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Photoinduced Vitamin B_{12}-Catalysis for Deprotection of (Allyloxy)arenes

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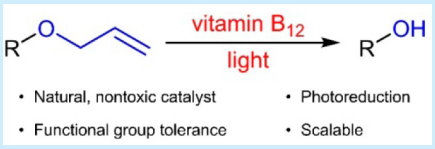
Supporting Information

ABSTRACT: Vitamin B_{12} is a natural cobalt complex that, while reduced to the "supernucleophilic" Co(I) form, can easily react with electrophiles via an S_N2 mechanism. It is also shown to react via an S_N2' mechanism with allylic compounds allowing for photochemical deprotection of (allyloxy)arenes. A sustainable alternative to commonly used noble metal-catalyzed deprotection reactions is presented.



Nature builds and decomposes complex molecules with the help of enzymes and light as the ultimate energy source. However, despite enzymes' fundamental benefits, their industrial application can be limited by bioavailability, instability toward certain reaction conditions, or narrow substrate tolerance. A complementary approach involves bioinspired methods and in this line vitamin B_{12} (**1**, cobalamin) (Figure 1),

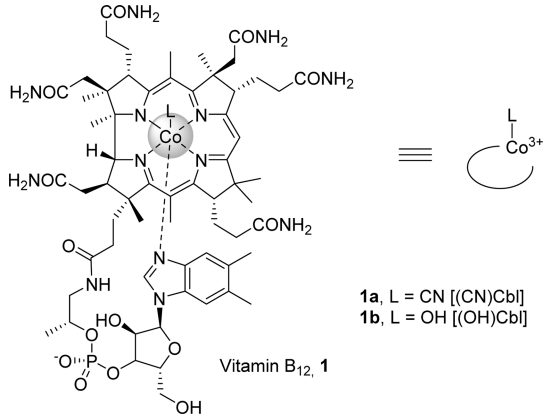
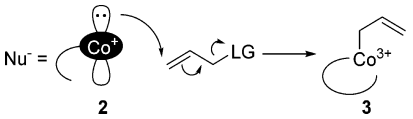


Figure 1. Structure of vitamin B_{12} (**1**, cobalamin, Cbl).

which in natural systems plays the role of cofactor for adenosyl- and methylcobalamin-dependent enzymes, creating numerous opportunities. Though underdeveloped, vitamin B_{12} catalysis is particularly appealing, due to the following: (a) a remarkable stability of this highly functionalized cobalt complex with no risk of metal leakage; (b) complete nontoxicity and easy consumption by nature; (c) commercial availability.[1]

To date, vitamin B_{12} **1** has been exploited in dehalogenation of polychlorinated compounds, functional group migration, dimerization of benzyl halides, cyclopropanation and cyclopropane ring opening, alkylation of olefins, and synthesis of esters and amides from (trichloromethyl)benzene, just to name a few.[2−4] These processes rely on the redox properties of the central Co(III) cation, which can be reduced to radical Co(II)- or "supernucleophilic" Co(I)-species **2**. Most vitamin B_{12}-catalyzed reactions involve Co(I)-form **2**, as it readily reacts with electrophiles affording alkylcobalamins, usually via a typical S_N2 mechanism.[1a,5] We envisaged that vitamin B_{12} "supernucleophilic" Co(I)-form **2** should also react with electrophiles in the S_N2' manner provided that a suitable partner is present (Scheme 1).

Scheme 1. A Hypothesized Nucleophilic Conjugated Substitution of the Allyl Group



Nucleophilic conjugated substitution is common for allylic compounds bearing a good living group. Hence, *O*-allylphenols should react with reduced vitamin B_{12} **2** generating allylcobalamin **3** and phenolate that upon protonation furnishes the desired phenol.[2] This concept can have broad ramifications if applied to the protection−deprotection strategy for the hydroxyl group, as phenols are common motifs in natural products and biologically active compounds.[6] Currently, the deprotection of (allyloxy)arenes involves the use of strong bases, acids, Pd, or other noble metals,[7] which renders development of environmentally benign alternatives highly desirable.

In order to test our hypothesis, 2-(allyloxy)naphthalene (**4a**) was reacted with a catalytic amount of vitamin B_{12} **1a** in the presence of the Zn/NH_4Cl reducing system (Scheme 2). The reaction worked very well, giving 2-naphthol (**5a**) in 87% yield. If such a result could be obtained so effortlessly, then progression into a much greener alternative is a must. Could

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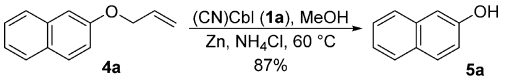
Scheme 2. Model Deprotection Reaction



native cyanocobalamin **1a** be activated by light e.g. photochemically reduced to Co(I) **2** and as such used in our deallylation reaction?

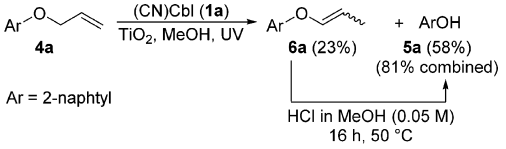
Recently, Hisaeda's group has succeeded in photochemical reduction of heptamethyl cobyrinate (Cby) and applying it to dehalogenation reactions,[8] but photochemical reduction of vitamin B_{12} **1a** still remains challenging.

In our initial experiments TiO_2 was used as the photoredox mediator, UV irradiation (254 nm) as the light source, and MeOH as both the solvent and sacrificial electron donor. In the presence of vitamin B_{12} **1a** the deprotection of (allyloxy)-naphthalene (**4a**) afforded desired product 2-naphthol (**5a**) in 59% yield. The reaction proved highly chemoselective; only *O*-allyl-ethers were cleaved while *O*-benzyl- and *O*-Me remained intact.

In the next step, the reaction conditions were optimized with respect to solvent, catalyst, crystalline type of TiO_2, and its loadings. Among all polar solvents tested, only simple alcohols afforded desired compound **5a**, and the highest yield was obtained for the reaction in MeOH (see Supporting Information (SI)). Reactions in the presence of pure mineral TiO_2 forms: rutile or anatase gave the same result as a polymorphic nanopowder mixture; therefore, the latter was used in subsequent experiments (see SI). The optimal loading of vitamin B_{12} **1a** was found to be 6 mol % (see SI), although even 2 mol % gave comparable results.

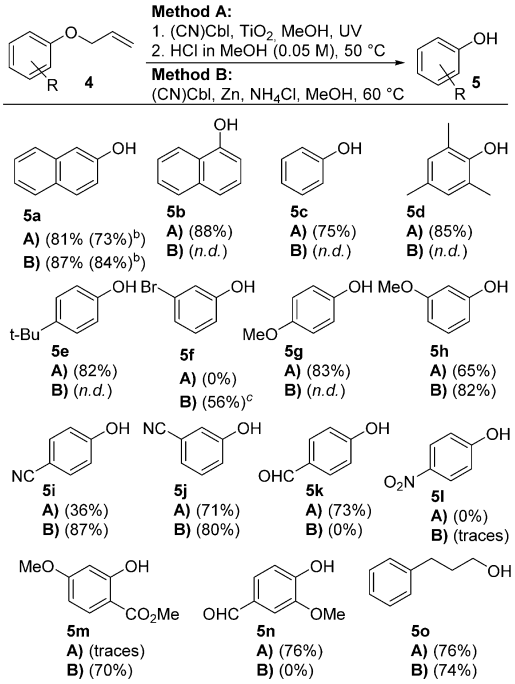
Moreover, a detailed analysis of the reaction mixture revealed the presence of a side product (**6a**), which could be quantitatively transformed into desired naphthol **5a** by treating it with HCl_{aq} in MeOH, at a concentration as low as 0.05 M, for 16 h at 50 °C (Scheme 3).

Scheme 3. Isomerization of 2-Alliloxynaphthalene (4a)



At this point, we had two sets of conditions: the first using the optimized photochemical **Method A** and the second involving our initial discovery using Zn/NH_4Cl (**Method B**). The scope and limitations of both methods were examined (Scheme 4). Under light irradiation (254 nm), phenols with electron-withdrawing and -donating substituents reacted equally well. For example, methoxy-derivative **5g** was obtained in 83% yield and *p*-hydroxybenzaldehyde (**5k**) in 73% yield with no formyl group reduction observed. Gratifyingly, photochemical **Method A** assured the formation of an even more synthetically important product, *p*-vanillin **5n**. Some (allyloxy)arenes were problematic; e.g., in the deprotection of (allyloxy)-3-bromo-benzene (**4f**) the unwanted debromination process predominated. This problem was diminished when catalyst **1a** was reduced with the Zn/NH_4Cl system, resulting in desired product **5f** being favored. **Method B** was also found to be superior for salicylic acid derivative **4m**, giving desired product **5m** in 70% yield. To our delight, also *O*-allyl-protected

Scheme 4. Scope and Limitation Studies



[a]Reaction conditions: **Method A**: (i) (allyloxy)arene (**4**, 0.5 mmol), TiO_2 (0.5 equiv), (CN)Cbl (**1a**, 6 mol %), MeOH (2 mL), 20 h, UV light (254 nm); (ii) HCl_{aq} in MeOH (0.05 M, 10 mL), 50 °C, the reaction was monitored by TLC until completion; **Method B**: (allyloxy)arene (**4**, 0.5 mmol), Zn (6 equiv), NH_4Cl (3.4 equiv), (CN)Cbl (**1a**, 6 mol %), MeOH (2 mL), 20 h, 60 °C. [b]Reaction conducted on a larger scale: 0.5 g (2.7 mmol). [c]In a 2.7:1 mixture of product **5f** and debrominated phenol **5c** (76% combined yield).

aliphatic alcohols can be deprotected utilizing our methodology in a very good yield.

In a subsequent study, the scale-up of our catalytic protocols was explored. The photochemical reaction of 2-(allyloxy)-naphthalene (**4a**) on a scale of 0.5 g (2.7 mmol) gave desired product **5a** in 73% yield, compared to the 81% yield in the test scale. Similarly, the reaction using the Zn/NH_4Cl system proceeded smoothly with only a 3% difference in the yield compared to the model reaction.

The use of protecting groups, for which deprotection could be achieved by photochemical means, is an attractive approach.[9] Thus, we considered our newly developed methodology as a promising tool in the synthesis of highly functionalized molecules bearing the phenol unit. This strategy is especially important in peptide synthesis; therefore, tyrosine was chosen to examine orthogonality with other protecting groups.

First, model compounds **7** and **9** bearing variously protected carboxyl or amino groups respectively were tested under developed conditions (Scheme 5). In both methods methyl ester **7a** gave product **8a** in a good yield while *tert*-butyl-2-(4-(allyloxy)phenyl)acetate (**7b**) proved to be more compatible with the Zn/NH_4Cl **Method B** system (88% yield). Expectedly, reducing conditions were incompatible with benzyl ester **8c**, which cleaved rapidly. In the case of an amino group, *O*-allyl tyramine derivatives protected with either Ac- (**9a**) or Boc- (**9b**) groups were subjected to our reaction. The photocatalytic method gave products **10a** and **10b** in moderate yields, but the use of Zn/NH_4Cl allowed for an increase in the yield up to 69%

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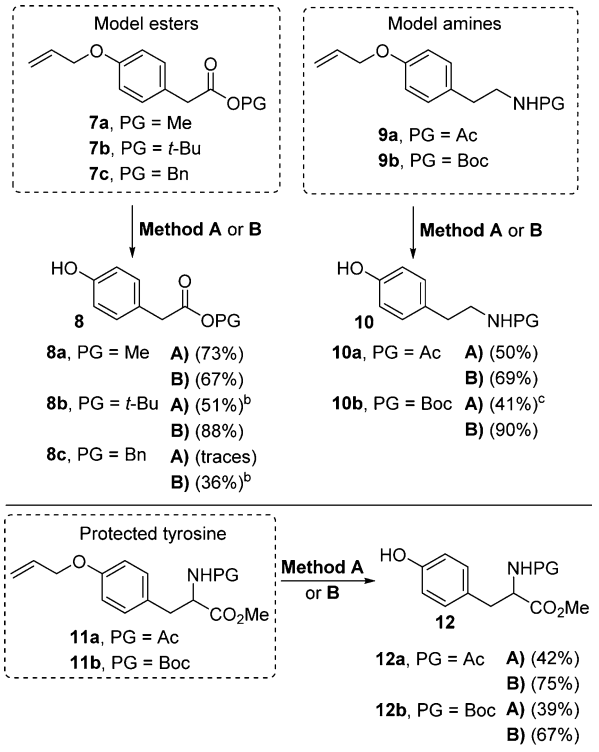
Scheme 5. Deprotection of Functionalized Phenols



[a]Reaction conditions: **Methods A** and **B** as described in Scheme 4. [b]Transesterification occurred; product **8a** was isolated. [c]No acid treatment was performed.

for substrate **9a** and 90% for *N*-Boc-protected derivative **9b**. Finally, we examined methyl esters of *N*-Ac- (**11a**) and *N*-Boc-protected (**11b**) L-tyrosine. In both cases chemical reduction proved superior, allowing for isolation of compounds **12a** and **12b** in 75% and 67% yield, respectively. The photochemical method also gave desired compounds in moderate yields.

In order to establish the mechanism for the deprotection of (allyloxy)arenes, several experiments were conducted. First, we proved that each reaction's component (vitamin B_{12}, TiO_2, and light, or Zn, NH_4Cl) is required for the reaction to take place (Table 1, entries 1–3, 7, and 8). Second, isolated (vinyloxy)-

Table 1. Mechanistic Studies

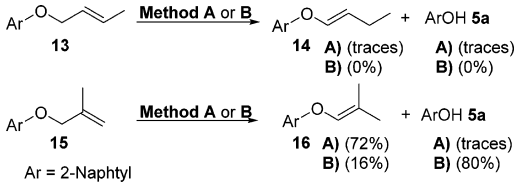
entry	substrate	catalyst	hν or *t*	reductant	**5a** (%)[b]
1	**4a**	**1a**	UV	TiO_2	81
2	**4a**	–	UV	TiO_2	10
3	**4a**	**1a**	–	TiO_2	0
5[a]	**4a**	**1c**	UV	HCO_2Na	traces
6	**6a**	**1a**	UV	TiO_2	0
7	**4a**	**1a**	60 °C	Zn, NH_4Cl	87
8	**4a**	–	60 °C	Zn, NH_4Cl	traces

[a]Cby(II) **1c** and HCO_2Na were used to ensure the presence of the Co(II) form in the reaction mixture. [b]Isolated yields.

arene **6a** did not decompose to 2-naphtol (**5a**) when subjected to standard reaction conditions (entry 6). Hence, this compound is not an intermediate but rather a byproduct. Third, the addition of TEMPO, a radical scavenger, did not allow for detection of carbon radical intermediates, and as a consequence, a radical mechanism was excluded. Moreover, the desired phenol **5a** did not form in the reaction catalyzed by heptamethyl cobyrinate possessing Co in the +2 oxidation state (Table 1, entry 5), contrary to reactions in which stronger reducing agents were employed (Table 1, entries 1 and 7). This observation corroborates the participation of Co(I)-form **2** as an active species. The reaction in deuterated methanol afforded products with deuterium exclusively incorporated at the terminal carbon of the double bond as revealed by NMR (see SI).

Moreover, it is known that the relative rate of cleavage versus isomerization depends on the substitution on the allyl moiety.[7c] On that account, we performed experiments with substituted allyloxy derivatives **13** and **15** (Scheme 6).

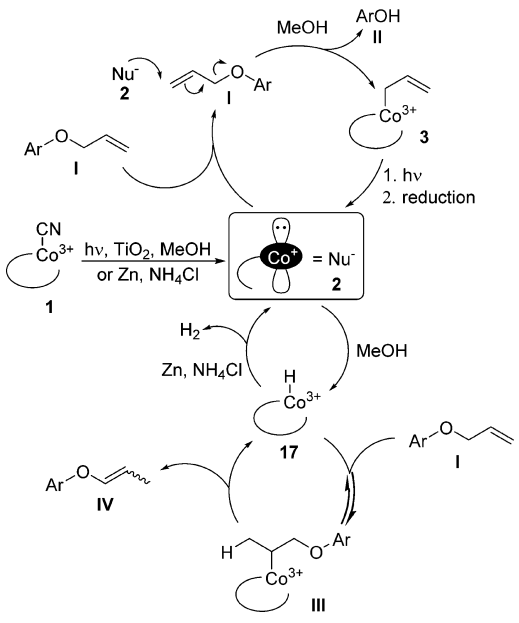
Scheme 6. Deprotection of Substituted (Allyloxy)naphthalenes



Expectedly, crotyl derivative **13** was inert in both methods. 2-Methylprop-2-enyl ether (**15**) furnished predominantly trisubstituted vinyl derivative **16** under photochemical conditions, but in the presence of Zn/NH_4Cl deprotection predominated. It can be rationalized by the accessibility of an acidic proton and the effect of a stronger reducing agent in the latter case. It has been firmly established that such conditions promote hydrogen evolution[10] thus lowering the concentration of Co(III)–H species. As a result, the contribution of the isomerization pathway is diminished.

The proposed mechanism for the vitamin B_{12}-catalyzed deallylation is presented in Scheme 7. Based on the experimental evidences, we assume that, first, vitamin B_{12} **1a** is reduced either photochemically or chemically to the catalytically active Co(I)-form **2**. Then, the nucleophilic

Scheme 7. Plausible Mechanism for Vitamin B_{12} Catalyzed Deallylation



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conjugated substitution yields phenol **II** and vinylcobalamin **3** possessing a Co−C bond that is easily cleaved under photochemical or thermal conditions. On the other hand, the isomerization reaction is believed to involve cobalamin hydride **17**, resulting from the reaction of supernucleophilic Co(I)-form **2** with MeOH. Such observations remain in good agreement with those of Norton, who reported the facile isomerization of double bonds mediated by cobalt hydride,[11] and of Hisaeda and Shimakoshi, who recently proposed a mechanism of hydrogen evolution in which vitamin B_{12} derived cobyrinic acid hydride is involved.[12] The alkylcobalamin **III** formed undergoes dehydrocobaltation generating isomerized product **IV** and hydridocobalamin (Co(III)-H) **17** that upon reduction regenerates the catalyst or reacts with the next molecule of (allyloxy)arene **I**.

In summary, native vitamin B_{12} **1** can be reduced photochemically to its catalytically active Co(I)-form **2** and as such catalyzes the cleavage of the C−O bond in allyl-aryl ethers. The photochemically induced reaction tolerates starting materials bearing various functional groups, including: −CN, $-CO_2Me$, −OMe, and even very reactive −CHO. The reaction seems also promising for deprotection of aliphatic alcohols. Additionally, for less reactive substrates, the Zn/NH_4Cl reducing system can be used. Newly developed methodology proved chemoselective; only *O*-allyl-ethers are cleaved while *O*-benzyl- and *O*-Me remained intact. Compared to known processes our methods do possess advantages, such as mild photochemical conditions, the exclusion of harsh acid or bases, and elimination of precious metal catalysts, e.g. Pd.

Mechanistic investigations imply that photochemically formed vitamin B_{12} "supernucleophilic" Co(I)-form **2** is an active form of the catalyst, and as such it reacts with *O*-allylphenols in the S_N2' manner. Moreover, our studies strongly support previous reports on the involvement of a cobalt-hydride intermediate in the isomerization of the double bond, though direct evidence has not yet been found.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01012.

Experimental procedures, optimization studies, ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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