

**Vitamin B12 catalysed reactions**

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VITAMIN B₁₂ CATALYSED REACTIONS

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Abstract

Vitamin B₁₂ (cobalamin, **1**) is one of a few naturally occurring organometallic molecule. As a cofactor for adenosylcobalamin-dependent and methylcobalamin-dependent enzymes, it plays a crucial role in biological processes, including DNA synthesis and regulation, nervous system function, red blood cell formation, etc. Enzymatic reactions, such as isomerisation, dehalogenation, and methyl transfer, rely on the formation and cleavage of the Co-C bond. Because it is a natural, nontoxic, environmentally benign cobalt complex, cobalamin (**1**) has been successfully utilised in organic synthesis as a catalyst for Co-mediated reactions. This tutorial review concisely describes cobalamin-catalysed organic reactions that hold promise for environmentally friendly cobalt catalysis, leaving the reader with basic knowledge and the ability to harness the catalytic potential of this fascinating molecule.

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Key learning points:

- (1) Rationale for B₁₂-catalytic activity
- (2) ‘Supernucleophilicity’ of cobalamin(I)
- (3) Radical activity of cobalamin(II)
- (4) B₁₂-catalysed reactions
- (5) Mechanisms of B₁₂-catalysed reactions

1 INTRODUCTION

Nature has always been the ultimate source of inspiration for scientists working across all disciplines. This statement certainly applies to catalysis, where continuous effort has been invested in mimicking and improving the function and effectiveness of enzymes. To this end, new synthetic catalysts have been developed and exploited to facilitate more efficient and selective transformations of organic compounds. However, many of these catalysts are poor replicas of naturally occurring enzymes, compromised by low stability or selectivity, high catalyst loading, or toxicity.

First isolated by Folkers and Smith in 1948, vitamin B₁₂ (B₁₂, cobalamin, **1**, Figure 1) has been recognised as a cofactor for enzymes that catalyse a range of biological processes, including isomerisation, methyltransfers, and dehalogenation.¹

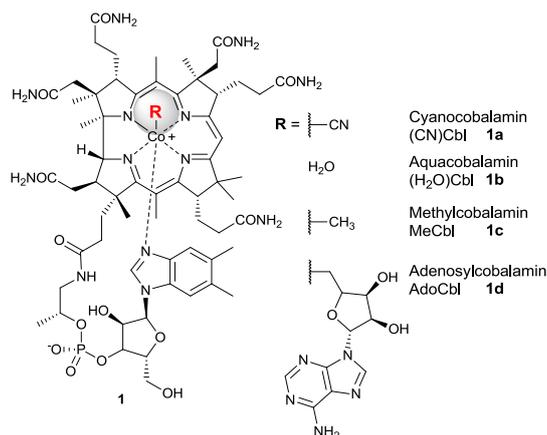
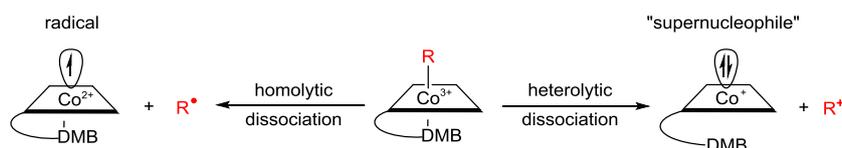


Figure 1 Chemical structures of cobalamin and its derivatives: cyanocobalamin (**1a**), aquacobalamin (**1b**), and B₁₂-coenzymes: methylcobalamin (**1c**) and adenosylcobalamin (**1d**). *Note: Aquacobalamin (1b) bears a neutral aqua ligand, which results in a positively charged molecule; therefore, it is always accompanied by a counter-ion. In the interest of clarity, counter-ions are not shown throughout this review.*

The ability of vitamin B₁₂ (**1**) to catalyse these thermodynamically challenging reactions has attracted the attention of synthetic chemists, which has eventually led to discoveries of new catalytic transformations. This review highlights the application of vitamin B₁₂ (**1**) as an environmentally benign catalyst for organic reactions; we leave enzymatic transformations aside, because they have been reviewed elsewhere.^{1,2}

Native vitamin B₁₂ compounds include AdoCbl (**1d**), which bears a 5'-deoxyadenosyl moiety covalently bound to the cobalt ion, and MeCbl (**1c**), which possesses the methyl group at the upper axial position. In all stable vitamin B₁₂ forms, the central cobalt cation has an oxidation state of +3. Under biological conditions, adenosylcobalamin (**1d**) undergoes homolytic Co-C bond cleavage, which provides a source of the Co(II) species and the 5'-deoxyadenosyl radical. In contrast, methylcobalamin (**1c**) is cleaved heterolytically, which yields the “supernucleophilic” Co(I) species with a lone electron pair (Scheme 1).²

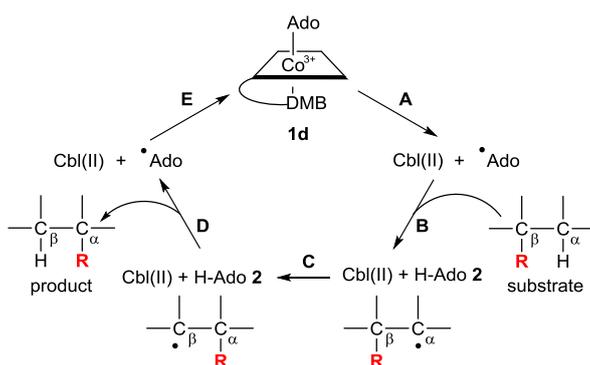


Scheme 1 Two possible Co-C bond cleavages: homolytic (*left*) and heterolytic (*right*).

B₁₂-dependent enzymes are therefore divided into three groups: a) 5'-deoxyadenosyl cobalamin-dependent isomerases, b) MeCbl-dependent transferases, present in mammalian cells, and c) reductive dehalogenases, found only in organohalide respiring bacteria.³

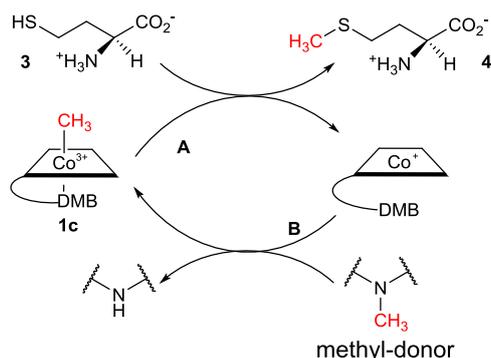
AdoCbl-dependent enzymes catalyse isomerisation (e.g., glutamate mutase, methymalonyl CoA mutase, dioldehydrase, etc.) and reduction reactions (e.g., ribonucleotide reductase).²

Due to the limited extent of this review, we briefly describe the mechanism of reactions involving a key, hydrogen-transfer step (Scheme 2). The catalytic cycle begins with the homolytic cleavage of the Co-C bond (**A**), assisted by specific interactions between an enzyme and AdoCbl (**1d**). Then, the resulting Ado radical abstracts hydrogen from a substrate, furnishing a radical (**B**), which undergoes rearrangement (**C**). Subsequent hydrogen exchange (**D**) yields the final product and the 5'-deoxyadenosyl radical, which allows regeneration of the catalyst (**E**).



Scheme 2 Hydrogen transfer pathway in AdoCbl-dependent rearrangements.

MeCbl-dependent enzymes, such as methionine synthetase, methane synthetase, or DNA-methylase, operate *via* the heterolytic Co-C bond cleavage (Scheme 3).



Scheme 3 Methyl transfer reaction catalysed by methionine synthase. MeCbl (**1c**) serves as an alkylating agent for a nucleophile (**3**), which results in a Co(I) intermediate (**A**). The Co(I) abstracts the methyl group from methyltetrahydrofolate (or related methyl-donor molecules), which regenerates the catalyst (**B**).

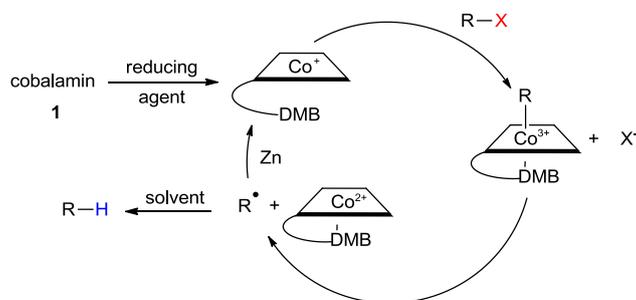
Currently, little is known about B₁₂-dependent reductive dehalogenases. However, recent work by Payne has suggested that the reduction of organic halides involves the halogen-cobalt bond formation, which represents a new activation mode in cobalamin-catalysed reactions.⁴

The unique role of vitamin B₁₂ (**1**) stems from the ability of reduced cobalt species (either radical Co(II) or “supernucleophile” Co(I)) to form the Co-C bond, which can be cleaved in a controlled manner to furnish highly reactive carbon species. In addition to enabling cobalamin (**1**) to catalyse thermodynamically challenging enzymatic reactions (described above), this property has piqued the interest of synthetic chemists, which has led to exciting new discoveries in this field. The following chapters describe isolated examples of B₁₂-catalysed reactions and highlight their practicality as tools in organic synthesis.

2 DEHALOGENATION

Microbes that possess B₁₂-dependent reductive dehalogenases can remove halogen substituents from organic halides. Over the years, these reactions have attracted a lot of attention, due to their potential application in remediation of persistent polyhalogenated pollutants. For example, aquacobalamin (**1b**) can be alkylated with organic halides, which

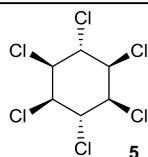
leads to dehalogenated products.⁵ Currently, it is generally accepted that these processes involve the reduction of Cbl(III) to the nucleophilic Co(I) species and subsequent reaction with an electrophilic halide (Scheme 4). However, based on Payne's new discoveries, other mechanisms involving Co-Cl bond formation should be also considered.⁴



Scheme 4 Proposed mechanism for dehalogenation catalysed by vitamin B₁₂ (**1**). First, cobalamin (**1**) is reduced to the nucleophilic Co(I) species. Then, it reacts with an electrophilic halide (R-X) to yield dehalogenated product.

Schrauzer's group was the first to show that (H₂O)Cbl (**1b**), in the presence of various reducing agents (e.g., NaBH₄, 1-thioglycerol, 2,3-dimercaptopropanol, and acetoin) could dechlorinate pesticides that contaminate the soil (mirex and kepone).⁵ Furthermore, extensive studies revealed that the dechlorination of CCl₄ to CHCl₃, CH₂Cl₂, or CH₃Cl and the dechlorination of lindane (**5**) worked well with other catalytic systems. These systems included various corrinoids, like (H₂O)Cbl (**1b**), MeCbl (**1c**), (CN)(H₂O)Cbi (**6b**), and various reducing agents, such as titanium(III) citrate, dithiothreitol, and cysteine. Unexpectedly, (CN)(H₂O)Cbi (**6b**), which lacked the nucleotide loop, was the most effective dechlorination agent (Table 1, Figure 2).^{5,6}

Table 1 The catalytic activity of corrinoids in the dechlorination of lindane (**5**).



| Catalyst | Activity ^a |
|-------------------------------------|-----------------------|
| (CN)Cbl 1a | 800 |
| AdoCbl 1d | 750 |
| (CN) ₂ Cbi 6a | 6750 |
| (CN)(H ₂ O)Cbi 6b | 6825 |

^aExpressed in nanomoles of lindane (**5**) dehalogenated per minute per milligram of a catalyst.

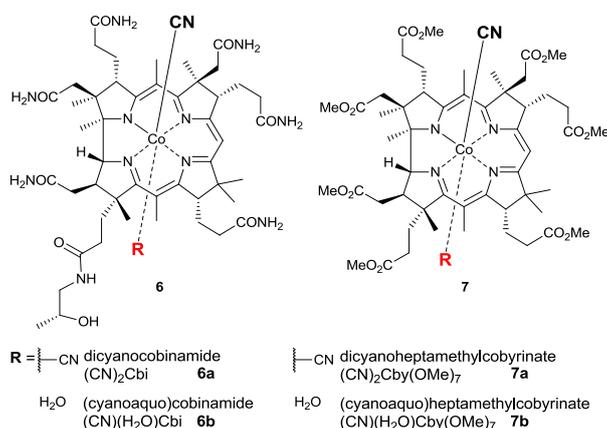
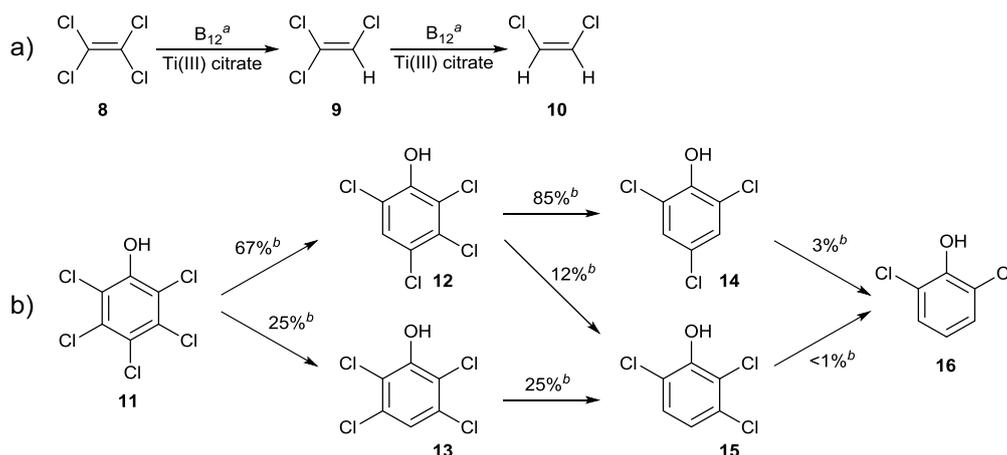


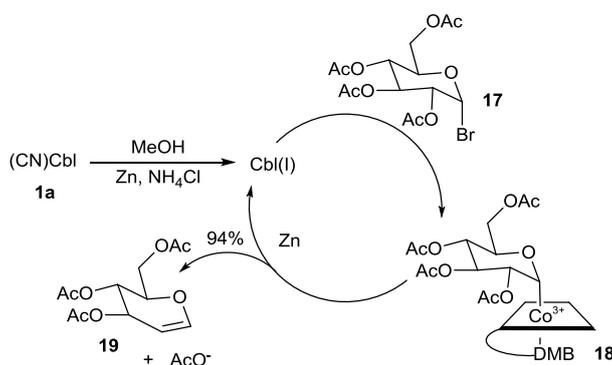
Figure 2 Structures of cobinamides **6** and heptamethylcobyrinates **7**. Note: Aquacobinamide (**6b**) and aquacobyrinate (**7b**), and the respective Co(II) species, **30**, **31**, and **111**, are all positively charged and accompanied by counter-ions, which are not shown for clarity.

In dechlorinating polyhalogenated ethylenes and phenols, one must be aware of regioselectivity and stereoselectivity issues. For example, the reductive dechlorination of tetrachloroethylene (**8**) furnishes predominantly Z-1,2-dichloroethylene (**10**) in a stereoselective manner (Scheme 5a).^{7,8} The mechanistic details of this process have been extensively described by Kliegman and McNeill; thus, they will not be discussed here.⁹ Polychlorophenols are dehalogenated regioselectively at *meta*- and *para*- positions to the hydroxyl group in the presence of (CN)Cbl (**1a**) (Scheme 5b).¹⁰ Typically, Ti salt is required in these reactions, which unfortunately, is inconvenient in the synthetic process.



Scheme 5 (a) Stereoselective dehalogenation of tetrafluoroethylene (**8**). ^a Form of vitamin B_{12} was not specified. (b) Regioselective dehalogenation of pentachlorophenol (**11**). ^b Reducing system: (CN)Cbl (**1a**), Ti(III) citrate

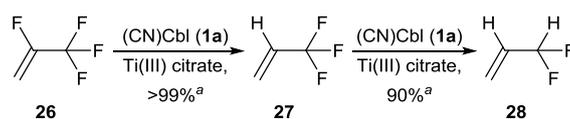
Forbes and Franck found that the reductive debromination of 1-bromotetracetylglucose (**17**) in the presence of (CN)Cbl (**1a**) and Zn/NH₄Cl (Scheme 6) eliminated the need for unusually acidic conditions (Fisher-Zach conditions).¹ The same methodology was used to synthesise 5-hexenoses from 6-iodopyranosides, which possess a good leaving group in the β -position.¹¹ In this reaction, 1-bromotetracetylglucose (**17**) is reductively debrominated in the presence of (CN)Cbl (**1a**) and Zn/NH₄Cl. Then, triacetyl glucal **19** is formed with concomitant elimination of the acetyl group.



Scheme 6 (CN)Cbl-catalysed version of the Fisher-Zach reaction.

Scheme 8 Synthesis of β -methylene glutamic acid derivatives from chlorinated oxazoline **23**. The yield was improved by replacing (CN)Cbl (**1a**)/DMF with (CN)₂Cby(OMe)₇ (**7a**)/THF.

Most B₁₂-catalysed dehalogenations are based on chlorine and bromine atoms, due to their relatively weak bonds with carbon. In contrast, the fluorine interaction is much stronger ($E_{\text{C-Cl}} = 339 \text{ kJ/mol}$ vs. $E_{\text{C-F}} = 485 \text{ kJ/mol}$). Nevertheless, a number of defluorinations of perfluorooctane sulfonates (PFOS) were performed in the presence of (CN)Cbl (**1a**) with Ti(III) citrate as a reducing agent.¹³ Partial defluorination was confirmed by fluorine release measurements: 18% for technical PFOS and 71% for branched isomers. Recently, the same method was applied for the defluorination of 2,3,3,3-tetrafluoropropene (**26**), a refrigerant frequently used in air-conditioning systems (Scheme 9).¹³

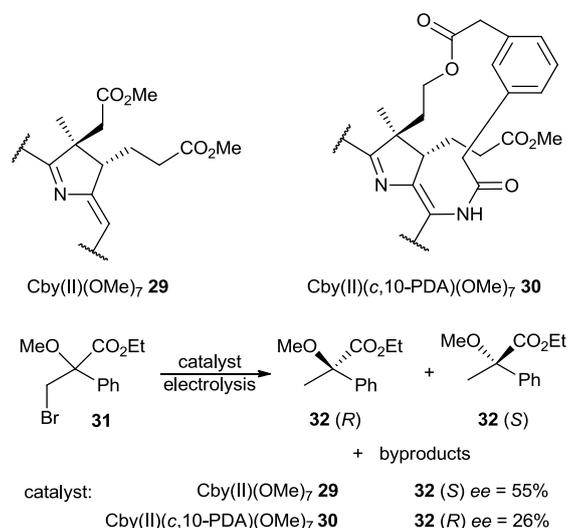


Scheme 9 The defluorination of 2,3,3,3-tetrafluoropropene (**26**) catalysed by (CN)Cbl (**1a**). ^aYields were calculated based on the converted substrate

Alternatively, vitamin B₁₂ (**1**) can be reduced electrochemically. Rusling and Soufflet utilised this technique to establish the dehalogenation mechanism and kinetics for bromoalkane and α -haloacetic acid in solution and in emulsion.^{14–17} Additionally, Savéant reported the positive effect of using protic solvents in the dehalogenation of chloroacetonitrile.¹⁶

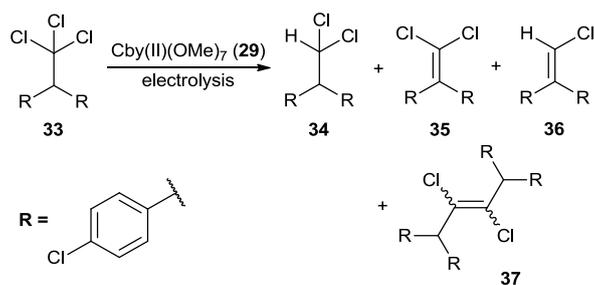
Cobyrinic acid derivatives other than simple Cby(OMe)₇ (**7**) can also be used as catalysts. For example, 8-aminocob(III)yrinic acid *c*-lactam in a liquid crystal film of cationic surfactant could catalyse the dehalogenation of trichloroacetic acid and 1,2-dibromoethane.¹⁸ Murakami went one step further and examined both Cby(II)(OMe)₇ (**29**) and Cby(II)(*c*,10-PDA)(OMe)₇ (**30**) in an asymmetric debromination of bromo-substituted ester **31** (Scheme 10).¹⁹

Interestingly, adding a strapped modification to the cobyrinate altered its stereoselectivity, which showed that substituents placed around the corrin ring influenced the reaction outcome.



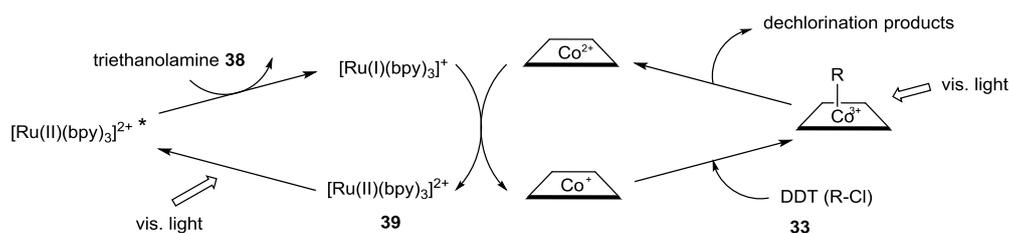
Scheme 10 Asymmetric debromination of bromo-substituted ester **31** catalysed with different cobyrinic acid derivatives showed different stereoselectivities

The advantage of merging electrochemical reduction with B₁₂-catalysis was further advanced by immobilising catalysts onto electrodes. Walder immobilised cobyrinate derivatives onto mesoporous TiO₂ film electrodes to convert dibromocyclohexane and 1,2-dibromoethane into the corresponding olefins.²⁰ In another study, hydrophobic cobyrinate was immobilised onto a platinum electrode to facilitate the electrolysis of (2-bromoethyl)benzene at -1.4 V vs. Ag/AgCl. A photo-sensitive compound with the Co-C bond formed; then, upon light irradiation it decomposed to styrene.²¹ Also, Hisaeda demonstrated the electrochemical dechlorination of 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane (DDT, **33**), a known environmental pollutant, in the presence of Cby(II)(OMe)₇ (**29**) (Scheme 11).²² In this reaction, the Co(II) complex **29** is electrochemically reduced to the supernucleophilic Co(I) species. Then, upon reacting with DDT (**33**), the alkylated complex is formed. After decomposition, this reaction furnishes a mixture of dehalogenated compounds **34-37**.



Scheme 11 The dechlorination of DDT (**33**) catalysed by heptamethylcobyrinate.

The Co(II) species can also be reduced to Co(I) with light irradiation (Co(II)/Co(I) \sim 0.65 V vs. SCE) in the presence of photoredox compounds, [Ru(II)(bpy)₃]Cl₂ (**39**), Rose Bengal, or Rhodamine B. This reaction can be achieved in EtOH, ionic liquid, and in heterogenic reaction with B₁₂ and Ru catalysts supported on a metal-organic framework (MOF) under mild conditions (Scheme 12).^{23–25}



Scheme 12 The photocatalytic dechlorination of DDT (**33**). Co(II) is reduced to Co(I) in the presence of [Ru(II)(bpy)₃]Cl₂ (**39**).

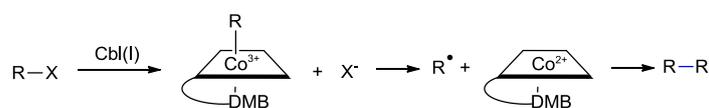
Hisaeda then superseded that work by using cobyrinic acid as both a catalyst and a photosensitiser under UV irradiation.²³ Note that here, the catalyst must already be in the reduced Co(II) form. The need for the Co(II) complex was eventually eliminated by the immobilisation of cobyrinic(III) acid on TiO₂, which facilitated its reduction to the Co(I) form with light irradiation (365 nm).²³ The catalyst and photosensitiser were then bound to a linear polymer macromolecule, which also permitted the use of the stable dicyano form of cobyrinic acid derivative **7a**, instead of the aqua form **7b**.

Other examples of solid-supported catalysts include a B₁₂-hyperbranched polymer²³ and corrin adsorbed to nano-mackinawite.²⁶ Electrochemically promoted dehalogenations in the presence of cobalamin derivatives can also be performed efficiently in ionic liquids.²⁷

In summary, over the last five decades, several B₁₂-catalysed dehalogenation protocols have been developed. Though different cobalamin derivatives can serve as catalysts, almost all require reducing conditions that generate nucleophilic Co(I) species, which display high affinity for organic halides. This catalysis promotes efficient dehalogenation of alkyl-, alkenyl-, and aryl compounds, and facilitates challenges, like asymmetric debromination or fluorine removal.

3 HALIDE COUPLING

Like dehalogenation, the first step in halide coupling relies on the formation of alkyl-cobalamin derivatives (Scheme 13).



Scheme 13 The general pathway for B₁₂-catalysed homocoupling of organic halides. Organic halides (R-X) form the Co-C bond in the presence of Cbl(I). Then, homolytic cleavage affords a radical (R[•]) that recombines to yield a dimer (R-R).

In the dimerisation process, the choice of catalyst and reducing agent is crucial. The system must be sufficiently strong to allow the generation of Cbl(I) from Cbl(III), and at the same time, it must assure the stability of a radical intermediate. In this respect, studies by Rusling and colleagues showed that vitamin B₁₂ (**1**) is a unique catalyst for the dimerisation of benzyl halides. The Co-CH₂Ph bond has a higher reduction potential (-1.10 V vs. SCE) than that of the benzyl radical (-1.43 V vs. SCE); thus assuring its stability under reaction conditions and subsequent coupling.¹⁴

Efficient dimerisation of primary and secondary benzyl bromides **40-43** is achieved with the (CN)Cbl (**1a**)/Ti(III) citrate catalytic system in aqueous EtOH. Unfortunately, it requires relatively high catalyst loading (10 mol%; Table 2).⁷

Table 2 Homocoupling of benzyl bromide derivatives catalysed by the (CN)Cbl (**1a**)/Ti(III) citrate system

| Substrate | Product | Yield [%] |
|-------------------------------|--|--------------|
| PhCH ₂ Br | 40 (PhCH ₂) ₂ | 44 98 |
| PhCH(CH ₃)Br | 41 [PhCH(CH ₃)] ₂ | 45 64 |
| PhCH ₂ Cl | 42 (PhCH ₂) ₂ | 44 68 |
| (2-naphtyl)CH ₂ Cl | 43 [(2-naphtyl)CH ₂] ₂ | 46 75 |

It was found that bromoalkanol homocoupling can proceed with only 2 mol% catalyst in the presence of Zn/NH₄Cl.²⁸ Under these conditions, bromoalknols undergo dehydrobromination with subsequent oxidative allylic coupling and hydration to give polyhydroxyalkanols.

Cobalamin (**1**) proved effective in the dimerisation of organic halides. Additionally, Hisaeda and co-workers examined hydrophobic heptamethyl cobyrinate(II) (**29**) as a catalyst.^{1,23} Its immobilisation on a hyperbranched polymer with light-induced photoreduction led to an increase in the yield of bibenzyl **45** (31%) compared to the reaction in solution (2%) (Table 3). This reaction primarily generated the 2-phenylethyl radical, which rearranged to the more stable benzyl radical, and subsequently dimerised.

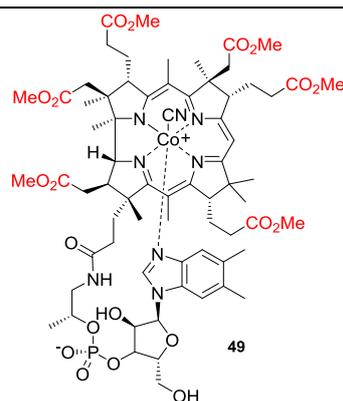
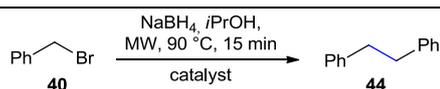
Table 3 Dimerisation of (2-bromoethyl)benzene (**47**) with Cby(II)(OMe)₇ (**29**), either free or immobilised on a hyperbranched polymer (HBP).

| Catalyst | Conversion [%] | Yield of 45 [%] |
|---|----------------|------------------------|
| Cby(II)(OMe) ₇ (29) | 92 | 2 |
| Cby(II)(OMe) ₇ (29)/HBP | 100 | 31 |

It was postulated that, in alkyl cobalamins, coordinating the cobalt cation with a dimethylbenzimidazole moiety would weaken the Co-C bond, and thus, it may alter the reaction rate.²⁹ To address this issue, Gryko's group tested diverse catalysts, both with and without a nucleotide moiety, in the microwave-assisted homocoupling of benzyl bromide (**40**) (Table 4).³⁰ Among all the catalysts tested, amphiphilic cobalester (**49**) was the most effective, which corroborated the long-standing hypothesis that the nucleotide loop influenced the catalytic efficacy of B₁₂ derivatives. Various substituted bibenzyls were synthesized in good to excellent yields, within only 15 min.

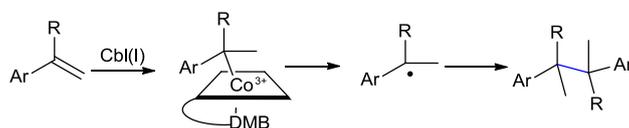
Table 4 Microwave-assisted benzyl bromide dimerisation, catalysed by vitamin B₁₂ derivatives.

| Catalyst | Conversion [%] | Yield [%] |
|---|----------------|-----------|
| (CN)Cbl 1a | 38 | 15 |
| (CN) ₂ Cbi 6a | 43 | 21 |
| cobalester 49 | 100 | 84 |
| cobinester 50 | 100 | 60 |
| (CN) ₂ Cby(OMe) ₇ 7a | 100 | 62 |



4 ALKENE COUPLING

In the presence of vitamin B₁₂ (**1**), benzyl radicals are also formed from styrene derivatives, which furnish the respective dimers (Scheme 14).



Scheme 14 The general pathway for B₁₂-catalysed homocoupling of styrene derivatives.

Van der Donk used this methodology to prepare various styrene derivatives, with (CN)Cbl (**1a**)/Ti(III) citrate, the same catalytic system that was established for benzyl halide

homocoupling (section 3, Table 5). Though new stereogenic centres were formed, no stereoselectivity was observed.⁷

Table 5 Styrene derivative homocoupling catalysed by (CN)Cbl (**1a**)/Ti(III) citrate.

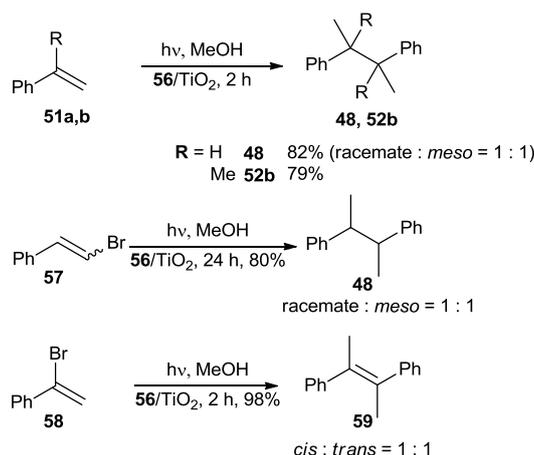
| Substrate 51 | Product | Yield [%] |
|---|---|-----------|
| a PhCHCH ₂ | [PhCH(CH ₃)] ₂ 45 | 50 |
| b PhC(CH ₃)CH ₂ | [PhC(CH ₃) ₂] ₂ 52b | 85 |
| d Ph ₂ CCH ₂ | [Ph ₂ C(CH ₃)] ₂ 52c | 90 |

The intramolecular reaction of dienes led to the formation of tetrahydrofuran derivatives **54** and **55** with **54:55** ratio strongly depending on the pH of the reaction mixture (Table 6).³¹

Table 6 Intramolecular reactions of diene **53**, catalysed by (CN)Cbl (**1a**)/Ti(III) citrate.

| pH | Yield [%] | | dr |
|----|-----------|-----------|---------|
| | 54 | 55 | |
| 8 | 36 | 18 | 1.5 : 1 |
| 6 | trace | 82 | 3.4 : 1 |

The light-induced methodology described in section 3 also worked well for dimerising substituted styrenes.³² Styrene (**51a**) and α -methylstyrene (**51b**) reacted equally well, with excellent yields of the corresponding dimers (Scheme 15). Interestingly, β -bromostyrene (**57**) afforded the same products, because (CN)(H₂O)Cby(OH)₇ (**56**)/TiO₂ exhibited catalytic activity for both hydrogenation and dehalogenation. Surprisingly, α -bromostyrene (**58**) gave 2,3-diphenylbut-2-en (**59**) in 98% yield. Although all the styrene derivatives used as substrates were prochiral, no asymmetric induction was observed, which suggested that the dimerisation of reactive intermediates took place outside the chiral microenvironment. (CN)(H₂O)Cby(OH)₇ (**56**)/TiO₂ allowed the use of a clean light energy source and eliminated the need for reducing agents in the reaction.



Scheme 15 Styrene (**51a**) and bromostyrene (**57**, **58**) homocoupling, catalysed by a TiO₂-immobilised catalyst **56**.

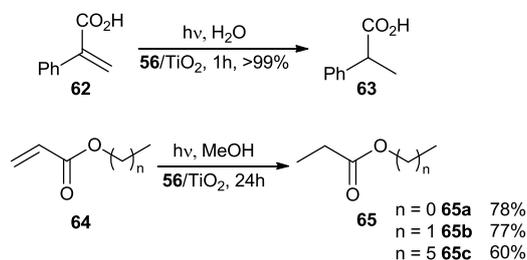
5 C=C AND C=X BOND HYDROGENATION

In the previous section, we only described the reactivity of non-activated double bonds, mainly styrene derivatives, in vitamin B₁₂ catalysed-reactions. This was not without reason. Early work by Fischli and recent work by Hisaeda showed that activated olefins, such as α,β -unsaturated carbonyl compounds, nitro compounds, nitriles, etc., do not form dimers. Instead, they undergo efficient hydrogenation when treated with a catalytic amount of B₁₂ (**1**) under reducing conditions (Table 7).^{32,33} Interestingly, even aromatic naphthalene-1-methylcarboxylate undergoes hydrogenation, but it produces a mixture of dihydro- and tetrahydro-compounds at low yield.³³

Table 7 Range of alkene **60** hydrogenation reactions, catalysed by (CN)Cbl (**1a**)/Zn in AcOH.

| $\text{R-CH=CH-CO}_2\text{R}^2 \xrightarrow[\text{AcOH, EtOH, H}_2\text{O}]{\text{h}\nu, \text{ (CN)Cbl (1a), Zn}} \text{R-CH}_2\text{-CH}_2\text{-CO}_2\text{R}^2$ | | | |
|---|---|----------------------|------------------------|
| | R | R² | Yield of 61 [%] |
| a | cyclo-C ₁₂ H ₂₃ | Me | 97 |
| b | CH ₃ (CH ₂) ₆ | Et | 81 |
| c | cyclo-C ₆ H ₁₁ | Et | 80 |
| d | Ph | Me | 80 |

The chemoselective reduction of aliphatic and aromatic alkenes can be achieved with TiO₂-immobilised catalyst **56** and light-induced hydrogenation, with water as a hydrogen source (Scheme 16).³²



Scheme 16 Alkene hydrogenation catalysed by TiO₂-immobilised catalyst **56**.

Among prochiral substrates, regardless of the catalyst, (*Z*)-alkenes exhibited low *S*-enantioselectivity (15 - 27%), and (*E*)-alkenes always furnished a racemate (Table 8).³³ These findings were attributed to the nucleophilic Co(I) species, which preferentially attacks the *re* side of the prochiral substrate, followed by reductive cleavage of the Co-C bond with high retention of the configuration. Because (CN)Cbl (**1a**) bears the nucleotide moiety, it exhibits a higher reaction rate and better enantioselectivity than heptamethyl cobyrinate (**7a**).

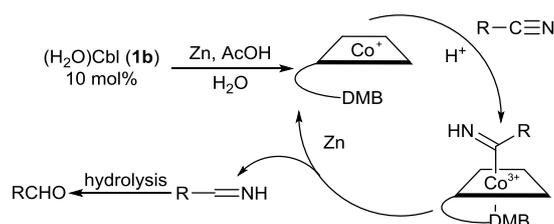
Table 8 Hydrogenation of olefin **66** catalysed by (CN)Cbl (**1a**) and (CN)₂Cby(OMe)₇ (**7a**)

| Catalyst | Yield [%] | <i>ee</i> [%] |
|---|-----------|---------------|
| (CN)Cbl 1a | 80 | 27 |
| (CN) ₂ Cby(OMe) ₇ 7a | 43 | 15 |

In addition to hydrogenation of activated double bonds, cobalamin-catalysed reactions also quantitatively reduce acetylenes that lack electron withdrawing substituents. These acetylenes are reduced to ethylenes when treated with (H₂O)Cbl (**1b**) and titanium(III) citrate at pH 8; it is proposed that vinylcobalamin is an intermediate in this reaction.³⁴

Likewise, carbon-carbon double bonds, carbon-heteroatom bonds are also hydrogenated in the presence of vitamin B₁₂ (**1**). For example, vitamin B₁₂ can catalyse the reduction of nitriles to

the corresponding aldehydes, but high catalyst loading is required.¹² This reaction is general and efficient for aliphatic nitriles (Scheme 17), but there is no evidence for the reduction of aromatic nitriles. In aromatic compounds, complete stability of the cyano group was observed during the microwave-assisted benzyl bromide homocoupling (section 3).³⁰ Here, the Co(I) species reacts with the nitrile group ($R-C\equiv N$), giving the cobalt-imine intermediate. Acidic hydrolysis produces an imine, and then, the respective aldehyde ($RCHO$).

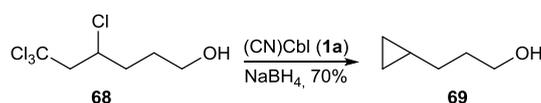


Scheme 17 Plausible mechanism for B_{12} -catalysed reduction of nitriles to aldehydes.

Vitamin B_{12} derivatives were also found to catalyse the reduction of inorganic species, such as oxygen, CO_2 , hydroxylamine, nitrite, nitrate, oxyhalogens, thiosulfate, sulfite, and dithionite, or inorganic cobalt(III) complexes.^{1,35}

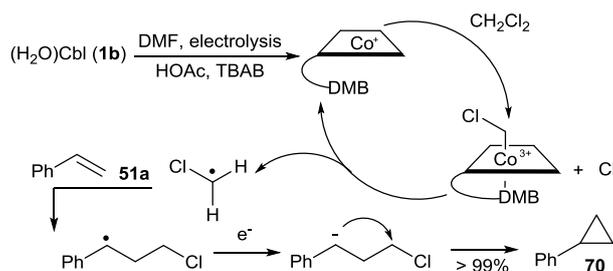
6 CYCLOPROPANATION

Petrović was the first to describe the formation of cyclopropanes in B_{12} -catalysed reactions. $(CN)Cbl$ (**1a**)/ $NaBH_4$ was used for the reductive cyclisation of tetrachloroalkanols, which subsequently underwent complete dehalogenation, and furnished nontoxic derivatives (Scheme 18).¹



Scheme 18 Reductive cyclisation of tetrachloroalkanol **68**, catalysed by $(CN)Cbl$ (**1a**).

The electrochemically induced cyclopropanation of styrene (**51a**) with CH_2Cl_2 in DMF yields cyclopropane derivative **70** quantitatively (Scheme 19).



Scheme 19 The electrochemical cyclopropanation of styrene (**51a**) with methylene chloride. Here, Cbl mediates the generation of the chloromethylene radical, which reacts with the olefin. After reduction, this generates a carbanion, which can either abstract a proton from the solvent or undergo cyclisation (**70**).

Typically, cyclopropanation of olefins with carbenoid species (diazo-reagents) are mediated by transition metals, like Cu, Pd, Ni, and Rh, but most recently, it was shown that Co(II) complexes could mediate this reaction.³⁶ Zhang and Chen examined four B₁₂ derivatives ((CN)Cbl (**1a**), (H₂O)Cbl (**1b**), MeCbl (**1c**), and AdoCbl (**1d**)) in a model reaction of styrene (**51a**) with ethyl diazoacetate (EDA, **71**), which predominantly produced *cis*-cyclopropane **72** (Table 9).³⁷ (H₂O)Cbl (**1b**) was the most effective B₁₂ derivative. The method worked well for α -substituted styrenes with either alkyl or aryl groups; however, *electron-deficient alkenes produced lower yields than electron-rich alkenes*.

Table 9 The influence of B₁₂ catalyst on the cyclopropanation of styrene (**51a**).

| Catalyst | | Yield [%] | <i>cis:trans</i> | <i>ee</i> [%] ^a |
|-----------------------|-----------|-----------|------------------|----------------------------|
| (CN)Cbl | 1a | 34 | 56:44 | 47(29) |
| (H ₂ O)Cbl | 1b | 98 | 61:39 | 64(54) |
| MeCbl | 1c | 86 | 61:39 | 62(52) |
| AdoCbl | 1d | 82 | 61:39 | 61(51) |

^a *cis(trans)*

It was proposed that this reaction required reduction of (H₂O)Cbl (**1b**) to the active Co(II) species, with a sacrificial molecule of EDA (**71**). Subsequently, the reduced species reacted

with second EDA molecule to form the proposed cobalt-carbene intermediate; then, cyclopropane was furnished with a carbene transfer to the olefin. This postulated mechanism was supported in reactions with other reducing agents (e.g., NaBH_4 , and HCO_2Na known to produce Co(II) species).

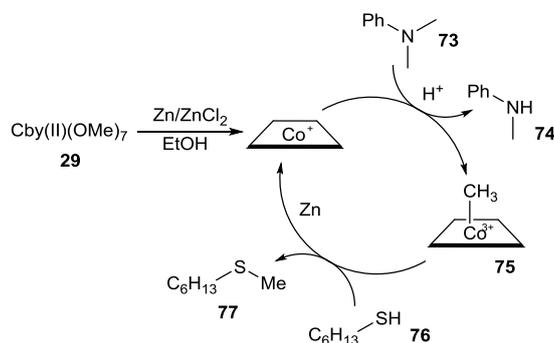
7 TRANSMETHYLATION

Methylation of alcohols or thiols is a fundamental transformation that requires a strong methylating reagent, such as methyl iodide, dimethyl sulphate, or dimethyl carbonate. Though an efficient process, it is often nonselective and cannot be performed under biological conditions. As described in the Introduction (section 1), nature has developed a milder system with methylcobalamin-dependent transferases.

Over the years, much effort has been dedicated to mimicking this bio-inspired reaction in a non-enzymatic manner. The catalytic cycle of transmethylation consists of two half-reactions: 1) methyl is transferred from a methyl donor to cobalamin, and 2) methyl is transferred from methylcobalamin (**1c**) to a methyl acceptor (Scheme 3). One key application for this reaction is to detoxify inorganic arsenic trioxide (As_2O_3) by methylating it in the presence of MeCbl (**1c**) to produce the less toxic, trimethyl arsine oxide.⁵

In 1999, Keese and Dabre pioneered studies in the area of B_{12} -catalysed transmethylation. They discovered a catalytic system that comprised *N,N*-dimethylaniline (**73**), as a methyl donor, and Cby(II)(OMe)_7 (**29**) (2.5 mol%), as a catalyst, for the methylation of 1-hexanethiol (**76**; Scheme 20).⁵ The reaction was conducted in EtOH, with Zn as a reducing agent, and ZnCl_2 was a necessary Lewis acid additive. Although this reaction was well conceived, the optimum yield was only 6%. The electrochemically induced reaction, with methyl tosylate as a donor, 1-octanethiol as an acceptor, and a sacrificial Zn electrode, afforded a 60% yield of methylated product, but this required high catalyst loading (15%); the total turnover number (TON) was 4, compared to the TON of 2.4 in the reaction of Keese and Dabre.⁵ It was shown

that the Zn^{2+} cation from the zinc sacrificial electrode was necessary for efficiency, because it both activated the methyl group and extended the lifetime of the nucleophilic Co(I) species.

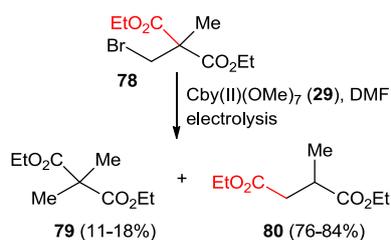


Scheme 20 Cobyrinate **29** catalyses the methyl transfer reaction cycle for *N,N*-dimethylaniline (**73**) and 1-hexanethiol (**76**) (6% yield).

8 REARRANGEMENTS

Once again, nature provided the chemist with a brief insight into perfection with the vitamin B_{12} -catalysed rearrangement reaction. The rearrangement occurs via an interchange of a hydrogen atom with a C, O, or N atom from neighbouring groups in reactions assisted by methylmalonyl CoA mutase, glutamate mutase, and α -methyleneglutarate mutase.

To mimic this natural method in a non-enzymatic way, the rearrangement catalysed by alkylcobalamins was studied. However, the first, strictly catalytic procedure was not reported until the 80's, by Murakami.³⁸ In that procedure (Scheme 21), 2,2-bis(ethoxycarbonyl)-1-bromopropane (**78**) underwent a catalytic rearrangement of the carbon skeleton under electrolysis, in the presence of Cby(II)(OMe)_7 (**29**). This reaction led to product **80** in 76-84% yield (with -2.0 V vs. standard calomel electrode), and the amount of byproduct **79** was minimized by carefully adjusting the reduction potential.



Scheme 21 A model of a rearrangement reaction catalysed by Cby(II)(OMe)_7 (**29**).

Similarly, rearrangements occur in reactive compounds in which one ester group is replaced with a thioester,³⁹ as well as 1-keto-2-bromomethyl-2-methylsuccinate.⁵ Migration rates for electron withdrawing substituents: $\text{COSR} > \text{COR} > \text{CO}_2\text{R} > \text{CN}$ strongly depend on both electronic and steric factors.³⁸ Smaller groups (*e.g.*, CO_2Et) tend to migrate faster than bulky groups (CO_2R), but regioselectivity is not very high (Table 10).

Table 10 Influence of steric hindrance on the 1,2-migration reaction

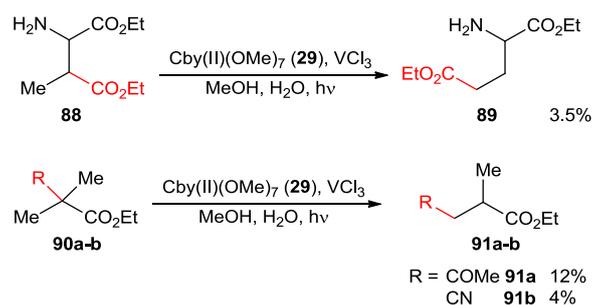
| R | Yield [%] | | |
|-----------------------|-----------|----|----|
| | 82 | 83 | 84 |
| a <i>t</i> -Bu | 29 | 44 | 24 |
| b cyclohexyl- | 24 | 47 | 22 |
| c Ph | 29 | 43 | 19 |

Furthermore, the $(\text{CN})(\text{H}_2\text{O})\text{Cby}(\text{OH})_7$ (**56**)/ TiO_2 hybrid catalyst and MOF-supported $\text{B}_{12}\text{-Ru}$ can catalyse 1,2-migration under, respectively, UV and visible light irradiation. This property eliminates the need for electrolytic conditions or the use of any additional reducing agent.^{5,25} In these reactions, the choice of solvent determines the rate of forming the unwanted reduced byproduct **87** (Table 11). *In DMF, the dehalogenation reaction predominates; but, in less polar solvents, 1,2-migration prevails.*

Table 11 The influence of solvent on product distribution in 1,2-migration reactions

| Solvent | Yield [%] | |
|---------|-----------|----|
| | 86 | 87 |
| DMF | 21 | 70 |
| MeCN | 39 | 44 |
| PhCN | 61 | 19 |

A common feature in all the substrates mentioned is the presence of bromine. However, Murakami demonstrated that simple diethyl β -methylaspartate (**88**; Scheme 22) and its analogues can undergo similar reactions in the presence of VCl_3 , under aerobic conditions, with Cby(II)(OMe)_7 (**29**) and light.^{5,38} Vanadium salt functions as a co-catalyst for activating the starting material and regenerating the Co(II) species. In these reactions, the migratory aptitude of electron-withdrawing groups follows the order: $\text{CN} < \text{CO}_2\text{C}_2\text{H}_5 < \text{COCH}_3$.

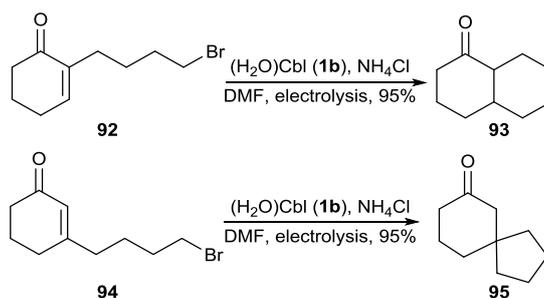


Scheme 22 The isomerisation of non-halogenated esters.

9 ADDITIONS TO DOUBLE BONDS

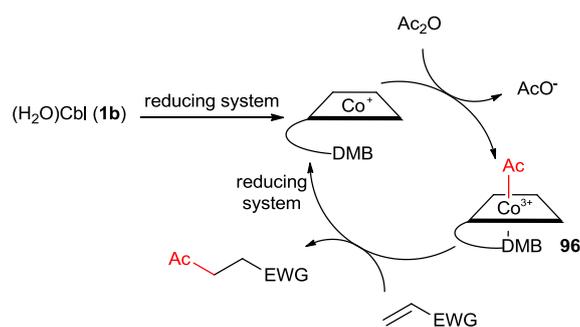
In our opinion, one of the most interesting B_{12} -catalysed reactions is the 1,4-addition to activated double bonds. Although *activated alkenes undergo hydrogenation when treated with reduced cobalamin in a protic environment* (section 5), *this can be eliminated by switching to aprotic conditions and adding a potential radical source; e.g., an alkyl halide.*

$(\text{H}_2\text{O})\text{Cbl}$ can catalyse bromoalkyl-cyclohexenone and 6-bromoalkyne cyclisation. This reaction leads to bicyclic products, under chemical or electrochemical conditions, and follows the Baldwin rules. It can afford six- and seven- membered rings by endocyclic closure or five- and six-membered rings by exocyclic closure (Scheme 23). Moreover, there is no evidence that tertiary alcohols form by carbonyl group attack or that polymeric products form by intermolecular 1,4-addition.¹²



Scheme 23 Intramolecular 1,4-additions catalysed by $(\text{H}_2\text{O})\text{Cbl}$ (**1b**).

Scheffold and Orliński described an intermolecular 1,4-addition of carboxylic anhydride to α,β -unsaturated aldehydes, ketones, nitriles, and esters.¹² This reaction started with the formation of acetylcobalamin (**96**), and after photolysis released an acetyl radical, which reacted with an olefin (Scheme 24).⁴⁰



Scheme 24 Proposed mechanism for acylating activated olefins, catalysed by $(\text{H}_2\text{O})\text{Cbl}$ (**1b**).

Scheffold formulated some basic principles for 1,4-addition reactions, as follows:

“[...] Cobalt complexes, suitable as catalysts in C-C bond forming reactions under reducing conditions should exhibit the following properties:

- 1) *they should easily and reversibly be reduced to the corresponding Co(I) complexes;*
- 2) *the Co(I) complexes should exhibit high nucleophilicity at Co and readily form organometallic intermediates that contain a Co-C bond with alkyl-, vinyl- and acyl-derivatives in rapid reactions;*

- 3) 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.
- 4) the cobalt complex should exhibit appropriate solubility and stability under the reaction conditions [...].⁴¹

Various alkyl-, vinyl- and acyl halides react equally well with activated olefins.^{41,42} With electrochemical reduction and microemulsion as a reaction medium, Rusling provided an alternative method for synthesis in conventional organic solvents.^{1,14,15,43} That methodology proved useful for synthesising prostaglandin derivatives and jasmonates, which corroborated its practicability for the synthesis of complex molecules.⁴²

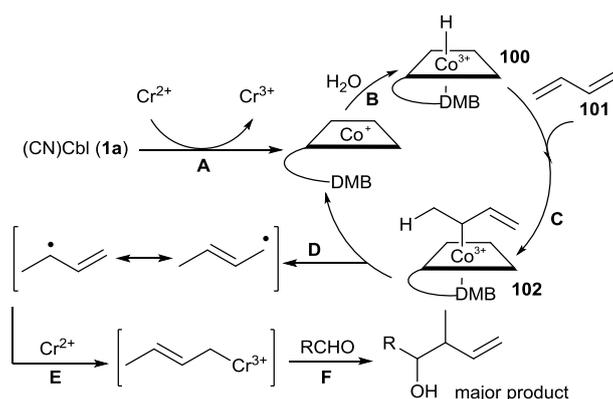
1,2-Stereoselection is highly efficient for adding alkyl bromides to prochiral, trisubstituted alkenes in the presence of (H₂O)Cbl (**1b**, 5% mol) and Zn. The steric hindrance imposed by the alkyl substituent increases both the yield and the diastereoselectivity (Table 12).⁴⁴

Table 12 Stereoselectivity in B₁₂-catalysed additions to unsaturated esters.

| R | Yield [%] | 98 : 99 ratio | |
|--------------------------|-----------|---------------|--|
| a <i>n</i> -hexyl | 63 | 60:40 | |
| b cyclohexyl | 81 | 96:4 | |
| c <i>t</i> -Bu | 90 | 99:1 | |

B₁₂ derivatives could catalyse additions to both a C=C bond and a C=O bond. When aldehydes react with simple 1,3-dienes in the presence of a catalytic amount of vitamin B₁₂ (**1**) and excess chromium(II) salt, they furnish unsaturated alcohols (Scheme 25).⁴⁵ This reaction gives excellent yields, exceeding 80%, both for aliphatic and aromatic aldehydes and for substituted and unsubstituted 1,3-dienes. *Note: high catalyst loading (10 mol%) was used.*

In the initial step (A), (CN)Cbl (**1a**) is reduced to the Co(I) form, which then reacts with water (B), giving Co(III) hydride intermediate **100**. Next, the diene **101** is added (C) to form organo-Co(III) species **102**. Then, it undergoes homolytic Co-C bond cleavage (D). This forms the allyl radical, which gives the corresponding allylchromium reagent (E), the latter then attaches to an aldehyde to afford an unsaturated secondary alcohol (F).



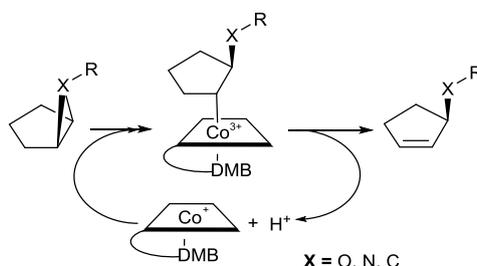
Scheme 25 Proposed mechanism for coupling of aldehydes with simple 1,3-dienes, catalysed by (CN)Cbl (**1a**).

10 RING-OPENING REACTIONS

The reactivity of cyclic compounds in ring-opening reactions strongly depends on ring size. Due to high strain, cyclopropanes, oxiranes, or aziridines are easily opened with various nucleophiles to provide acyclic derivatives. *Because reduced cobalamin displays strong nucleophilic properties, it effectively promotes this class of reactions.*

Cyclopropane ring cleavage was first achieved with reduced (CN)Cbl (**1a**) from cyclopropanes that possessed electron-withdrawing groups.³⁸ The corrin Co(I) species, generated *in situ*, attacks the unsubstituted position in cyclopropane, which results in C-C bond cleavage, and formation of an asymmetric centre at the substituted carbon atom. In final protonation of the generated anion gave two enantiomers, with low to moderate stereoselectivity, depending on the steric bulkiness imposed by cyclopropane substituents.

A similar mechanism operates for all ring-opening reactions catalysed by vitamin B₁₂ (**1**). For instance, when epoxides, aziridines, and cyclopropanes⁴⁶ are treated with the Co(I) catalyst, corresponding alkyl-cobalt(III) complexes form, and after dehydrocobaltation, they give allylic alcohols, amines, and olefins, respectively (Scheme 26).



Scheme 26 B₁₂-catalysed ring-opening reactions for epoxides, aziridines and cyclopropanes.

For epoxides, the nucleophilic attack on the ring is fast, but the elimination step proceeds slowly, and the reaction mixture has a red colour, characteristic of Co(III) compounds. Conversely, aziridines slowly react with the Co(I) species, which gives a brown-green mixture. In all cases, the S_N2 attack of a chiral catalyst determines the enantioselectivity of the reaction, and the following hydro-cobalt-elimination is a non-stereospecific process.

Other ring-opening reactions catalysed by (CN)Cbl (**1a**) or (H₂O)Cbl (**1b**) and reduced with Zn/NH₄Cl were used to synthesise optically-active allylic alcohols, amides, and compounds with malonic-acid-derivatives (Figure 3).

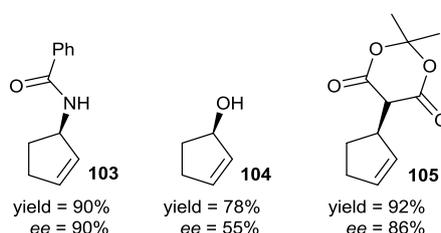


Figure 3 Optically-active products synthesised in (H₂O)Cbl-catalysed ring-opening reactions.

Opening of 1,2-epoxycyclopentane can be conducted in microemulsions. The best results were obtained in bicontinuous microemulsions of SDS/tetradecane/*n*-butanol/water, which

produced the desired product in 58% yield and 52% *ee*.⁴³ When the bicontinuous system was changed to a water-in-oil SDS microemulsion, the stereoselectivity of the reaction decreased, presumably due to lower solubility of the catalyst.

11 RING-EXPANSION REACTIONS

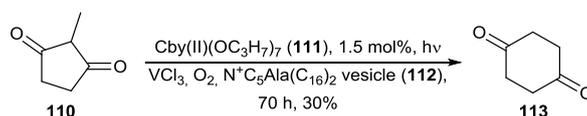
Ring-expansion reactions are important in the synthesis of cyclic compounds, particularly those difficult to access with other approaches. Typically, ring expansions operate by migrating to an exocyclic leaving group (e.g., Tiffeneau-Demjanov rearrangement) or by forming and opening a bicyclic intermediate (e.g., Buchner reaction). The latter pathway was suggested by Dowd for a one-carbon ring-expansion of cyclic α -(bromomethyl)- β -ketoesters. A radical mechanism for this process was also proposed;³⁸ The application of Bu_3SnH as a radical promoter for ring expansion reactions is significantly limited in organic synthesis, because numerous side reactions may occur. In contrast, *cobalamin derivatives provide a gentler, greener alternative*. Cby(II)(OMe)_7 (**29**) could electrochemically form a Co(III) -alkyl complex that after homolysis generated a radical, which rearranged to afford a ring-expanded product.³⁸ Ring size strongly influences the reactivity of different substrates. Eight-membered rings have the lowest reactivity (Table 13). The major expanded product of type **108** was accompanied by small amounts of esters **109** and reduced compounds **107**.

Table 13 Potential-controlled electrolysis of cyclic α -(bromomethyl)- β -keto esters, catalysed by Cby(II)(OMe)_7 (**29**)

| | | Electrolysis conditions | | | Yield [%] | | |
|----------|---------------------|---|------------|-----|-----------|--------|--|
| n | | Charge [$\text{F}\cdot\text{mol}^{-1}$] | Period [h] | 107 | 108 | 109 | |
| a | 1 (5-membered ring) | 1.0 | 8 | 1.5 | 43 | 0 | |
| b | 2 (6-membered ring) | 1.3 | 18 | 14 | 49 | 12 | |
| c | 3 (7-membered ring) | 1.2 | 12 | 3 | 44 | Traces | |
| d | 4 (8-membered ring) | 1.1 | 8 | 2 | 21 | 4 | |

Applying a photoredox catalyst and UV irradiation significantly increased the yield of product **108**. For example, when compound **106a** was reacted in the presence of the Cby(II)(OMe)₇ (**29**)/Rose Bengal system, the yield of the expanded ring product was 59%,²³ moreover, in the presence of the (CN)(H₂O)Cby(OH)₇ (**56**)/TiO₂ system, the yield was 80%.⁵

Similar to rearrangement reactions (section 9), ring-expansion does not always require a halogenated substrate. For instance, Cby(II)(OC₃H₇)₇ (**111**) efficiently catalyses the conversion of 2-methyl-1,3-cyclopentanedione to the respective, 6-membered cyclic product (Scheme 27).⁴⁷ In that reaction, vanadium trichloride acted as a reducing agent, which enabled formation of an alkyl-Co(III) complex, and UV-irradiation facilitated Co-C homolysis.



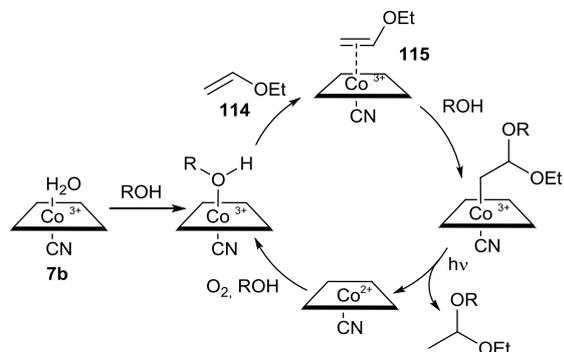
Scheme 27 Ring-expansion of non-halogenated cyclopentanedione **110**, catalysed by Cby(II)(OC₃H₇)₇ (**111**).

12 OXIDATION

The vast majority of vitamin B₁₂-catalysed reactions, but not all, proceed *via* the reductive pathway. Here, we describe oxidation reactions, where Cbl is an active catalyst in its +3 oxidation state.

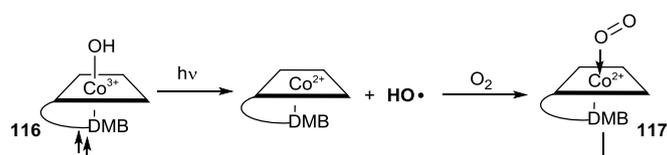
In 1976, Dolphin reported that double bond activation with cobalamins formed stoichiometric alkylcobalamins.⁴⁸ More recently, Murakami and Hisaeda provided a clear example, where the addition of alcohols to ethyl vinyl ether (**114**), catalysed by B₁₂-derivatives, afforded acetaldehyde acetals (Scheme 28).⁴⁹ Between (CH₃)(H₂O)Cby(OMe)₇ and (CN)(H₂O)Cby(OMe)₇ (**7b**) as catalysts, compound **7b** was more effective (TON = 10 and TON = 60, respectively). It was postulated that the axial cyano ligand imposed a substantial *trans* effect, which facilitated cleavage of the Co(III)-C bond in an intermediate. Then, acetal

was formed, and the resulting Co(II) species was oxidized to the active Co(III) form by ambient oxygen. The reaction was only efficient for electron-rich olefins; non-activated olefins, like pentene or cyclohexane, provided only modest yields.



Scheme 28 Addition of alcohols to vinyl ethyl ether, catalysed by $(\text{CN})(\text{H}_2\text{O})\text{Cby}(\text{OMe})_7$ (**7b**)

Shell and Lawrence recently reported another example of oxidation catalysed by vitamin B₁₂ (**1**; Scheme 29).⁵⁰ With light irradiation, the Co(III)-OH bond in hydroxocobalamin (**116**) was homolytically cleaved, which released a hydroxyl radical that cleaved DNA plasmid strands. In the presence of oxygen, the catalyst **116** was regenerated, and it catalysed multiple turnovers.



Scheme 29 Generation of the hydroxyl radical in the presence of (HO)Cbl (**116**) and oxygen.

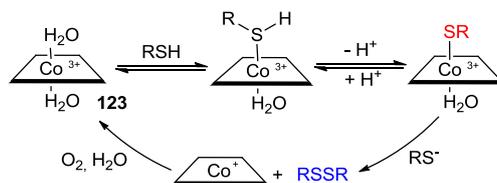
Vitamin B₁₂ (**1**) also catalyses the oxidation of organic and inorganic compounds, like thiols, hydrazine, nitric oxide, and nitrite.^{35a,51} For example, aerobic oxidations of 2-mercaptoethanol (**118**) and dithioerythritol strongly depend on which catalyst is used. Surprisingly, cobinamides without a nucleotide loop displayed much higher reaction rates than the corresponding cobalamin derivatives. $(\text{H}_2\text{O})_2\text{Cbi}$ (**123**) was the most effective (Table 14).⁵¹

Table 14 Rates for oxidation of 2-mercaptoethanol (**118**) with different B₁₂-derived catalysts.

| $2 \text{ HO-CH}_2\text{-CH}_2\text{-SH} \xrightarrow{\text{catalyst, O}_2} \text{HO-CH}_2\text{-CH}_2\text{-S-S-CH}_2\text{-CH}_2\text{-OH}$ | | |
|---|------------|-------------------------|
| $\begin{matrix} 118 & & 119 \end{matrix}$ | | |
| Catalyst | | Rate [s ⁻¹] |
| (CN)Cbl | 1a | 0.003 |
| (H ₂ O)Cbl | 1b | 0.003 |
| MeCbl | 1c | 0.080 |
| AdoCbl | 1d | 0.180 |
| AdoCbi ^a | 120 | 0.230 |
| MeCbi ^a | 121 | 0.560 |
| (CN)Cbi ^a | 122 | 191 |
| (H ₂ O) ₂ Cbi | 123 | 211 |

^a Second ligand was not specified.

The catalytic mode of action starts by substituting the aqua ligand with a thiol molecule to form a Co(III)-S complex, which reacts with the thiolate anion (Scheme 30). In this process, a disulphide bond is formed, and the cobalt species is reduced to its first oxidation state. In the final step, the catalyst is regenerated by molecular oxygen. Catalysts that are derivatives with alkyl ligands require a preliminary step, where light induces the decomposition of the Co-alkyl species to give an active aqua form.



Scheme 30 Catalytic oxidation of thiol derivatives.

13 CONCLUSIONS

Since its first isolation, vitamin B₁₂ (**1**) has been regarded as a co-enzyme, important for many biological processes. Subsequently, extensive studies in the field of organic chemistry have successfully applied cobalamin (**1**) as a catalyst in numerous organic reactions, including: dehalogenation, aryl and alkyl halide dimerisations, 1,4-additions to activated double bonds, hydrogenation of double bonds, *etc.* Also, because it does not adversely affect the environment, this exceptionally eco-friendly, natural, nontoxic, organometallic compound holds promise as an environmentally benign catalyst. Vitamin B₁₂ (**1**) catalytic activity relies

on its rich redox chemistry and its unique ability to form and cleave the Co-C bond. Most B₁₂-catalysed reactions require reducing conditions, where the stable Cbl(III) undergoes reduction. The reduced species, either the radical Co(II) or the “supernucleophilic” Co(I), form a Co-C bond that can be cleaved with electrolysis or light irradiation, in a controlled manner, to furnish highly reactive carbon species, which then react with various radicals or carbon-electrophiles.

Furthermore, the catalytic activities of vitamin B₁₂ (**1**) and its derivatives strongly depend on the presence of the nucleotide loop. Catalysis can be influenced by various reducing agents, solvents, and light. For example, activated alkenes undergo hydrogenation when treated with reduced cobalamin in a protic environment. This reaction can be eliminated by switching to aprotic conditions and adding a potential radical source; e.g., alkyl halide.

In this review, we highlighted many different types of synthetic organic reactions catalysed by vitamin B₁₂ (**1**). This knowledge will provide a starting point for further in-depth studies.

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GRAPHICAL ABSTRACT

Vitamin B₁₂ Catalysed Reactions

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This tutorial review focuses on cobalamin as a natural, nontoxic, environmentally benign cobalt catalyst for synthetically useful organic reactions.

