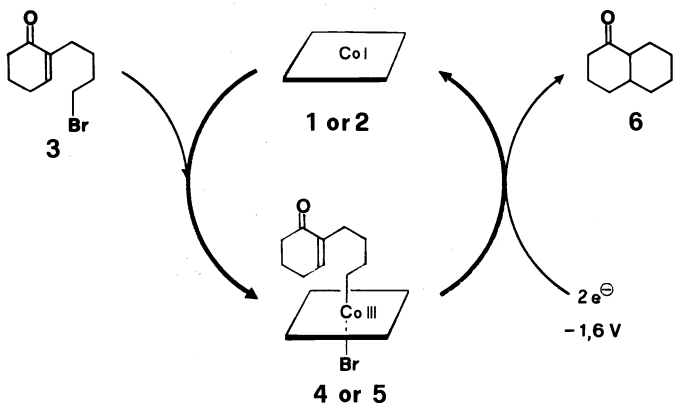
$$R\text{-}X + \underset{}{\overset{Z}{=\!\!/}} + H^+ \xrightarrow[\text{catalyst } \underline{1} \text{ or } \underline{2}]{2e^-} \underset{R}{\overset{Z}{/\!\!-\!\!/}} + X^- \qquad (1)$$

Z = π-acceptor group

$$R\text{-}X + H^+ \xrightarrow[\text{catalyst } \underline{1} \text{ or } \underline{2}]{2e^-} R\text{—}H + X^- \qquad (2)$$

In order to elucidate the sequence of reaction steps a starting material 3 has been chosen, which contains the alkylhalide and the activated olefin within the same molecule. Its electrochemical reduction (in a conventional, divided cell at a Hg-pool cathode) in presence of one equivalent of 1 (or 2) at -1,0 V in the dark led to the alkylcobalt complexes 4 (or 5) in almost quantitative yield. The structure of the complex 4 (or 5) was determined by elemental and instrumental analysis. Further electrolysis of 4 (or 5) at more negative potential (-1.6 V (SCE)) resulted in almost quantitative formation of decalone 6 and the recycled Co(I) complexes of 1 (or 2) (Ref. 19).

Intramolecular (C-C)bond formation. - The experimental results provided in Table 1 reveal the two competing reactions (conjugate addition leading to bicyclic- or spiroketones and proton capture leading to products exhibiting a hydrogenolyzed side-chain). Cyclisation predominates if the reactive center in the side chain can easily adopt a spatial position favourable for an attack on the activated olefin.



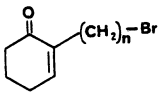
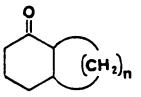
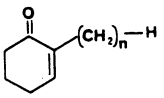
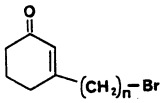
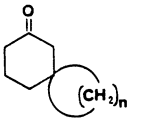
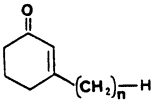
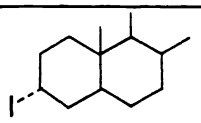
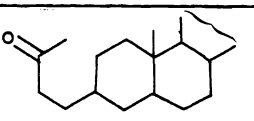
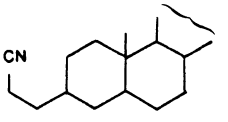
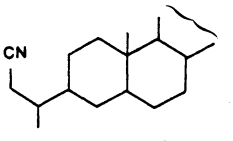
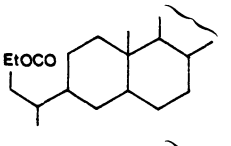
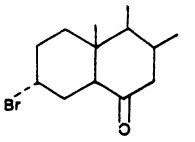
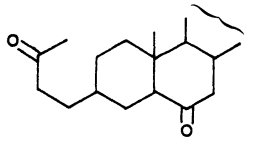
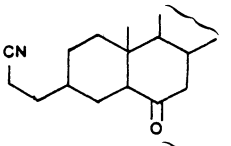
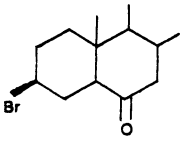
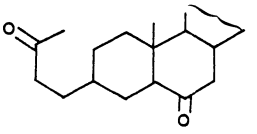

| | Substrate | Products | Yield |
|---|---|---|---|
| endo trig |  |  |  |
| 5-ring (n=3) | | — | 90 % |
| 6-ring (n=4) | | 95 % | — |
| 7-ring (n=5) | | 70 % | 10 % |
| exo trig |  |  |  |
| 4-ring (n=3) | | — | 90 % |
| 5-ring (n=4) | | 95 % | — |
| 6-ring (n=5) | | 45 % | 40 % |

Table 1: Electroreduction of bromocyclohexenones catalyzed by 5 mol% 1 or 2 (yields are equal in both cases) at -1.5 to -1.6 V (SCE) in DMF or methanol (Ref. 19).

Intermolecular (C-C)bond formation. - Intermolecular coupling reactions according to equation 1 have been studied in case of 3-halocholestanes and different Michael acceptors. Preliminary studies reveal that either 3α- and 3β-iodo- or bromo-cholestane on electrolysis with 2 at -1.0 V (SCE) result in the formation of one alkyl-cobalt complex exclusively, which bears the Co-substituent in 3β-position. Results of the catalyzed intermolecular coupling are compiled in Table 2.

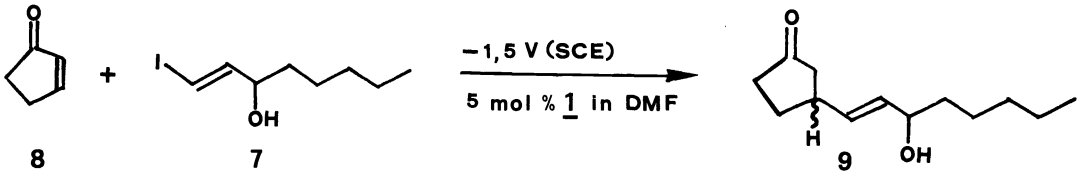
Table 2: Intermolecular coupling of 3-halosteroids and activated olefins under standard conditions in the dark [a].

| Entry | Halo-steroid | Activated Olefin | Applied reduction potential V (*vs* SCE) | Product | Total yield % [b] | Ratio of Isomers [c] 3α : 3β |
|---|---|---|---|---|---|---|
| 1 |  |  | -1,4 |  | 98 (65) | 75 : 25 |
| 2 | |  | -1,4 |  | 95 (30) | 70 : 30 |
| 3 | |  | -1,6 |  | 73 (12) | 35 : 65 [d] |
| 4 | |  | -1,7 |  | 72 (12) | 5 : 95 [d] |
| 5 |  |  | -1,4 |  | 76 | 80 : 20 |
| 6 | |  | -1,4 |  | 86 | 72 : 28 |
| 7 |  |  | -1,4 |  | 51 | 80 : 20 |

a) Standard condition for electrochemical reduction: molar ratio RY:olefin = 1:5, 4 mol% vitamin $B_{12a}$ 1 in electrolyte (0.1 N $LiClO_4$, 0.05 N $NH_4Br$ in DMF), electrolysis at the indicated potential. Standard condition for Zn-reduction: reducing agent = activated Zn-powder. - b) The yield of isolated material is indicated (values in brackets concerne isolated yield in the Zn-version). As by-product cholestane is formed. - c) Determined by NMR-spectrometry. - d) Four diastereomers are formed due to the additional centre of chirality.

It is noteworthy that under these mild reaction conditions an unprotected carbonyl group in the alkylhalide remains unattacked (cf. entry 5 to 7). The α:β ratio of the coupling products is obviously related to the relative reactivity of the Michael acceptor. Highly reactive acceptors lead predominantly to less stable 3α-isomers, whereas less reactive acceptors lead to the thermodynamically more stable 3β-isomer (cf. entry 4).

For the coupling of allyl groups to activated olefins only the allylchlorides are suitable, the corresponding bromides and iodides being too reactive. On the other hand, the coupling of vinyl derivatives to Michael acceptors is possible only with the corresponding vinyliodides. An example is the vitamin $B_{12}$-catalyzed conjugate addition of the unprotected hydroxyvinyliodide 7 to cyclopentenone 8 leading to the hydroxyketone 9 (mixture of two diastereomers).




8 7 9

Conjugate addition of the acyl group to activated olefins. - There exist several methods for the "Umpolung" of the acyl group (Ref. 20). A convenient way for the introduction of the acyl group by a conjugate addition is the thiazolium-salt catalyzed addition of aldehydes to activated olefins (Stetter reaction) (Ref. 21). This method however is restricted to activated olefins, which do not contain an aldehyde function.

Macrocyclic cobalt (I) complexes are known to react with carboxylic anhydrides and other acyl derivatives to form the corresponding Co(III)-acyl compounds (Ref. 22). The (Co-C)bond of these compounds is cleaved either reductively or on irradiation. The acyl fragment adds then to an activated olefin and Co(I) is regenerated electrochemically. Kinetic studies reveal that both, the oxydative addition of the acid anhydride to Co(I) leading to the intermediate acyl-Co derivative and its light induced cleavage in presence of Michael acceptor follow second order kinetics. In an actual $B_{12}$-catalyzed conjugate addition of acyl groups to activated olefins the most convenient way consists of electrolysing a mixture of carboxylic anhydride and activated olefin under visible light irradiation in presence of a catalytic amount of 1 or 2.

In table 3 and 4 first results of the preparative application of this $B_{12}$-catalyzed nucleophilic acylation of Michael acceptors have been compiled.

Table 3: Vitamin $B_{12}$-catalyzed reductive photochemical acylation of α,β-unsaturated nitriles and ketones

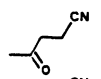
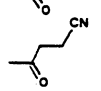
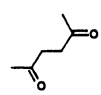
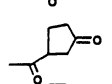
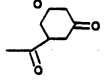
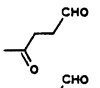
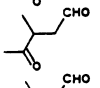
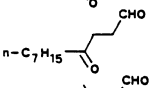
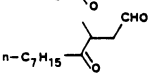
| Substrates | $B_{12a}$ 1 (mol%) | Product | isol.Yield (%) |
|---|---|---|---|
| $(CH_3CO)_2O$  | 4 |  | 60 |
| $CH_3COCl$  | 4 |  | 6 |
| $(CH_3CO)_2O$  | 4 | no product formed | - |
| "  | 4 |  | 63 |
| "  | 4 |  | 42 |
| "  | 4 |  | 40 |

Table 4: Vitamin $B_{12}$-catalyzed reductive photochemical acylation of α,β-unsaturated aldehydes

| Substrates | $B_{12a}$ (mol%) | Product | isol. Yield (%) |
|---|---|---|---|
| $(CH_3CO)_2O$  | 2 |  | 47 |
| "  | 2 |  | 34 |
| "  | 2.5 |  | 50 |
| "  | 5 |  | 30 |
| $(n\text{-}C_7H_{15}CO)_2O$  | 14 |  | 71 |
| $(n\text{-}C_7H_{15}CO)_2O$  | 14 |  | 80 |

The new vitamin $B_{12}$-catalyzed conjugate addition of alkyl-, vinyl- and acyl derivatives to activated olefins represents an attractive method for the formation of (C-C)bonds in a one-step procedure under mild reaction conditions.

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