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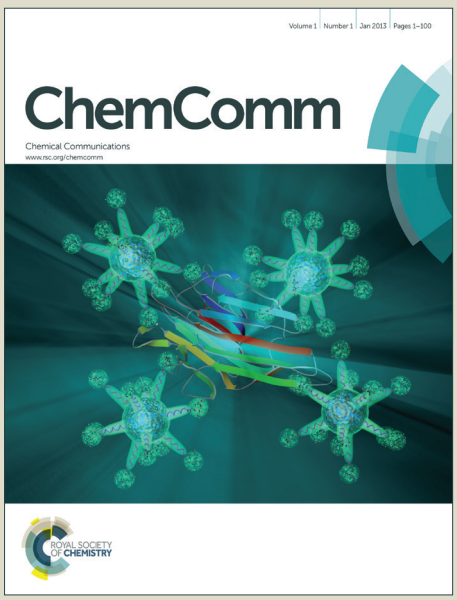

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Amphiphilic, catalytically active, vitamin B_{12} derivative

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

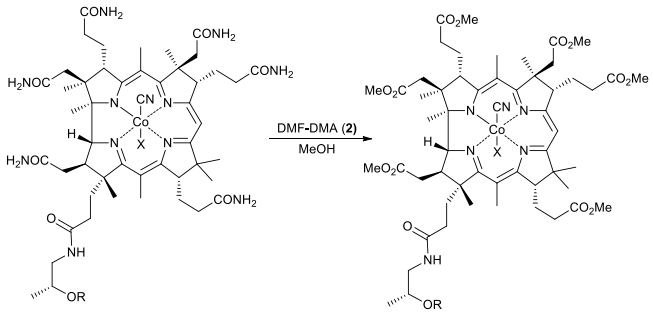
We reacted vitamin B_{12} with *N,N*-dimethylformamide dimethyl acetal for primary amide activation, and added MeOH as a nucleophile, to afford cobalester, the first amphiphilic cobalamin derivative. The unique combination of redox properties and solubility represents an asset for its use as a catalyst in C-C bond forming reactions.

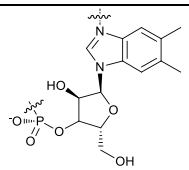
Among many biologically important metals, Co, in the form of vitamin B_{12} (cyano-cobalamin **1**), plays a unique role.[1,2] B_{12} coenzymes are indispensable for catalyzing enzymatic rearrangements (coenzyme B_{12}, adenosylcobalamin) and methylation reactions (methylcobalamin).[1] The special ability of vitamin B_{12} (**1**) and other corrinoids to form a Co-C bond, combined with its facility in furnishing alkyl radicals *via* homolysis, has attracted the interest of many researchers, because corrinoids can be used as catalysts for C-C-bond forming reactions, which belong to the most challenging processes in organic synthesis.[3] These catalytic reactions typically involve alkyl-cobalt complexes, which are formed in reactions of Co(I) species and an electrophile or a Co(II) and a radical.[4] The most common chemical procedure utilizes the 'supernucleophilicity' of the Co(I) species (B_{12}s) toward alkylating agents, such as alkyl halides. Homolysis of the Co-C bond generates a carbon-centered radical, which can, *in situ*, disproportionate, abstract H˙, or self-couple. In these reactions, B_{12} alkyl derivatives can be considered 'reversible carriers' of an alkyl radical.

To study the catalytic function of corrinoids in the hydrophobic microenvironment of enzyme active sites, Hisaeda and co-workers used cobyrinic acid derivatives as artificial enzymes. They were successfully used for dehalogenation, rearrangement, and ring expansion reactions.[4–7] These corrinoids, devoid of the nucleotide loop, possess chemical and physical properties different from those of the parent vitamin B_{12}. Importantly, in alkylcobalamins, the intramolecular nucleotide enhances the ease of abstraction of the cobalt-alkyl group by an electrophile.[8]

We hypothesized that a hydrophobic derivative that retained the nucleotide loop would provide a better model for such haloenzymes and serve as better catalysts for organic reactions. This B_{12} derivative would require the conversion of cobalamin's amide groups into esters. Typically, transformation of primary carboxamides into esters entails harsh reaction conditions. Brocchetta[9] and Myers,[10] however, showed that primary amides can be selectively activated and transformed into esters or secondary amides under mild conditions *via* the formation of formamidine, which subsequently reacts with nucleophiles (Table 1). Because the secondary amides remained intact, we reasoned that this methodology might be promising for selective modification of the primary amides in vitamin B_{12} leaving the nucleotide unaffected.

Table 1. Synthesis of cobalester (**3**) and cobinester (**5**)



Entry	R	X	Substrate	Product
1		-	**1**	**3**
2	H	CN	**4**	**5**

We report herein the synthesis of an amphiphilic, catalytically active, analog of cobalamin (**1**), prepared *via* a one-step procedure, starting with vitamin B_{12} (**1**).

Initially, CNCbl (**1**) was treated with DMF-DMA (**2**) in MeOH, at room temperature for up to 4 days. The reaction led mainly to pentamethyl ester with an intact nucleotide loop. By increasing the amount of activating reagent and prolonging the reaction time, the desired cobalester (**3**) formed in very low amounts (1%). A substantial improvement in yield and selectivity was achieved when HFIP (hexafluoroisopropanol) was used as a solvent; this afforded cobalester (**3**) at 72% yield (for detailed optimization studies, see the ESI†). The positive influence of this polar, low nucleophilic solvent was previously reported; a similar effect was recently observed in hypervalent iodine-catalyzed reactions.[11–13] Our method was also applied successfully to the synthesis of cobinester (**5**), a hydrophobic derivative of cobinamide (**4**).

The structure of cobalester (**3**) was confirmed by MS spectrometry, UV-Vis and NMR spectroscopy, and elemental

analysis. The ESI-MS showed a signal at *m/z* = 1445.57, which corresponded to a pseudomolecular ion $[M+H]^+$. In the ^{1}H NMR spectra, six proton resonances at 3.45, 3.68, 3.71, 3.72, 3.75, and 3.76 ppm, which were assigned to six -OMe groups, confirmed the replacement of six -$CONH_2$ with -CO_2Me groups. Ultimately, crystallization of the product by vapor diffusion of Et_2O into EtOH gave crystals suitable for X-ray analysis, which unambiguously confirmed its structure (Figure 1). As expected, product **3** displays UV-Vis characteristics that are nearly identical to the parent vitamin B_{12} (**1**), but significantly different from from heptamethyl cobyrinate ($(CN)_2$Cby$(OMe)_7$ (see ESI†). The spectrum also confirmed that cobalester (**3**) exists in a 'base on' form.[14] The derivative **3** did not bind to the specific B_{12}-transporting proteins at the concentrations as high as 1 μM, which confirms the crucial role of side chain amides in the B_{12} binding.

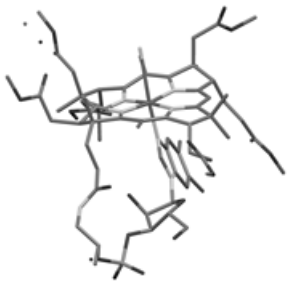


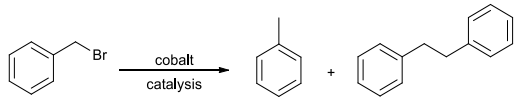
Fig. 1. Cobalester (**3**) X-ray structure

The corrinoid catalysis goes via the reduced forms, Co(II) and Co(I), whose formation depend on the nature of the axial ligands attached.[1] In cobalamin and cobalester, these ligands are identical; consequently, their reduction potentials are very similar. Both compounds displayed the same cathodic E_{pc*} values of -1.04 V vs. Ag/AgCl electrode (see ESI†), measured in an aqueous solution ([Tris] = 0.2 M, pH = 8.0) with CV.

With this redox behavior and excellent solubility in a broad range of organic solvents, the new amphiphilic ester **3** is capable of catalyzing C-C bond forming reactions. Reduced cobalamin can serve as a catalyst in various organic reactions, including dehalogenation,[15] cyclopropane ring cleavage,[16] additions to activated alkenes,[15] functional group migrations,[17] and alkene dimerization.[18] Typical obstacles encountered in B_{12}-catalyzed reactions include the low solubility of vitamin B_{12} (**1**) in organic solvents, high catalyst loading, and a limited number of reducing agents suitable for synthetic applications.

The radical homocoupling of benzyl bromide (**6**) is a typical model reaction for measuring the catalytic activity of reduced vitamin B_{12} (**1**). It was previously found that, depending on the Co-catalyst (vitamin B_{12}, salen, CoPcTS), the reaction furnishes either toluene (**7**) or bibenzyl (**8**) *via* an anionic or a radical pathway, respectively.[19]

The benzyl radical formed can undergo further reactions, such as H radical abstraction from a solvent, homocoupling, or addition to activated double bonds.[15,19,20] The cobalamin-catalyzed reaction predominantly afforded bibenzyl (**8**), but at a moderate yield (64%).



Scheme 1. Homocoupling of benzyl bromide (**4**)

Tanaka *et al*. showed that benzyl radicals can also be obtained by the photoinduced cleavage of cobalt (III) complexes, *cis*-$[R_2Co(bpy)_2]ClO_4$, in the presence of benzyl halides.[21] Other methods for producing this conversion include the homocoupling of halides in the presence of various metals[22,23] (Ni, Mg, Mn, Zn, Cu, In, Cr, Fe, Ti), the homocoupling of Grignard compounds,[24] oxidative coupling,[25] Heck cross coupling,[26] the Wittig reaction followed by reduction[27] etc. Though effective, these methods involve expensive reagents and/or ligands, high catalyst loading, environmental hazards, and difficulties in catalyst recycling. Consequently, interest remains high for the discovery of new, environmentally-benign methods that address these issues.

In our studies, the chemical reduction of cob(III)alester (**3**) to Co(I) species was performed with $NaBH_4$/*i*-PrOH at an elevated temperature; then, it was reacted with benzyl bromide (**6**). In a typical experiment, all reagents were placed in a flask and allowed to react under deoxygenated conditions. The reaction at room temperature was very sluggish, but under microwave irradiation, it quickly proceeded to completion. A short optimization study demonstrated that the cobalester-catalyzed, microwave-assisted, reaction of benzylbromide (**6**) at 90 °C for 15 min furnished the desired bibenzyl (**8**) in 84% yield (Table 2, entry 4). Gratifyingly, the catalyst loading could be as little as 0.5 mol%, which represents the lowest amount required to date in similar B_{12}-catalyzed reactions. Surprisingly, when the reaction was heated in an oil bath, it furnished bibenzyl (**8**) at a low yield, despite the prolonged reaction time required for full conversion (entries 6, 7). For a detailed description of the optimization studies, see ESI†.

Table 2. Optimization studies[a]

Entry[a]	Catalyst loading [mol%]	Temperature [˚C]	Time [min]	Yield [%][b]
1	1.5	120	15	84
2	0.5	120	15	86
3	0.25	120	15	42
4	0.5	90	15	84
5	0.5	60	15	10
6[c]	0.5	reflux	15	traces
7[c]	0.5	reflux	60	58[d]

[a] Reaction conditions: BnBr (0.25 mmol), *i*-PrOH (1 mL), $NaBH_4$ (0.5 mmol), unless otherwise noted, the reactions were performed in a microwave reactor. [b] Isolated yields. [c] Oil bath was used instead of microwave irradiation. [d] Full conversion.

These reaction conditions render the method significantly simpler and more useful than other procedures reported to date; for example requiring electrochemical reduction, which limits their synthetic applicability.[15,19–21,28] After establishing optimized reaction conditions, we investigated the scope of benzyl bromide (**6**) dimerizations catalyzed by our cobalester (**3**). Benzyl bromides with either electron donating or electron withdrawing substituent were tested (Table 3).

Table 3. Substrate scope[a]

Entry	R	Catalyst loading [mol%]	T [°C]	Product	Yield [%]
1	H	0.5	90	**8**	84
2	4-I	0.5	90	**9**	74
3	3-I	0.5	90	**10**	70
4	4-NO_2	0.5	90	**11**	traces
5	4-NO_2	2.5	120	**11**	56
6	2-CN	2.5	120	**12**	52
7	4-F	0.5	90	**13**	90
8	3-OMe	0.5	90	**14**	91

[a] Reaction conditions: $ArCH_2Br$ (0.25 mmol), *i*-PrOH (1 mL), $NaBH_4$ (0.5 mmol), 15 min; all reactions were performed in microwave reactor.

All reactions with cobalester (**3**) gave the desired products, with yields exceeding 50%. Benzyl bromides with electron withdrawing substituents initially formed toluene derivatives. However, an increase in the catalyst loading (to 2.5%) and temperature (to 120 °C) led to the formation of the desired products, **11** and **12** (entries 5 and 6). Although the range of substrates was not exhaustive, the reaction appeared to be quite general. It has been shown that intramolecular coordination of the nucleotide function labilizes the organometallic C-Co bond in alkylcobalamins, which facilitates subsequent reactions.[2]

With our series of vitamin B_{12} derivatives, with and without the 5,6-dimethylbenzimidazole moiety, we were in a position to verify this hypothesis (assuming formation of benzyl-Cbl as an intermediate of the reaction). We evaluated effectiveness of catalysts in the dimerization of benzyl bromide (**6**) under optimized conditions. A comparison of reactions in the presence of reduced cobalester (**3**) and $(CN)_2Cob(OMe)_7$ indicated that the nucleotide moiety increased the yield of bibenzyl (Table 4, entries 3, 5). Interestingly, ester derivatives were by far more efficient than vitamin B_{12} (**1**) and cobinamide, presumably due to differences in solubility (Table 4).

Table 4. Catalyst evaluation[a]

Entry	Catalyst	Conversion [%]	Yield [%][b]
1	Vitamin B_{12} (**1**)	38	15
2	Cobinamide (**4**)	43	21
3	Cobalester (**3**)	100	84
4	Cobinester (**5**)	100	60
5	$(CN)_2Cob(OMe)_7$	100	62

[a] Reactions were conducted with BnBr (0.25 mmol), *i*-PrOH (1 mL), $NaBH_4$ (0.5 mmol), catalyst (0.5 mol%), at 90 ˚C (microwave heating) for 15 min. [b] Isolated yields.

Conclusions

In summary, we have developed a new, efficient method for preparing cobalester (**3**), an amphiphilic vitamin B_{12} derivative. This derivative has esters instead of six amide groups, and an intact nucleotide. The reaction of vitamin B_{12} (**1**) with DMA-DMF (**2**) in HFIP provided the desired compound **3** in 72% yield. As expected, cobalester (**3**) displayed UV-Vis spectra and oxidation-reduction characteristics similar to those of vitamin B_{12} (**1**). Both compounds differed significantly from the ”incomplete” corrinoid heptamethyl cobyrinate, where the nucleotide moiety is absent, and instead, the second cyanide is coordinated. We confirmed the hypothesis that the intramolecular coordinating ligand plays a role in the radical reactions catalyzed by vitamin B_{12} derivatives. The microwave-assisted homocoupling of benzylbromide (**6**) catalyzed by cobalester (**3**) produced a higher yield when compared to reactions catalyzed by reduced $(CN)_2Cob(OMe)_7$. The amphiphilic character of this newly synthesized derivative (**3**) will facilitate a broader range of applications for vitamin B_{12}-catalyzed reactions in organic synthesis.

Generous support from the Ministry of Science and Higher Education, grant no. 0145/DIA/2012/41.

Notes and references

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† Electronic Supplementary Information (ESI) available: detailed synthetic procedures, full characterisation of new compounds, biological tests and stability tests. CCDC 981457. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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