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Vitamin B_{12} and a metal–organic framework enable the photocatalytic generation of alkyl radicals†

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A versatile Co-catalyst-vitamin B_{12} (cobalamin)-can be photochemically reduced to its catalytically active Co(I) form under visible light irradiation, in the presence of MIL-125-NH_2(Ti) as a photocatalyst and utilized for the generation of alkyl radicals. The prior reduction of cobalamin to the Co(II) form is not required in this method.

Vitamin B_{12} (**1**, cobalamin, Fig. 1) is a natural cobalt complex that acts as a cofactor in many biochemical processes including isomerisations, methyl transfer, and dehalogenation.[1] Inspired by these natural processes, chemists have utilised this unique biomolecule as a Co-catalyst in multiple transformations,[2,3] including dehalogenations,[4] alkylations, dimerizations, strained ring openings,[5,6] cyclopropanations,[7,8] ester and amide formation,[9] tandem addition to double bonds,[10] *etc.*[11] The redox chemistry of the central cobalt cation plays a crucial role in these processes, and the oxidation state of the central metal ion defines the philicity and, consequently, the chemical behaviour of the entire molecule. Vitamin B_{12} in the +3 oxidation state can be reduced to either the radical Co(II) or supernucleophilic Co(I) species.[1] The effective reduction of cobalamin(III) to the catalytically active Co(I) form can be achieved by either chemical, photochemical, or electrochemical means (Ep = −0.04 V *vs.* SCE for Co(III) to Co(II) and Ep = −0.85 V *vs.* SCE for Co(II) to Co(I).[12] Thus, reducing agents, such as activated metals (Zn, Mn) or sodium borohydride, are most commonly used. However, some functional groups, such as aldehydes, halides, and disulphides, are not compatible with the reductive conditions.

Recently, photochemical approaches to the generation of the supernucleophilic Co(I) species have been broadly investigated. The Hisaeda group reported the photochemical reduction of vitamin B_{12} derivatives under (a) homogeneous conditions, utilizing iridium[13] or ruthenium[9] photocatalysts and blue light irradiation, and (b) heterogeneous conditions using TiO_2 and ultraviolet (UV) irradiation.[14] These approaches, however, usually require: (1) pre-reduction of the Co(III) to the Co(II) state, or (2) irradiation with a highly energetic UV light, or (3) the use of precious transition metals as photocatalysts. Recently, Barata–Vallejo *et al.* described the first photochemical reduction of vitamin B_{12}, which was achieved *via* electron transfer from Rose Bengal in the excited state, with TMEDA as a sacrificial reductant under green light irradiation.[15] As important as this advance is, the system appears to function only in water and is limited to perfluoroalkyl partners in aromatic substitution. Thus, a more general and greener photocatalytic system is needed for the vitamin B_{12} reduction, that will broaden the applications of this sustainable Co-catalyst.

Photoredox-active metal–organic frameworks (MOFs) have emerged as versatile photocatalysts due to their modular, easily tuneable architectures, ultrahigh porosity, good e–h separation, and visible light absorption capacity.[16] This prompted us to explore vitamin B_{12}-mediated catalysis with MOFs acting as electron transfer agents under visible light irradiation. Thus

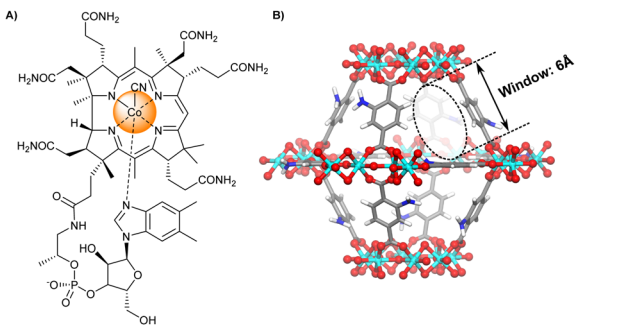

Fig. 1 (A) Vitamin B_{12} (**1**, cyanocobalamin); (B) MIL-125-NH_2(Ti) structure, grey-carbon, white-hydrogen, red-oxygen, light blue octahedral-titanium, blue-nitrogen.

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far, the only precedent of a photocatalytic system composed of vitamin B_{12} and a MOF, was published by Xu *et al.*, who immobilised $[Ru(bpy)_3]^{+2}$ and heptamethyl cobyrinate perchlorate, a hydrophobic vitamin B_{12} derivative, on a mix-metal zirconium–ruthenium MOF ($Zr_4Ru_2(bpdc)_4 \cdot 4C_2NH_8 \cdot 9DMF$, bpdc = biphenyl-4,4′-dicarboxylic acid).[17] In this system, however, the MOF acts as a solid support only and the pre-prepared Co(II) complex is reduced to Co(I) by electron transfer from the Ru-photocatalyst.

Herein, we demonstrate the visible light-induced photochemical reduction of vitamin B_{12} employing MIL-125-NH_2(Ti) as the sole photoredox catalyst and its use in the generation of alkyl radicals.

Among the numerous photocatalytic MOFs, Ti(IV)-based MIL-125-NH_2 (MIL-125-NH_2(Ti)) has attracted our attention because of its exceptional hydrolytic stability and the ability to absorb visible light due to the presence of amino groups in the organic linker (Fig. 1B). It has a band gap of 2.7 eV and its UV-Vis adsorption band extends to around 550 nm, exhibiting two maxima at 330 and 375 nm.[18] Upon light irradiation, MIL-125-NH_2(Ti) undergoes reversible ligand-to-metal charge transfer (LMCT) with transient formation of mixed-valent Ti^{+4}/Ti^{+3} clusters, that makes it an attractive candidate for an electron transfer reagent.[19] There are, indeed, several reports describing photocatalytic applications of this MOF, mainly focussing on CO_2 reduction,[20–22] N_2 fixation,[23] water remediation,[24–26] hydrogen evolution,[27] and the synthesis of *N*-benzyl-1-phenylmethane-imines.[28,29]

These reports on MIL-125-NH_2(Ti) acting as a photoredox catalyst under blue light irradiation made us question whether it can serve as a photoreductant for cobalamin (**1**). To test this hypothesis, a mixture of vitamin B_{12} (**1**) and a large excess of MIL-125-NH_2(Ti) in EtOH was irradiated with blue light (450 nm) for 15 minutes. The mixture turned orange-brown, suggesting efficient reduction of cobalamin(III) to cobalamin(II) (Fig. 2A, blue line). Comparison of the UV-Vis spectrum of the supernatant (with maximum at 470 nm) with the reported spectroscopic features of different forms of vitamin B_{12} (**1**) corroborates the generation of cobalamin in the +2 oxidation state.[30] Thus, MIL-125-NH_2(Ti) alone can reduce vitamin B_{12} (**1**), but only in a single electron transfer process. As the addition of amines have an impact on the catalytic property of MOFs,[31] the reduction was performed in the presence of DIPEA. Efficient photogeneration of the Co(I) species occurred, as confirmed by the optical absorption of the reaction mixture at 390 nm (green line). To shed light on the role of DIPEA, a mixture of MIL-125-NH_2(Ti) and DIPEA in EtOH was irradiated with blue light for 15 minutes. After this time, the MOF changed colour from yellow to blue – a characteristic for Ti(III) complexes (for details see ESI†).[20] Charge transfer from DIPEA, acting as a sacrificial electron donor, fills electron holes on the MOF linkers and stabilizes the photogenerated Ti(III). The photoreduced Ti^{4+}/Ti^{3+} MOF (blue) was separated, washed to remove DIPEA, and reacted with cob(II)alamin in the dark. The UV-vis spectrum of the supernatant shows that under these conditions, the MOF alone is able to reduce cob(II)alamin to its catalytically active Co(I) form, although the reduction is not complete (for details, see ESI†). Apparently, Ti^{3+} in the pre-reduced blue MOF, having a negatively charged framework, is a stronger reductant than the short-lived, charge separated Ti^{3+} species, which are formed in the absence of DIPEA. Despite that an excess of MOF was used, the reduction of the Co(II) species was not complete. We presume that the whole process takes place on the surface of the MOF, that and electron hopping through the porous semiconducting MOF is negligible. Reek, van der Vlugt, and Gascon have shown that even cobaloximes that are smaller than vitamin B_{12} do not penetrate the MIL-125-NH_2(Ti) framework (6 Å).[32]

Next, the newly developed MOF-based catalytic system for the photoreduction of vitamin B_{12} to the Co(I) intermediate was tested in a model C–C bond forming transformation. We chose a simple cyclization of *N*-substituted tosylamides (Table 1),[33] as this intramolecular reaction was proved to be catalysed by cob(I)alamin. Indeed, in the presence of vitamin B_{12}, MIL-125-NH_2(Ti) and DIPEA, desired product **3a** formed in 59% yield

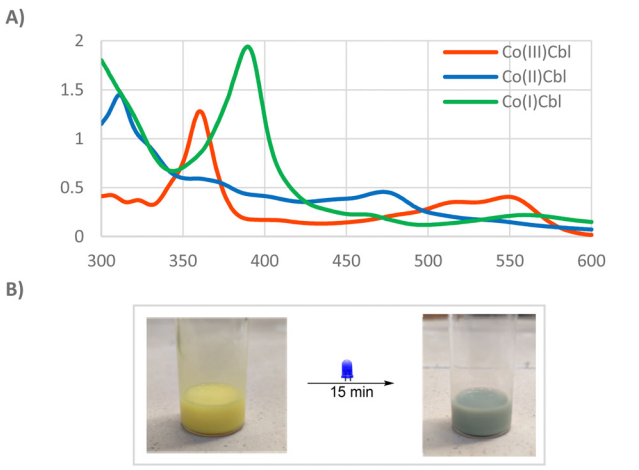
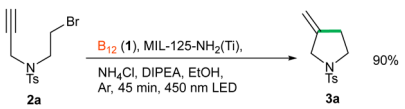


Fig. 2 (A) Measured UV-Vis spectra of cobalamin (**1**) with cobalt in different oxidation states; cob(III)alamin (orange), cob(II)alamin (blue), and cob(I)alamin (green). (B) A mixture of MIL-125-NH_2(Ti), DIPEA in EtOH before and after irradiation with 450 nm LED irradiation for 15 min.

Table 1 Summary of the optimisation studies



Entry	Deviation from optimal conditions	Yield (%)
1	^{i}PrOH, NH_4Cl (53 mg, 4 equiv.), DIPEA (175 µl, 4 equiv.) 7 W single LED, 18 h	59[a]
2	no **1** or no MIL or no DIPEA or no Ar or no light	0
3	TiO_2 and amino terephthalic acid instead of MIL	Traces
4	$[Ti(Cp)_2]Cl_2$ instead of MIL, 450 nm and 525 nm	Traces
5	TiO_2 instead of MIL-125-NH_2, 254 nm irradiation	Traces
6	TPP(Co) instead of **1**	20
7	Cobaloxime $ClCo(dmgH_2)py$ instead of **1**	3
8	No NH_4Cl	49
9	TEA instead of DIPEA	49
10	4-cyanophenol instead of NH_4Cl	39

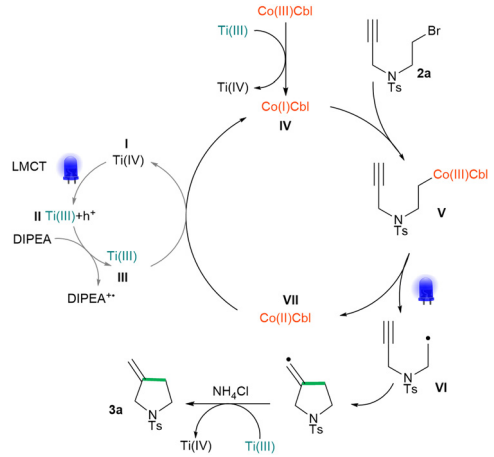
Reaction conditions: B_{12} (**1**, 0.5 mol%), MIL-125-NH_2(Ti) (2.5 mol%), substrate (**2a**, 0.25 mmol), DIPEA (2 equiv.), NH_4Cl (0.5 equiv.), EtOH (2 ml), inert gas (Ar), 450 nm LED 100%, 45 min; yields determined by GC. [a] Isolated yield.

(Table 1, entry 1). Background experiments revealed that the reaction does not proceed without catalysts, sacrificial electron donor, Ar atmosphere, or light (entry 2). The reaction in the presence of TiO_2 and 2-amino terephthalic acid gave only traces of product, pointing to the key role of the intimate connection between the organic ligands and titanium-oxide clusters (entry 3, TiO_2 (-0.25 V *vs.* NHE), MIL-125-NH_2 (-0.75 V *vs.* NHE)). Swapping MIL-125-NH_2 for other titanium compound like $[Ti(Cp)_2]Cl_2$ or TiO_2 while under proper irradiation, (entries 4 and 5) gave the same results. Evaluation of various reaction's parameters, such as Co-catalyst type, sacrificial electron donors, additives, reaction time, wavelength of light, and intensity of light (for full data, see ESI†) enabled the synthesis of the desired product in 90% yield. The use of simplified models of vitamin B_{12}, such as cobaloxime or cobalt porphyrin, results in strongly decreased yields (entries 4 and 5). The presence of NH_4Cl improves the yield (entry 8), yet other proton donors do not exhibit a similar behaviour (entries 9 and 10), a feature often encountered in Zn-assisted reductions of vitamin B_{12}.[5,10] Interestingly, among several other ammonium salts tested (see ESI†), only those with the NH_4^+ cation increased the yield, suggesting that the salt acts as a proton donor. For a closer investigation, reactions were performed in C_2D_5OD and in the presence of ND_4Cl. We not only observed a strong kinetic isotope effect (>8 h reaction time *vs.* 45 min) but also 95% incorporation of the deuterium atom in the product (according to ^1H NMR, see ESI†) corroborating the formation of a carbanion during the catalytic cycle. Other MOFs (MIL-101-NH_2, UiO-66-NH_2, MUV-11, MIL-101-SO_3H/Na, HKUST-1) absorbing in the visible region do not catalyse the cyclization reaction (for details see ESI†), suggesting that the synergistic action of Ti clusters and 2-aminoterephthalate antennas is indispensable for efficient photoreduction of cobalamin.

To confirm the crucial role of MIL-125-NH_2(Ti) and the heterogeneous nature of the process, a split test was performed. Thus, the reaction mixture was irradiated for 25 min and then divided into two halves (yield 8%). One half of the mixture was irradiated for another 20 min, while the other half was filtrated before irradiation for another 20 min. The first part afforded product **3a** in 87% yield, while the second part in only 10%, meaning that the reaction does not proceed without the solid MOF photocatalyst, and is not catalysed by any species leaking from the MOF during the reaction.

One of the most important features of the newly developed heterogeneous system is the possibility to recover the MOF catalyst. Thus, a set of three consecutive reactions was performed that gave the desired product in 69% (I run), is 74% (II run), and 83% (III run). Although the MOF was thoroughly washed after each round, the increase in yield might be attributed to the adsorption of vitamin B_{12} on the MOF surface, thus increasing the catalyst loading.

Based on the literature data and experimental indications, we propose the following mechanism for the cyclisation reaction (Scheme 1). First, the electron pair on the MOF linker is excited with 450 nm LED light, and LMCT from the amino group to the Ti(IV) node occurs. Next, DIPEA donates an electron and fills the positively charged hole on the linker.

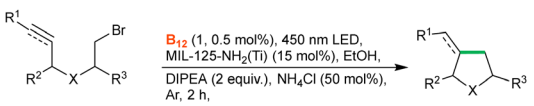


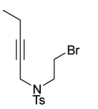
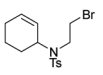
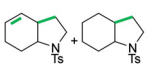
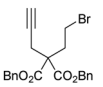
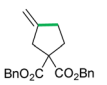
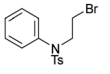
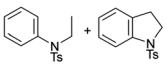
Scheme 1 The proposed mechanism for radical cyclization.

The Ti^{3+}/Ti^{4+} nodes of the now negatively charged framework reduce vitamin B_{12} **1** to cob(I)alamin **IV**. The latter reacts in an S_N2 manner with alkyl bromide **2a** to form Co–C complex **V**. The weak Co–C bond is then homolytically cleaved with 450 nm LED light to yield alkyl radical **VI**, which undergoes intramolecular cyclization followed by reduction and protonation to form final product **3a**. The radical character of the reaction was corroborated by the radical trap experiment (see ESI†).

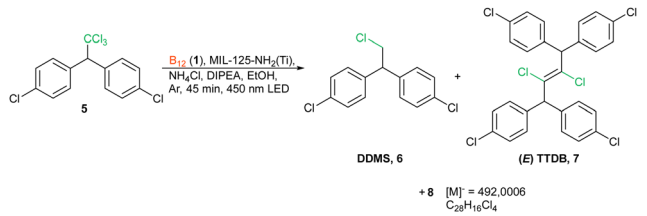
In the next step, several analogues of the model substrate were tested under the same reaction conditions (Table 2). In all six cases, very good to excellent yields were obtained. Interestingly, for compound **2c**, the intermediate radical does not

Table 2 Photocyclization of several analogues of the model substrate **2a**



Entry	Substrate		Product		Yield (%)
1		**2a**		**3a**	85
2		**2b**		**3b**	85 $E:Z$ ~ 1:1
3		**2c**		**3c**	77
4		**2d**		**3da + 3db 7 : 1**	90
5		**2e**		**3e**	76
6		**2f**		**3fa + 3fb**	20 + 17

Reaction conditions: B_{12} (**1**, 0.5 mol%), MIL-125-NH_2(Ti) (6.0 μmol per molar weight), substrate (**2a**, 0.25 mmol), DIPEA (0.5 mmol, 2 equiv.), NH_4Cl (0.125 mmol, 0.5 equiv.), EtOH (2 ml), inert gas (Ar), 450 nm LED, 2 h; isolated yields.



Scheme 2 Photochemical dehalogenation of DDT.

rearrange to the more stable benzyl radical. Substrate **2d** yielded a side product with fully saturated cyclohexyl ring (**3db**), which is consistent with the literature precedents wherein olefinic precursor transforms into a mixture of saturated and unsaturated compounds. About group tolerance, aldehydes and chlorides are well tolerated while *E*-olefin isomerizes into *Z*-form (50%) and disulphide fully decomposes (for details see ESI†).

The excellent activity and heterogeneous nature of the MOF predisposed them to water and soil remediation for the degradation of organic pollutants. This is also true for cobalamin and its derivatives, which are effective in dechlorination reactions.[34] Consequently, we used our newly developed system in the dehalogenation of 4,4′-dichlorodiphenyl-trichloroethane (**5**, 4,4′-DDT). Usually, the reaction leads either to a mixture of various derivatives[4,35] or to dichlorodiphenyl-dichloroethane (4,4′-DDD) as the main product.[13,17,36] In the presence of our newly developed catalytic system, the reaction yields three main products **6–8** with full substrate conversion (Scheme 2). Compound **8** has a dimeric structure and possesses only four chlorine atoms. Interestingly, mono dehalogenation (4,4′-DDD) was not observed, in contrast to previously known methods. This compound forms solely when the reaction was performed in the presence of only MOF (40% conversion), corroborating the crucial role of vitamin B_{12}.

In conclusion, we have developed the first direct, visible light-induced photochemical reduction of native vitamin B_{12} to the supernucleophilic Co(I) form using an easily available and inexpensive MOF photocatalyst, MIL-125-NH_2. Gratifyingly, the method does not require a prior reduction of vitamin B_{12} to the Co(II) form. Furthermore, the amount of vitamin B_{12} in these reactions is as low as 0.5 mol%, and the MOF co-catalyst can be recovered without substantial loss of activity. The utility of the system is demonstrated in the synthesis of pyrrolidine derivatives and the dehalogenation of DDT.

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Conflicts of interest

There are no conflicts to declare.

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