Vitamin B_{12} Catalyzed Radical Cyclizations of Arylalkenes

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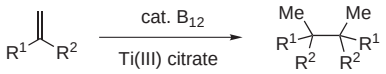
Abstract: The use of vitamin B_{12} for synthetic organic transformations has been extensively studied. Herein, we report the intramolecular cyclization reaction of a series of arylalkene substrates catalyzed by vitamin B_{12}. These reactions proceed in good yields in environmentally benign solvents and do not require the use of a toxic heavy metal catalyst. Variation of the reaction pH can predictably alter the product distribution.

Key words: vitamin B_{12}, radical cyclization, arylalkenes

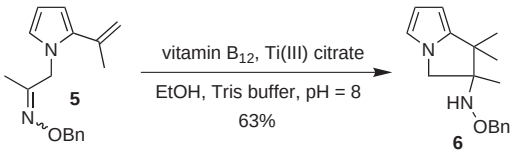
Vitamin B_{12} and its derivatives have received considerable attention for their use in synthetic organic chemistry,[1] including several recent new applications.[2,3] Vitamin B_{12} contains a cobalt atom surrounded by an equatorial corrin ring system. The chiral environment of the corrin ring has been utilized for the development of stereoselective B_{12} catalyzed reactions.[4] Covalently linked to the corrin is a dimethylbenzimidazole that reversibly occupies one of the axial coordination sites.[1] Herein we report an extension of our previously reported work on a novel reaction that utilizes vitamin B_{12} as a catalyst and Ti(III) citrate as a reducing agent. In that earlier study, the coupling of styrene derivatives or benzylic halides was reported with unusual regioselectivity providing α,α-dimers (Equation 1).[2] Mechanistic studies suggested that the reaction takes place through the intermediacy of benzylic radicals. This letter expands the scope of this reaction to intramolecular cyclization processes. In addition, the reaction mechanism was explored uncovering an interesting reversal of product distribution by altering the reaction pH.



Equation 1

The applicability of the reaction with respect to intramolecular cyclizations was initially investigated using a series of N-substituted pyrroles **1** (Table 1). These substrates were reacted with catalytic vitamin B_{12} and Ti(III) citrate at pH 8.0. After 24 hours, the reactions were stopped and the products isolated by extraction with hexanes. For compounds **1a** and **1b**, cyclization proceeded smoothly affording the **2a**,**b** in good yield. Only the 2-propenyl group is activated in this process as the B_{12}-catalyzed reaction is selective for mono- or 1,1-disubstituted arylalkenes,[2] and no products from activation of the trisubstituted arylalkene were detected. Hence the phenyl substituted alkene functions only as a radical trap. With pyrroles **1c** and **1d**, a mixture of products was observed containing both the saturated and unsaturated cyclized pyrroles **2** and **3**. Pyrrole **1e** yielded primarily the cyclized saturated product **2e**, but dimerization products were also observed. This observation reflects the lower reactivity of the unsubstituted alkene as a radical trap compared to the alkyl and aryl substituted alkenes in substrates **1a**–**d**. Upon cyclization compound **1e** would afford a less favorable primary radical intermediate causing the bimolecular dimerization process to become competitive. The 2-vinylpyrrole substrates **1f** and **1g** (R^1 = H) were also reactive under these conditions, but dimerization products were almost exclusively recovered with less than 10% cyclized products observed. Hence, the initiating arylalkene must be 1,1-disubstituted for the cyclization reaction to be successful. No products were detected containing an exocyclic alkene **4**.

Alternative intramolecular traps of the initially formed radical were also evaluated. Recently, several examples have been reported of oximes as effective radical acceptors.[5,6] Therefore, oxime **5** was subjected to the vitamin B_{12} catalyzed conditions affording *N*-hydroxylamine **6** in moderate yield and good purity (Equation 2).



Equation 2

The range of potential substrates was further explored through the use of α-alkyl styrenes **7**. Ethers **7a**–**c** all reacted in good yields affording the cyclized reduced products with modest diastereoselectivities (Table 2). Similar to the observations with the vinylpyrroles, ether **7d** containing a dimethylalkenyl group yielded a mixture of the cyclized saturated and unsaturated products **8** and **9**, respectively. Compounds **10** containing an exocyclic alkene were not observed.

While the results in Table 1 and Table 2 show that the cyclized products can be obtained in moderate to good yields, the reaction would be substantially more useful for synthetic purposes if the distribution of the reaction

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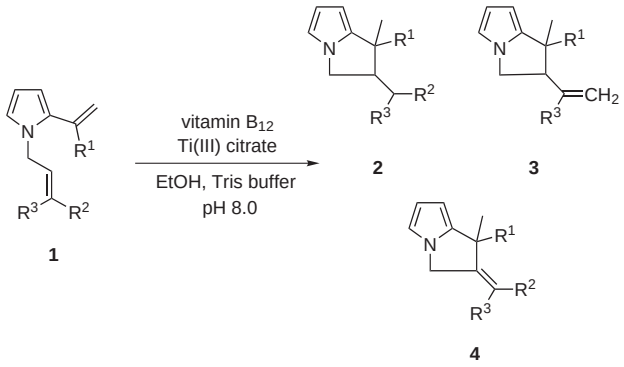
Table 1 Initial Screen of Substrates for Intramolecular Vitamin B_{12} Catalyzed Cyclizations at pH 8.0[a]



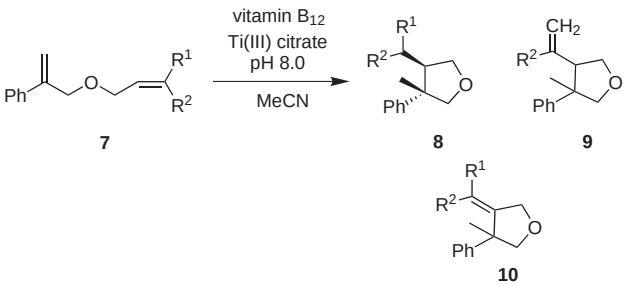
Entry	R^1	R^2	R^3	Yield of **2** (%)	Yield of **3** (%)	Yield of Dimer (%)
1a	Me	Ph	H	70	0	0
1b	Me	Ph	Ph	80	0	0
1c	Me	Me	H	60	40	0
1d	Me	Me	Me	28	42	0
1e	Me	H	H	72	0	16
1f	H	H	Me	<2	0	>72
1g	H	H	H	6	0	84

[a] Listed values are based on NMR integration and GCMS analysis of isolated crude reaction products.

products could be more predictably controlled. Furthermore, it would be highly desirable if the unsaturated products such as **3** and **9** would be the major or exclusive product since they possess an alkene functionality that provides a convenient handle for further manipulation. In order to achieve this, we inspected the proposed[2] catalytic cycle for the reaction shown in Scheme 1.

The vitamin B_{12} pre-catalyst is first reduced by Ti(III) citrate to the catalytically active cob(I)alamin, which displays a characteristic purple color with a UV maximum near 380 nm. The reduced metal catalyst activates the substrate in a process that is not completely understood[2] to generate the stabilized radical **I**. Most likely the activation involves an inner sphere process that may involve an

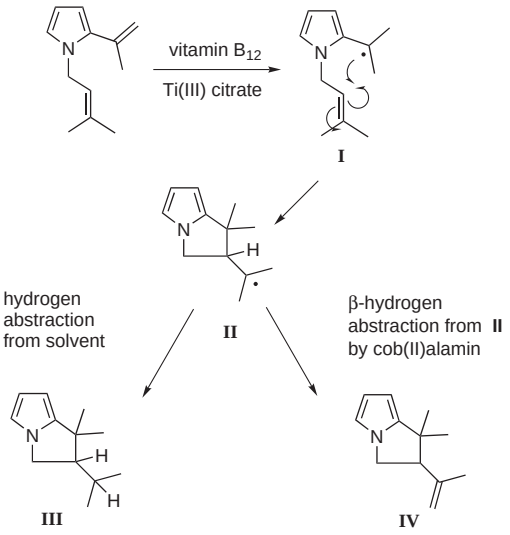
Table 2 Vitamin B_{12} Catalyzed Cyclization of α-Methylstyrene Derivatives[a]



Entry	R^1	R^2	Yield of **8** (%)	Yield of **9** (%)[b]	Yield of **10** (%)	dr of **8**[c]
7a	H	H	78	–	0	3.6:1
7b	Ph	Ph	68	–	0	3.2:1
7c	Ph	H	80	–	0	4.1:1
7d	Me	Me	36	18	0	1.5:1

[a] Yields based on NMR analysis of crude isolated products.
[b] Product **9** cannot be formed from substrates **7a–c**.
[c] The stereochemistry of the major isomer was assigned by NMR spectroscopy (HMQC, COSY, NOE).

organocobalamin followed by homolytic cleavage of the Co–C bond to produce **I**.[2] Radical **I** subsequently reacts intramolecularly with the alkene to generate radical **II**. The fate of this radical is dependent on the reaction conditions. It can either be reduced to yield product **III**, or cob(II)alamin can abstract a β-hydrogen atom to give the unsaturated product **IV**. This would also produce hydridocobalamin, which would be rapidly deprotonated (pK_a ca. 1)[7,8] regenerating the active cob(I)alamin catalyst. Several studies have provided strong support for such a homolytic mechanism for generation of alkenes as opposed to a β-hydride elimination mechanism from an alkylcobalamin species.[9–11]

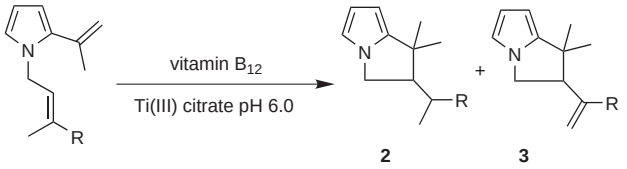


Scheme 1 Proposed catalytic mechanism for the B_{12}-catalyzed cyclization reaction

According to Scheme 1, the formation of the unsaturated product **IV** is dependent on β-hydrogen atom abstraction by cob(II)alamin. However, the concentration of the latter at any time is quite low since it is rapidly reduced to cob(I)alamin by Ti(III) citrate. Thus, it was envisioned that by slowing this reduction step and using solvents without readily available hydrogen atoms, the product ratio might be changed to favor product **IV**. The reduction potential of Ti(III) citrate has been shown to decrease in a pH-dependent manner.[12,13] A smaller thermodynamic driving force for reduction of Co(II) to Co(I) at lower pH could result in a kinetically slower reduction process, which might make the hydrogen atom abstraction from **II** more competitive.

To test this hypothesis, the cyclization of pyrrole **1c** was first performed at pH 8.0 in *tert*-butanol to minimize formation of product **III** but this resulted only in a very small change (ca. 5%) in the product distribution. The reaction was then repeated at pH 6.0. After 24 hours, essentially exclusive formation of the unsaturated product **3c** was observed in good yield (Table 3). On the basis of these results the increased formation of **3c** at the expense of **2c** is attributed to more effective hydrogen atom abstraction from intermediate **II** by cob(II)alamin at pH 6.0. The procedure was repeated using pyrrole **1d** and at pH 6.0 the unsaturated product **3d** was again the predominant product (Table 3).

Table 3 Vitamin B_{12} Catalyzed Cyclization of Pyrroles **1** at pH 6.0[a]

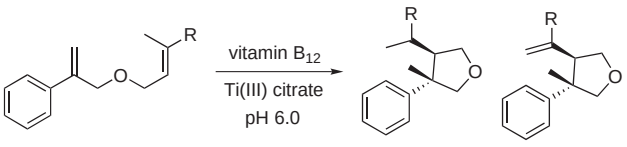


Substrate	R	Yield of **2** (%)	Yield of **3** (%)
1c	H	Trace	66
1d	Me	5	70

[a] Yields based on NMR analysis of crude isolated products.

The product distribution in the cyclization of ethers **7a** and **7d** could also be biased toward formation of the cyclized unsaturated products **9a** and **9d** (Table 4). Hence the lowering of the reaction pH provides a general solution for the production of these types of products. One limitation was encountered with substrates such as **1b** and **7b**, which cannot form products **3b** or **9b**. It was hoped that lowering of the pH might provide access to products **4b** and **10b** instead. However, reaction of **1b** did not produce the unsaturated product **4b** under all conditions investigated. The intermediate radical for this type of phenyl-substituted alkene substrate does not contain a readily accessible β-hydrogen atom since it resides at a tertiary carbon, rather than on a primary carbon. Evidently, this hydrogen atom is not reactive towards cob(II)alamin.

Table 4 Vitamin B_{12} Catalyzed Cyclization of Ethers **7** at pH 6.0



Substrate	R	Yield of **8** (%)	Yield of **9** (%)	dr
7a	H	Trace	64	4.0:1
7d	Me	Trace	82	3.4:1

In summary, we present a novel cyclization reaction for substituted arylalkenes that is mild, environmentally friendly, and can be tuned with respect to the product distribution by adjusting the pH.[14] In comparison with other strategies, the regiochemistry of the activation of the arylalkene is well-defined, resulting in the formation of a quaternary center, which is not readily achieved by other means. Efforts to improve the stereoselectivity of the reaction are underway.

Acknowledgment

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(14) Solvents used for cyclization reactions were deoxygenated under reduced pressure (10 min) and purged with N_2; this was repeated three times before storage under argon. When *t*-BuOH was used as a solvent, it was distilled over CaH_2. All cyclizations were conducted on a 0.1 mmol scale, and initiated in the dark before covering the flask with aluminum foil. Representative procedures are provided for a select set of substrates.
A flask was charged with **1d** (20.3 mg, 0.116 mmol) and vitamin B_{12} (12.8 mg, 0.009 mmol) and purged with Ar. Degassed *t*-BuOH (15 mL) was added, followed by a Ti(III) citrate solution, pH 6.0 (8 mL) prepared as previously described.[2] The purple solution was stirred in the dark for 24 h. The reaction was poured into H_2O (50 mL) and extracted with hexane (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 75 mL), dried with $MgSO_4$, filtered and concentrated, yielding 15.9 mg of total product (1:14 mixture of **2d** and **3d**, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 3 H), 1.41 (s, 3 H), 1.75 (s, 3 H), 3.12 (t, *J* = 7.9 Hz, 1 H), 4.01 (m, 2 H), 4.79 (m, 1 H), 4.95 (pentet, *J* = 1.5 Hz, 1 H), 5.73 (dd, *J* = 3.6, 1.3 Hz, 1 H), 6.19 (t, *J* = 2.9 Hz, 1 H), 6.53 (dd, *J* = 2.6, 1.3 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.0 (CH_3), 23.8 (CH_3), 28.6 (CH_3), 41.4 (Cq), 48.7 (CH_2), 60.5 (CH), 96.7 (CH), 111.5 (CH), 113.1 (CH), 113.6 (CH_2), 143.0 (Cq). HRMS (EI): *m/z* calcd for $C_{12}H_{17}N$ [M^+]: 175.1361; found: 175.1360.
A flask was charged with **7b** (29.4 mg, 0.090 mmol) and vitamin B_{12} (12.4 mg, 0.009 mmol) and purged with Ar. Degassed MeCN (20 mL) was added followed by aqueous Ti(III) citrate pH 8.0 (7 mL). The purple solution was stirred in the dark for 23 h, then poured into H_2O (50 mL) and extracted with hexane (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 75 mL), dried with $MgSO_4$, filtered and concentrated yielding 20.0 mg of product **8b** (68%) as a colorless oil. Both diastereomers were separated by HPLC and the stereochemistry of the major isomer was determined using NOE after assignment of the protons by HMQC and COSY spectroscopy. ^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer): δ = 1.47 (s, 3 H), 3.63 (m, 2 H), 3.77 (d, *J* = 8.8 Hz, 1 H), 3.87 (d, *J* = 7.7 Hz, 1 H), 3.98 (dt, *J* = 1.8, 7.4 Hz, 1 H), 4.22 (d, *J* = 8.8 Hz, 1 H), 6.84–6.90 (m, 3 H), 7.05–7.35 (m, 12 H). Minor diastereomer: δ = 1.57 (s, 3 H), 3.16 (d, *J* = 11.4 Hz, 1 H), 3.38 (m, 1 H), 3.52 (dd, *J* = 10.2, 9.7 Hz, 1 H), 3.85 (dd, *J* = 8.1, 8.3 Hz, 1 H), 3.91 (d, *J* = 8.6 Hz, 1 H), 4.21 (d, *J* = 8.7 Hz, 1 H), 7.05–7.35 (m, 15 H). ^{13}C NMR (125.6 MHz, $CDCl_3$, major diastereomer): δ = 18.7 (CH_3), 47.9 (CH_2), 55.0 (CH), 77.0 (CH_2), 85.0 (CH_2), 125.7 (CH), 126.0 (CH), 126.7 (CH), 127.5 (CH), 128.0 (CH), 128.1 (CH), 128.9 (CH), 144.4 (Cq). HRMS (EI): *m/z* calcd for $C_{24}H_{24}O$ [M^+]: 328.1827; found: 328.1826
A flask was charged with **7d** (18.8 mg, 0.093 mmol) and vitamin B_{12} (13.2 mg, 0.01 mmol) and purged with Ar. Degassed MeCN (20 mL) was added, followed by aqueous Ti(III) citrate pH 6.0 (8 mL). The dark red solution was stirred in the dark for 24 h, and then the reaction was poured into H_2O (50 mL) and extracted with hexane (3 × 60 mL). The combined organic layers were washed with H_2O (2 × 75 mL), dried with $MgSO_4$, filtered and concentrated yielding 15.4 mg of product **9d** (82%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.48 (s, 3 H), 3.11 (t, *J* = 8.1 Hz, 1 H), 3.82 (d, *J* = 8.6 Hz, 1 H), 4.05 (t, *J* = 8.8 Hz, 1 H), 4.18 (d, *J* = 8.7 Hz, 1 H), 4.15 (t, *J* = 8.2 Hz, 1 H), 4.70 (s, 1 H), 4.89 (s, 1 H), 7.25–7.35 (m, 3 H), 7.48–7.50 (m, 2 H). ^{13}C NMR (125.6 MHz, $CDCl_3$): δ = 19.8 (CH_3), 24.2 (CH_3), 57.5 (CH), 71.4 (CH_2), 82.7 (CH_2), 112.4 (CH_2), 126.5 (CH), 127.4 (CH), 128.1 (CH), 128.6 (CH), 146.5 (Cq). HRMS (EI): *m/z* calcd for $C_{14}H_{18}O$ [M^+]: 202.1358; found: 202.1357.