Green molecular transformation by a B_{12} -TiO₂ hybrid catalyst as an alternative to tributyltin hydride[†]

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The B_{12} -TiO₂ hybrid catalyst was effectively used for the radical reactions, such as 1,2-migrations of phenyl groups and acyl groups under irradiation by UV light, and the selectivity of the reaction was controlled by the solvent system.

A compound with a cobalt–carbon bond, which was found as the key intermediate in the B_{12} (cobalamin derivative)dependent enzymic reaction, is a useful reagent for the generation of an organic radical species.¹ The cobalt-carbon bond can be homolytically cleaved by photolysis, electrolysis or thermolysis to form Co(II) and the corresponding radical species.² Therefore, application of the alkylated complex for the radical-mediated organic synthesis is quite interesting from the viewpoint of organometallic and catalytic chemistries.³ Based on this idea, we have been investigating the cobalamin derivative, heptamethyl cobyrinate perchlorate, which has ester groups in place of the peripheral amide moieties of the naturally occurring vitamin B₁₂, and succeeded in performing various molecular transformations, such as the 1,2-migration of functional groups, asymmetric reductions, ring expansion reactions, the addition of alkyl radicals to olefins and the reductive dechlorination of organic halides by an electrochemical technique.4-8 To achieve these reactions, one of the most significant properties of cobalamin is the high nucleophilicity toward various alkyl halides in its Co(I) state.9 Recently we reported the new catalytic system of the B₁₂-TiO₂ hybrid catalyst where B₁₂ was immobilized on the surface of TiO2.¹⁰ As band gap excitation of the TiO₂ produced a conduction band electron under irradiation by UV light,¹¹ it was strong enough to reduce the Co(II) state of B_{12} to form the reactive Co(1) species by TiO2.10 This hybrid catalyst was used for the dechlorination of various chlorinated organic compounds, such as 1,1-bis(4-chlorophenyl)-2,2,2trichloroethane (DDT), under irradiation by UV light. Therefore, the B₁₂-TiO₂ hybrid catalyst was considered to be an efficient and green catalyst while using a simpler and more facile system. We now report the further application of this green catalyst for molecular transformation. Utilizing the property of the B_{12} -TiO₂ hybrid catalyst to form a radical species, the 1,2-migration of the functional group with a radical intermediate was successfully mediated by the B12-TiO2 hybrid catalyst. The mechanism of the reaction was also investigated.

The B_{12} -TiO₂ hybrid catalyst was prepared by the reaction of cyanoaquacobyrinic acid [(CN)(H₂O)Cob(III)7COOH]Cl



Fig. 1 Structure of B₁₂ derivative.

(Fig. 1) (ESI[†]) and TiO₂ powder (P-25; a mixture of rutile (20%) and anatase (80%) with a BET surface area of 50 m² g⁻¹, Japan Aerosil) as the reported method.¹⁰

A diethyl 2-bromomethyl-2-phenylmalonate (1) substrate and authentic sample of diethyl 2-methyl-2-phenylmalonate (3) were synthesized from diethyl phenylmalonate (ESI†). The catalytic reaction was carried out using the following procedure. To a solution of 1 (29.5 mg, 9.0×10^{-5} mol) in 30 mL of ethanol, 20 mg of the hybrid catalyst (B₁₂ content, 5.6×10^{-7} mol) was added, and nitrogen gas was bubbled through to degas the oxygen. The solution was stirred for 10 h at room temperature under irradiation by 365 nm UV light (1.76 mW cm⁻² at 12 cm distance). After the reaction, the hybrid catalyst was readily separated from the products by centrifugation or filtration.

Table 1 1,2-Migration of a phenyl group catalyzed by B_{12} -TiO₂ system^a

Entry	Catalyst	Conversion ^b (%)	Products (yield ^{b} (%))	
			2	3
1	B ₁₂ -TiO ₂	95	28	65
2	B_{12} -Ti O_2^c	Trace	_	
3	B_{12} , Ti O_2^d	43	12	29
4	B_{12} , Ti O_2^e	46	14	31
5	TiO ₂ ^f	Trace		
6	\mathbf{B}_{12}^{g}	Trace	_	_

^{*a*} Condition: [substrate] = 3.0×10^{-3} M, catalyst (B₁₂-TiO₂) = 20 mg (B₁₂,1.86 × 10⁻⁵ M), solvent C₂H₅OH 30 mL under N₂ at room temperature, reaction time = 10 h. ^{*b*} Conversions were estimated by the recovery of the substrate. Yields were based on initial concentration of the substrate. ^{*c*} In the dark. ^{*d*} Condition: [substrate] = 3.0×10^{-3} M, TiO₂ (P-25, 20 mg), [(CN)(H₂O)Cob(III)7COOH]Cl, 0.6 mg, solvent C₂H₅OH 30 mL under N₂ at room temperature, reaction time = 10 h. ^{*e*} Condition: [substrate] = 3.0×10^{-3} M, TiO₂ (P-25, 20 mg), heptamethyl cobyrinate perchlorate, 0.6 mg, solvent C₂H₅OH 30 mL under N₂ at room temperature, reaction time = 10 h. ^{*f*} Unmodified TiO₂ (P-25, 20 mg) was used as the catalyst. ^{*g*} [(CN)(H₂O)Cob(III)7COOH]Cl, 0.6 mg.

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The products were analyzed by NMR and GC-mass spectroscopies. Formation of the phenyl migrated product, diethyl benzylmalonate (2), was confirmed by spectroscopic comparison to a commercially available authentic sample. The results are summarized in Table 1. Almost all of the substrate was converted to products, and the phenyl migrated product (2) was formed along with the formation of the simply reduced product (3) as expressed by eqn (1). When TiO₂ and the B₁₂ derivative were separately added, conversions were decreased to half as shown by entries 3 and 4 in Table 1, respectively. The reaction did not proceed when we used the unmodified TiO₂ or B₁₂ alone as shown by entries 5 and 6 in Table 1, respectively. Therefore, the B₁₂–TiO₂ system is expected to be an efficient and green alternative for the *n*-Bu₃SnH–AIBN system.¹²‡

In order to determine the source of the hydrogen in the products, the reactions shown in eqn (2) were carried out in C_2D_5OD , C_2D_5OH and C_2H_5OD . The distributions of the products were analyzed by GC-MS, and the results are summarized in Table 2. Both 2' and 3' gained hydrogen from the ethanol solvent as shown by entry 1 in Table 2. The incorporation of deuterium into 2' did not occur during the reaction in C₂D₅OH as shown by entry 2 in Table 2. Eighty eight percent of the deuterium ion was incorporated into 2' in C₂H₅OD as shown by entry 3 in Table 2. Therefore, 2 was mainly produced from the anionic intermediate and was not directly formed from the radical intermediate. In contrast, 92% of the deuterium was incorporated into the simply reduced product 3' in C₂D₅OH as shown by entry 2 in Table 2. Thus, the selectivity of the reaction should be controlled by the solvent. Based on these results, the reaction was carried out in a less hydrogen radical donating solvent to improve the product selectivity. When we used DMF as the reaction solvent, the yield of the phenyl migrated product 2 decreased to 21% as shown in Table 3 since DMF is a good hydrogen radical donor.¹³ In contrast, the yield of 2 was increased in CH₃CN and significantly increased in PhCN, since PhCN has a strong C-H bond.

 Table 2
 Deuterium atom incorporation ratio from solvent^a

		D-atom incorporation ratio ^{b} (%)	
Entry	Solvent	2'	3'
1	C ₂ D ₅ OD	95	94
2	C ₂ D ₅ OH	4	92
3	C ₂ H ₅ OD	88	8

^{*a*} Condition: [substrate] = 3.0×10^{-3} M, catalyst (B₁₂-TiO₂) = 20 mg (B₁₂, 1.86×10^{-5} M), solvent 30 mL under N₂ at room temperature, reaction time = 10 h. ^{*b*} Deuterium atom incorporation ratios were determined by GC-MS.

 Table 3
 Solvent dependence of product distribution^a

	Conversion ^c (%)	Products (yield ^c (%))	
Solvent ^b		2	3
DMF	95	21	70
CH ₃ CN	85	39	44
PhČN	97	61	19

^{*a*} Condition: [substrate] = 3.0×10^{-3} M, catalyst = 20 mg (B₁₂, 1.86×10^{-5} M), solvent 30 mL under N₂ at room temperature, reaction time = 10 h. ^{*b*} Triethanolamine (200 mg, 1.35 mmol) was used as a sacrificial reagent. ^{*c*} Conversions were estimated by the recovery of the substrate. Yields were based on initial concentration of the substrate.

The reaction mechanism was also examined by the spin-trapping technique with α -phenyl *N*-(*tert*-butyl)nitrone (PBN). An ESR spectrum was observed for the PBN spin adduct formed during the photo-reaction: g = 2.006, $A_N = 14.6$ G, $A_H = 3.7$ G (10^4 G = 1 Tesla). Upon the addition of PBN, the formations of both products were inhibited. These results indicated that both **2** and **3** are formed from the same radical intermediate (**4**) under the present conditions.

The proposed reaction mechanism is shown in Fig. 2. The Co(II) complex is reduced to Co(I) by electron transfer from TiO₂ under irradiation by UV light.§ The hole was quenched by the solvent, ethanol (or triethanolamine). The corresponding alkylated complex is generated by the reaction of the supernucleophilic Co(1) with the substrate. The cobalt-carbon bond of the alkylated complex is subsequently cleaved by photolysis to form the substrate radical 4, which was detected by an ESR spin-trapping experiment. The hydrogen radical abstraction from the solvent simply afforded the reduced product 3. In PhCN, the primary formed substrate radical 4 was effectively converted to the phenyl migrated radical (5). The radical 5 should be reduced by TiO_2 or other reductant under irradiation by UV light to form the anionic intermediate (6) due to the two-electron-withdrawing group at the α position. The protonation of the thus formed 6 probably afforded 2. To confirm this step (B12-independent step), we synthesized the probe compound, diethyl 2-benzyl-2bromomalonate. Diethyl 2-benzyl-2-bromomalonate was transformed to the reduced product with an 88% deuterium incorporation in C₂H₅OD by the reaction of TiO₂ under irradiation with UV light as shown in Scheme 1 (ESI[†]).



Fig. 2 Proposed reaction mechanism.



This catalytic system was applied for ring-expansion reactions of alicyclic ketones (5, 6 and 7-membered rings) with a carboxylic ester and a bromomethyl group^{6,14} as shown in eqn (3). The reactions largely proceeded for all the substrates as shown in Table 4.



Table 4Ring expansion reaction catalyzed by the B_{12} -TiO2 system^a

1	Time/h	Conversion ^{b} (%)	Products (yield ^{b} (%))
	10	~99	80
2	12	~99	77
3	13	~99	80

^{*a*} Condition: [substrate] = 3.0×10^{-3} M, catalyst (B₁₂-TiO₂) = 35 mg (B₁₂, 1.21×10^{-5} M), solvent C₂H₅OH 30 mL under N₂ at room temperature, reaction time = 10-13 h. ^{*b*} Conversions were estimated by the recovery of the substrate. Yields were based on initial concentration of the substrate.

In summary, the B_{12} -TiO₂ hybrid catalyst inspired from the natural coenzyme B_{12} showed a high reactivity for molecular transformation under mild conditions. The present system was clean and economical in contrast to the conventional radical reagent from the viewpoint of green chemistry. Therefore, the present system would be readily applicable for the design of an eco-friendly catalyst.

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Notes and references

[‡] The same reaction was carried out using the conventional *n*-Bu₃SnH–AIBN system as follows. A solution of *n*-Bu₃SnH (10 μ L, 3.3 × 10⁻⁵ mol) and AIBN (0.5 mg, 3.0 × 10⁻⁶ mol) in benzene (10 mL) was added dropwise over 3 h to a refluxing solution of 1 (10 mg, 3.0 × 10⁻⁵ mol) in 10 mL of benzene. The products were analyzed and quantified by GC-MS with diphenyl as the internal standard. Yields: 2, 50%; 3, 47%.

§ Formation of Co(1) species of B_{12} on TiO₂ was confirmed by diffusion UV-vis spectroscopy with a reflectance maxima at 390 nm (Fig. S2 in ESI†).

¶ As the oxidized product, acetoaldehyde diethyl acetal was detected by GC-MS in C₂H₃OH. GC-MS (EI, *m/z*): $[M]^+$, 118; $[M - CH_3]^+$, 113; $[M - CH_3CH_2 + 1]^+$, 90. The decomposition of oxidized product for triethanolamine proceeds *via* a well-known sequence to diethanolamine and glycolaldehyde.¹⁵

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