Mechanistic Investigation of a Novel Vitamin B_{12}-Catalyzed Carbon−Carbon Bond Forming Reaction, the Reductive Dimerization of Arylalkenes

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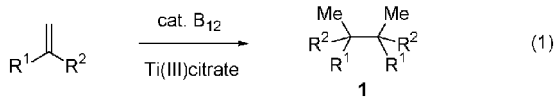
In the presence of catalytic vitamin B_{12} and a reducing agent such as Ti(III)citrate or Zn, arylalkenes are dimerized with unusual regioselectivity forming a carbon−carbon bond between the benzylic carbons of each coupling partner. Dimerization products were obtained in good to excellent yields for mono- and 1,1-disubstituted alkenes. Dienes containing one aryl alkene underwent intramolecular cyclization in good yields. However, 1,2-disubstituted and trisubstituted alkenes were unreactive. Mechanistic investigations using radical traps suggest the involvement of benzylic radicals, and the lack of diastereoselectivity in the product distribution is consistent with dimerization of two such reactive intermediates. A strong reducing agent is required for the reaction and fulfills two roles. It returns the Co(II) form of the catalyst generated after the reaction to the active Co(I) state, and by removing Co(II) it also prevents the nonproductive recombination of alkyl radicals with cob(II)alamin. The mechanism of the formation of benzylic radicals from arylalkenes and cob(I)alamin poses an interesting problem. The results with a one-electron transfer probe indicate that radical generation is not likely to involve an electron transfer. Several alternative mechanisms are discussed.

Introduction

The properties and reactivity of vitamin B_{12} derivatives have been extensively investigated ever since it was shown to possess a cobalt−carbon bond in the biological cofactors adenosyl- and methylcobalamin.[1−5] These versatile organometallic complexes are used in a variety of enzymes to catalyze radical rearrangements and methyl transfers. Moreover, vitamin B_{12} has found use in organic chemistry for carbon−carbon bond formations.[6−11] In this study, we report a previously unknown B_{12}-catalyzed reaction that forms a new carbon−carbon bond between two alkenes providing dimerization products **1** (eq 1). It is noteworthy that the regiochemistry of this coupling is opposite to that expected for radical chemistry involving alkenes. The transformation employs catalytic vitamin B_{12} and an auxiliary reductant such as Zn or Ti(III)citrate and can be carried out at 25 °C in a mixture of aqueous buffer (pH 8) and polar organic solvents such as ethanol, methanol, or acetonitrile.[12] Perhaps the most interesting aspect of this transformation involves the mechanism by which it takes place. We describe in this report the scope of the reaction and a detailed investigation of its mechanism.



(1)

1

Results and Discussion

Scope of B_{12}-Catalyzed Dimerization of Alkenes. The range of substrates that can be coupled is shown in Table 1. Monosubstituted arylalkenes gave a 1:1 ratio of diastereomeric products, whereas the disubstituted substrates produced two quaternary carbon centers in high yields (entries 4−7). When either vitamin B_{12} or Ti(III)-citrate was omitted from the reaction mixture, only starting alkenes were recovered. Other methods have been reported for the preparation of these types of compounds, but they have generally relied on relatively harsh reaction conditions[13−18] or photochemical[19] reac-

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(2) Hodgkin, D. C. *Science* **1965**, *150*, 979−988.
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(11) Branchaud, B. P.; Friestad, G. K. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, 1995; pp 5511−5514.
(12) The content of aqueous buffer is determined by the volume of aqueous Ti(III)citrate added. The reaction rates in these solvents systems follow the general trend: aqueous buffer > MeOH > EtOH ≈ MeCN.
(13) Brown, W. G.; McClure, D. E. *J. Org. Chem.* **1970**, *35*, 2036−2037 and references therein.
(14) McMurry, J. E.; Silvestri, M. *J. Org. Chem.* **1975**, *40*, 2687−2688.
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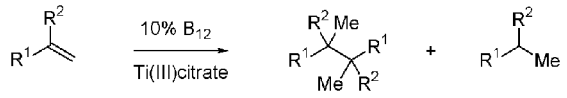
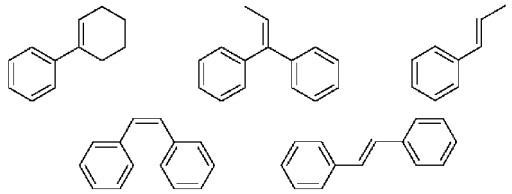
Table 1. Vitamin B_{12}/Ti(III)-Mediated Dimerization of Alkenes



	alkene		yield (%)[a]	
entry	R^1	R^2	dimer	reduction product
1	Ph	H	50	4
2	4-MeC_6H_4	H	80	13
3	2,5-$(Me)_2C_6H_3$	H	56[b]	7
4	Ph	Me	85	7
5	4-ClC_6H_4	Me	80	3
6	4-FC_6H_4	Me	70	0
7	Ph	Ph	90	5

[a] Typical reaction times for complete conversion varied from 8 to 12 h. [b] In aqueous *tert*-butyl alcohol.

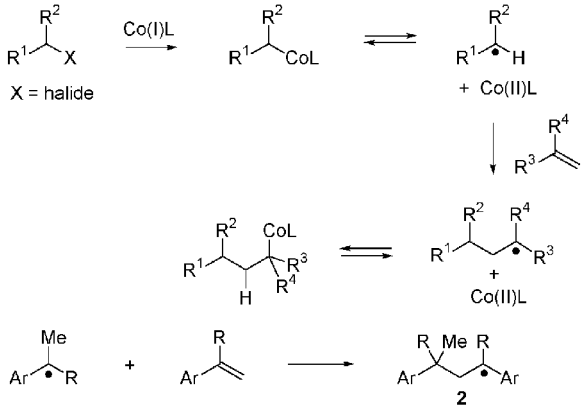
Chart 1



tions of benzylhalides or benzyl alcohols.[20] The B_{12}-catalyzed dimerization, on the other hand, utilizes readily available styrene derivatives, mild reaction conditions, and environmentally friendly solvent systems. Several 1,2-disubstituted and trisubstituted alkenes (Chart 1) as well as alkyl-substituted alkenes that were examined proved unreactive.

Mechanistic Considerations: Testing the Intermediacy of Alkylcobalamins. The transformations in Table 1 have synthetic utility, but they are more interesting from a pure mechanistic viewpoint. A solution of Ti(III)citrate (10 equiv) and vitamin B_{12} displays the characteristic strong absorption around 385 nm indicative of Co(I),[3] suggesting the highly nucleophilic cob(I)alamin (B_{12} in its Co(I) oxidation state) could be the reactive form of the catalyst. Cob(I)alamins and related cobalt complexes have been used previously by several groups for catalytic or stoichiometric carbon−carbon bond formations.[21−28] In general, these reports describe cou-

Scheme 1



plings between alkylhalides and alkenes, or in some cases alkene polymerizations. In the former, an alkylhalide is reacted with a cobalt(I) complex to form an organocobalt intermediate, which in turn serves as a precursor for a reactive radical via homolytic cleavage of the weak Co−C bond (e.g. Scheme 1). This radical subsequently initiates either an inter- or intramolecular addition to an alkene to generate a product radical that is then trapped by Co(II) to form a second organocobalt complex that can be further elaborated. The structures of both starting materials and reaction products in Table 1 imply that they must be formed via pathways that are different from that in Scheme 1. If the catalyst were to act as a source of radicals that would add to the arylalkene, either the regioisomeric product radical **2** or a polymer would be produced instead of the symmetrical dimerization product **1**.

Cob(I)alamin has been reported to react with styrene at acidic pH to provide a product that was tentatively assigned as α-phenethylcobalamin.[29] The complex was too reactive to be isolated, but the authors did not report formation of dimerization products. Although cob(I)alamin reportedly[29,30] does not react with styrene under the slightly basic reaction conditions used here (pH 8.0), the regiochemistry of the coupling reactions in Table 1 suggests that substituted benzylcobalamins (**3**) may be intermediates along the reaction pathway. Cob(I)alamin is an exceptionally strong nucleophile that readily reacts with organohalides to form organocobalamins.[31,32] We therefore tested for the intermediacy of alkylcobalamins by reaction of various benzyl halides under the reaction conditions used for the coupling of alkenes (Table 2). Dimerization products were obtained in good to excellent yields with identical regiochemistry as observed for the corresponding alkenes (e.g., compare entry 1, Table 1

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(21) For reviews, see refs 8, 11, and Ali, A.; Gill, G. B.; Pattenden, G.; Roan, G. A.; Kam, T. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1081−1093.
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(30) Cob(I)alamin has been reported not to react with styrene under neutral or alkaline conditions, but cob(I)aloximes do react with styrene under these conditions to give α-phenethylcobaloxime. Schrauzer, G. N., Windgassen, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 1999−2007.
(31) Schrauzer, G. N.; Deutsch, E.; Windgassen, R. J. *J. Am. Chem. Soc.* **1968**, *90*, 2441−2442.
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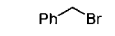
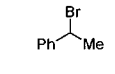
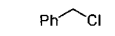
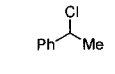
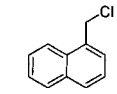
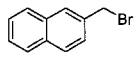
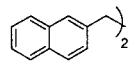
Table 2. Vitamin B_{12}/Ti(III)-Mediated Dimerization of Alkylhalides in Aqueous Ethanol

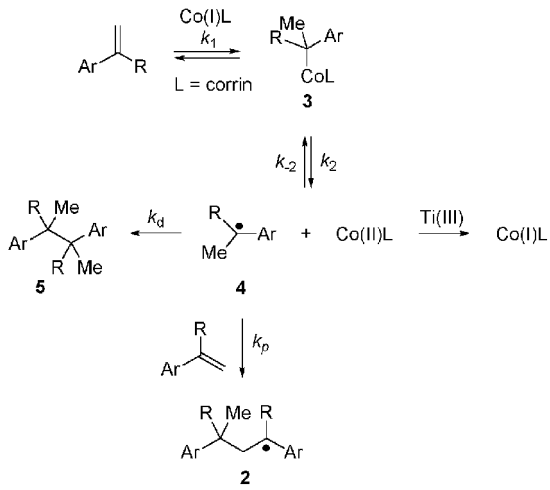
Entry	Reactant	Product	Yield (%)[a]	
			dimer	reduction product
1			98	1
2			64	3
3			68	1
4			75	3
5			75	20
6			31 79[b]	31 13[b]

[a] Reactions were complete within 1 h. [b] Reaction run in acetonitrile/water.

with entry 2, Table 2).[33] These observations suggest that benzylcobalamins **3** may indeed be common intermediates in the coupling of alkenes and benzylhalides, although the latter reactions required significantly shorter reaction times.[34]

Probing the Intermediacy of Alkyl Radicals. Alkylcobalamins have weak Co−C bonds, with the bond strengths decreasing with more bulky alkyl groups.[35−39] Benzylcobalamin contains one of the weakest Co−C bonds (~23 kcal mol^{-1}) among alkylcobalamins for which the bond dissociation energies have been determined quantitatively.[36,38−41] Therefore, if alkylcobalamins such as **3** are formed in the reaction of cob(I)alamin with arylalkenes, they may produce benzyl radicals **4** that can dimerize to provide the observed products **5** (Scheme 2). Such dimerization of radicals is supported by the lack of diastereoselectivity that was observed in the reaction products in Tables 1 and 2. If the coupling products were derived directly from alkylcobalamins, some stereoselectivity would be expected by virtue of the chirality of B_{12}, as was previously found in various synthetic processes.[7,42−46]

Scheme 2



Given the well-established radical polymerization of styrene, it appears unlikely at first glance that two benzylic free radicals **4**, present in very low concentrations, would combine to give the observed products in the presence of excess alkene.[47] However, a look at the rate constants of these competing processes shows that such a mechanism is feasible. If one takes the known rate coefficient for the propagation step in homopolymerizations of bulk styrene, 85 M^{-1} s^{-1} at 25 °C,[48−51] as a reasonable approximation for the rate constant for addition of radical **4** to the alkene (k_p), the rate of formation of products such as **2** from radical **4** would be 85 × [styrene][**4**]. On the other hand, the rate constant for the competing dimerization of two radicals **4** will be close to diffusion-controlled ($k_d \approx 10^9$ $M^{-1}s^{-1}$ at room temperature), giving a rate of $10^9 \times [\mathbf{4}]^2$ for the production of products **5** from **4**. Thus, at the alkene concentrations used (4 mM initial) the radical concentration needs to exceed only ~2×10^{-9} M to provide a >10-fold preference for dimerization over polymerization. For substituted styrene derivatives the concentration of radicals can be even lower as the propagation rate coefficient is even smaller (e.g., 0.62 M^{-1} s^{-1} for α-methylstyrene).[52,53] Indeed, the higher yields obtained from α-substituted styrene derivatives (Table 1) may reflect this higher

(33) Reductive dimerization of benzylhalides using stoichiometric $(PPh_3)_3CoCl$ has been reported. Momose, D.-I.; Iguchi, K.; Sugiyama, T.; Yamada, Y. *Chem. Pharm. Bull.* **1984**, *32*, 1840−1853.

(34) This difference in reaction rates implies that the overall rates cannot be governed by a step after the formation of the common intermediate. Instead, the kinetics of formation of the intermediates must be different for the two classes of compounds. This is not unexpected given the anticipated difference in mechanism of alkylcobalamin formation from alkenes vs alkylhalides.

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(47) In this scenario, the observed α,α-dimer products **1** could form directly by dimerization of benzylic radicals or by rearrangement of initially formed α,*para*- and/or α,*ortho*-semibenzenes. (For a detailed discussion, see: Langhals, H.; Fischer, H. *Chem. Ber.* **1978**, *111*, 543−553. Skinner, K. J.; Hochster, H. S.; McBride, J. M. *J. Am. Chem. Soc.* **1974**, *96*, 4301−4306.) In fact, small but significant amounts (3%) of the α,*p*-dimer were observed in entry 4, Table 1. When this reaction was stopped after a short reaction time (1 h, <40% completion), the ratio of α,α- to α,*p*-dimers was 6:1, suggesting α,*p*-dimers may rearrange to α,α-dimers in these reactions.

(48) Buback, M.; Gilbert, R. G.; Hutchinson, R. A.; Klumperman, B.; Kuchta, F. D.; Manders, B. G.; O'Driscoll, K. F.; Russell, G. T.; Schweer, J. *Macromol. Chem. Phys.* **1995**, *196*, 3267−3280.

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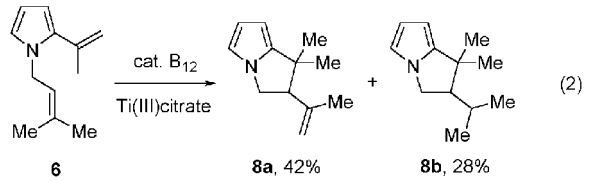
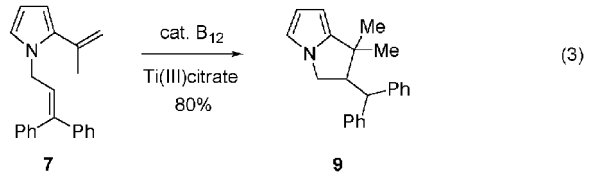
selectivity for radical dimerization. Furthermore, when reactions with styrene were performed at higher concentrations (100 mM), insoluble material was formed and the yield of dimers dropped to ~20−25%, suggesting effective competition by oligomerization.

To test for the involvement of radicals, dienes **6** and **7**, envisioned as potential intramolecular radical traps, were reacted with B_{12} in the presence of Ti(III)citrate (eqs 2 and 3).[54] Since trisubstituted alkenes are unreactive

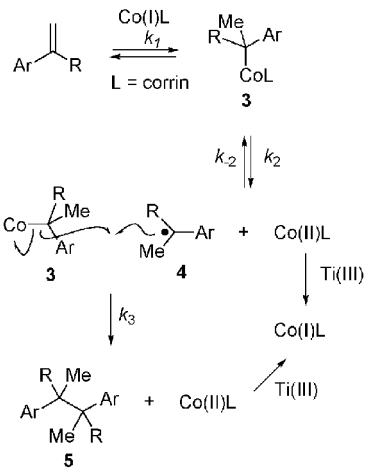




(see above), it was anticipated that the disubstituted alkene would generate a radical at the carbon α to the pyrrole that would subsequently react with the trisubstituted alkene in 5-exo-trig fashion. Both compounds provided the expected cyclized products in good yields, providing further support for the involvement of radicals. Furthermore, these transformations show synthetic promise for cyclization under mild conditions in either polar organic or aqueous solvents. When the reaction in eq 2 was carried out with *tert*-butyl alcohol as the organic cosolvent, the reduced cyclization product **8b** was not formed. Unlike ethanol, *tert*-butyl alcohol does not contain a relatively weak C−H bond. The improved ratio of **8a** to the reduction product **8b** suggests therefore that the latter is formed via hydrogen atom abstraction by a radical intermediate. The retention of the olefin in **8a** in *tert*-butyl alcohol is important as it provides a handle for further functionalization increasing the value of the cyclization reaction.

An alternative dimerization mechanism can be written on the basis of a recent report by Mosimann and Kräutler.[55] This study showed that alkyl radicals can react with methylcobalamin to form a methylated product and cob(II)alamin. Similarly, reaction of the radical **4** with alkylcobalamin **3** could yield the observed dimerization product (Scheme 3). The rate constant for homolytic bond dissociation of benzylcobalamin (k_2) is ~2.0 × 10^{-3} s^{-1} at 25 °C.[36,38,40,56] Taking a value of 1 × 10^9

Scheme 3



M^{-1} s^{-1} for k_{-2},[57] the equilibrium constant K_2 can be estimated as 2.0 × 10^{-12} M^{-1}. Therefore, the concentrations of **3** are significantly higher than the concentrations of radicals **4** for benzylcobalamin. (See below for a discussion of more hindered alkylcobalamins and the possible effect of Ti(III)citrate on this equilibrium.) The rate of product formation from radical **4** in Scheme 3 would thus be k_3[**3**][**4**], whereas that of Scheme 2 would be k_d[**4**]^2. At present, rate constants for the reaction of radicals with alkylcobalamins (e.g., k_3) are not known, but as pointed out previously,[55] thermodynamically it should be highly favorable to form a C−C bond at the expense of a Co−C bond. Thus, this mechanism may be kinetically competitive with simple free radical dimerization for the formation of the observed products, although it is a less likely mechanism for more sterically hindered intermediates **3** and **4**. Another (indirect) argument against this mechanism is the lack of observed diastereoselectivity, since one might expect some degree of stereoselectivity in a reaction between a chiral organometallic compound and an achiral radical. The dimerization of two organic radicals on the other hand is known to take place nonstereoselectively.[13,58]

Overcoming the Persistent Radical Effect. Ti(III)citrate, which is present in excess over vitamin B_{12}, plays an important dual role in the dimerization reaction. The homolysis of the Co−C bond in benzylcobalamins is usually a very slow process under anaerobic conditions ("too slow to be measured accurately")[36] as a result of the efficient trapping of the benzyl radical by Co(II), thereby regenerating benzylcobalamin. In the reactions described here, for every dimerization event two molecules of Co(II) are irreversibly formed, and thus without Ti(III)citrate, product formation would slow and eventually be inhibited by build-up of Co(II) that will scavenge organic radicals, a manifestation of the "persistent radical effect".[59−61] In previous studies, recombination of alkyl radicals with cob(II)alamin has been prevented either by

(53) It is interesting to compare and contrast the discussion of the possible involvement of free radicals in this report with an in depth analysis by Newcomb and Curran of the use of 5-hexenyl halides as radical probes for the mechanism of nucleophilic substitution (Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206−214, footnote 52). In that Account, the authors show that diffusion-controlled coupling of *free* radicals (R• and Nu•) cannot account for product formation because the limitations on the maximum radical concentrations imposed by the known rate constants of competing reactions would give untenably low rates of product formation. Here product formation by coupling of free radicals may be possible because of the slow rates of competing reactions such as the propagation rate for oligomerization.

(54) Attempts to detect radicals using intermolecular radical traps such as TEMPO failed as they reacted with Co(I)/Ti(III).

(55) Mosimann, H.; Kräutler, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 393−395.

(56) Blau, R. J.; Espenson, J. H. *J. Am. Chem. Soc.* **1985**, *107*, 3530−3533.

(57) Endicott, J. F.; Ferraudi, G. *J. Am. Chem. Soc.* **1977**, *99*, 243−245.

(58) Greene, F. D.; Berwick, M. A.; Stowell, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 867−874.

(59) Daikh, B. E.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 2938−2943.

(60) Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925−3927.

(61) Branchaud, B. P.; Yu, G.-X. *Organometallics* **1993**, *12*, 4262−4264.

intercepting the alkyl radical using trapping agents such as TEMPO,[62,63] O_2,[36] and bis(dimethylglyoximato)cobalt(II)[64,65] or by removing cob(II)alamin via oxidation to Co(III).[61] In the current system, we speculate that the persistent radical effect is circumvented by *reduction* of cob(II)alamin back to the catalytically active Co(I) form.

We experimentally verified this hypothesis by preparing authentic benzylcobalamin from cob(I)alamin and benzylbromide and submitting the isolated complex to a solution containing Ti(III)citrate. Whereas an anaerobic control reaction showed no appreciable decrease of the characteristic bands of an alkylcobalamin in the UV−vis spectrum over a period of 3 h, in the presence of 8 equiv of Ti(III)citrate benzylcobalamin was converted into cob(I)alamin. These observations can be rationalized according to Scheme 2 in which Ti(III)citrate intercepts cob(II)alamin produced in the rate-limiting step (k_2), or they may be interpreted as a bimolecular reaction in which Ti(III)citrate directly reduces benzylcobalamin. Such Co−C bond cleavage induced by one-electron reduction of alkylcobalamins has been extensively studied,[66−68] showing that the reduction becomes more facile with sterically hindered alkyl groups and/or groups that can stabilize the radical product by delocalization.[69] Both features are present in alkylcobalamins **3**, supporting a potential bimolecular reduction by Ti(III)citrate.

A distinction between these two possibilities can be made on the basis of the predicted kinetic profiles. According to Scheme 2 the rate of benzylcobalamin consumption should be independent of Ti(III)citrate concentration at sufficiently high concentrations of the latter when homolytic Co−C bond cleavage is fully rate limiting. On the other hand, a bimolecular mechanism should be first order in Ti(III)citrate at all concentrations. Monitoring the reduction of 0.2 mM benzylcobalamin in the presence of various concentrations of Ti(III)citrate at pH 8.0 resulted in apparent first-order decay of the absorption bands of benzylcobalamin (eg Figure 1) and a concomitant increase in the characteristic bands of cob(I)alamin with an isosbestic point at 424 nm. The observed rate constants increased nonlinearly with Ti(III)citrate concentration, leveling off above 75 equiv to become zeroth order in Ti(III)citrate (Figure 2). The observed first-order rate constant at these Ti(III)citrate concentrations ($1.68 \pm 0.1 \times 10^{-3}$ s^{-1} at 22 °C) is within experimental error of the rate constant for Co−C bond cleavage of benzylcobalamin (k2, Scheme 2) determined in various studies[36,38,40,56] (eg 1.79×10^{-3} s^{-1} at 22 °C).[36] Thus, the kinetic data is fully consistent with the mechanism presented in Scheme 2, indicating that Ti(III)citrate "traps" cob(II)alamin once formed.[70]

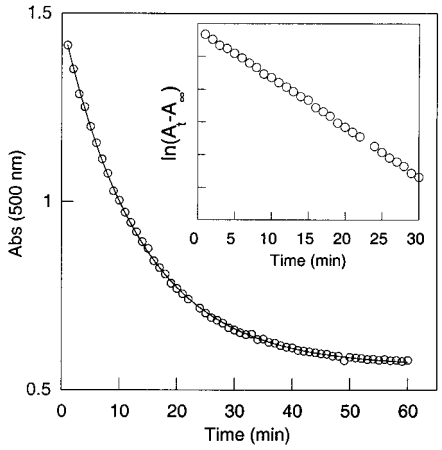


Figure 1. Time dependence of the conversion of benzylcobalamin to cob(I)alamin by Ti(III)citrate monitored at 500 nm. Conditions: 0.2 mM benzylcobalamin, 9.7 mM Ti(III)citrate, 50 mM Tris buffer, pH 8.0. The solid line represents a single-exponential fit using the rate expression for a first-order decay. Inset shows the linearity of the logarithmic plot over several half-lives.

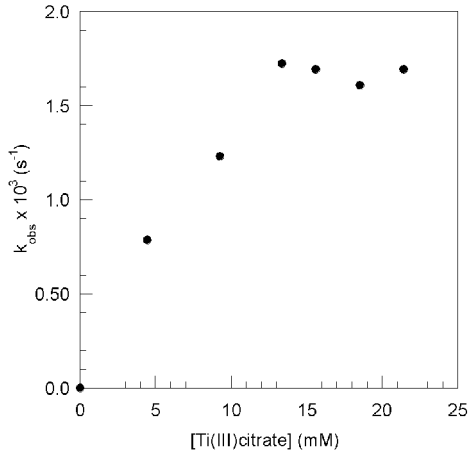


Figure 2. Dependence of the observed apparent first-order rate constant on the Ti(III)citrate concentration in the anaerobic reductive dealkylation of benzylcobalamin (0.2 mM) in aqueous buffer, pH 8.0. The observed rate constant approaches zero order dependence on the concentration of Ti(III)citrate.

Our studies show that reduction of cob(II)alamin formed during the coupling reaction not only regenerates the active Co(I) catalyst (Scheme 2) but also prevents the highly efficient (re)combination of cob(II)alamin with organic radicals, which would otherwise interfere with the catalytic cycle. This stands in direct contrast to cobalt-catalyzed free-radical chain transfer[71−73] and cobalt-mediated living radical polymerization[28,74] in which the cobalt macrocycles are introduced to *decrease* the steady-state concentration of free radicals. In other words, the current process promotes the rate of the "termination" reaction of combination of two radicals that is prevented in these polymerization strategies. In comparison with previously employed reducing agents for the catalytic use

(62) Finke, R. G.; Hay, B. P. *Inorg. Chem.* **1984**, *23*, 3041−3043.
(63) Hay, B. P.; Finke, R. G. *Polyhedron* **1988**, *7*, 1469−1481.
(64) Halpern, J.; Kim, S. H.; Leung, T. W. *J. Am. Chem. Soc.* **1984**, *106*, 8317−8319.
(65) Halpern, J. *Polyhedron* **1988**, *7*, 1483−1490.
(66) Lexa, D.; Savéant, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3220−3222.
(67) Elliott, C. M.; Hershenhart, E.; Finke, R. G.; Smith, B. L. *J. Am. Chem. Soc.* **1981**, *103*, 5558−5566.
(68) Shepherd, R. E.; Zhang, S.; Dowd, P.; Choi, G.; Wilk, B.; Choi, S. C. *Inorg. Chim. Acta* **1990**, *174*, 249−256.
(69) Zhou, D.-L.; Tinembart, O.; Scheffold, R.; Walder, L. *Helv. Chim. Acta* **1990**, *73*, 2225−2241.
(70) This conclusion is valid for benzylcobalamin. More sterically hindered alkylcobalamins generally have lower reduction potentials. Therefore, Ti(III)citrate might be a sufficiently strong reductant to reduce more hindered alkylcobalamins in a bimolecular reaction. Because of the inherent instability of hindered secondary alkylcobalamins we could not verify this possibility experimentally.

(71) Enikolopyan, N. S.; Smirnov, B. R.; Ponomarev, G. V.; Belgovskii, I. M. *J. Polymer Sci.* **1981**, *19*, 879−889.
(72) Burczyk, A.; O'Driscoll, K. F.; Rempel, G. L. *J. Polym. Sci.* **1984**, *22*, 32255−3262.
(73) Gridnev, A. A. *Polym. Sci. U.S.S.R.* **1989**, *31*, 2369−2376.
(74) Matyjaszewski, K.; Patten, T. E.; Xia, J. H. *J. Am. Chem. Soc.* **1997**, *119*, 674−680.

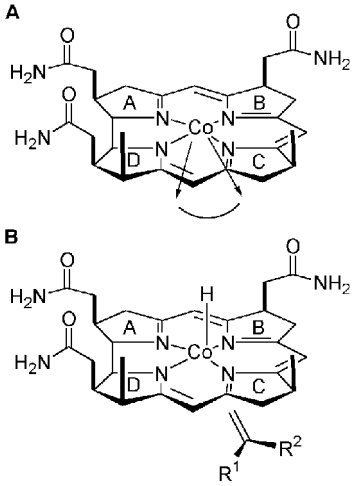


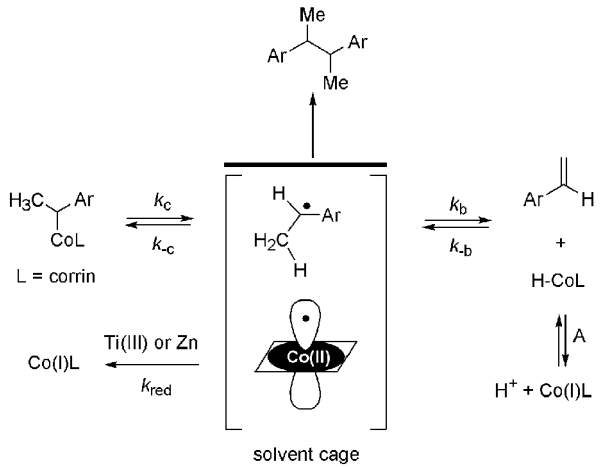
Figure 3. (A) Schematic representation of the steric requirements of the corrin ligand in B_{12} derivatives. Only the side chains at the β-face are shown for clarity, and the pucker of the corrin is not shown. The arrows indicate the general direction of the $C_\alpha-C_\beta$ bond of the axial ligand in primary alkylcobalamins for which structures have been determined. (B) Proposed approach of mono- and 1,1-disubstituted alkenes to a putative hydridocobalamin.

of vitamin B_{12} in C−C bond forming reactions, such as $NaBH_4$/NaOH,[22,23] Zn,[24,26] or electrochemistry,[6,25,27,75] Ti(III)citrate is an attractive alternative as it is a significantly less strong reductant. Ti(III)citrate is not required, however, for these reactions as similar yields and product distributions are obtained using Zn dust as the stoichiometric reductant.

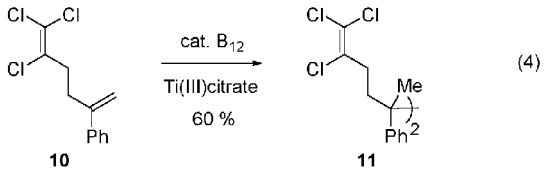
Mechanism of Radical Formation. The results discussed so far are consistent with mechanisms for product formation that involve radicals **4**, and the findings in the previous section support formation of these benzylic radicals from benzylcobalamins. The pathway for formation of these radicals in the dimerization of α-*substituted* styrenes warrants further discussion. According to Schemes 2 and 3, these substrates would form alkylcobalamins with α-branched tertiary ligands (**3**, R = alkyl), which have never been detected before.[76] Sterically crowded alkylcobalamins have unfavorable interactions between the axial alkyl ligand and the substituents on the equatorial corrin (see Figure 3), and therefore tertiary alkylcobalamins may be so unstable that they are not viable intermediates. For instance, Scheffold and co-workers reported preliminary computational studies that suggested that no low-energy solution is possible for *tert*-alkylcobalamins.[69] More recent theoretical studies on Co−C bond dissociation energies of alkylcobalamins suggest that this bond would be weaker by about 15−20 kcal/mol for tertiary alkyl ligands compared to secondary and primary alkyl ligands.[41] The bond energies calculated for tertiary alkylcobalamins are so low that again their intermediacy is questionable.[77]

Electron transfer (et) from Co(I) to the alkene would constitute an alternative route to radicals **4** that does not involve alkylcobalamins. To investigate such pathways

Scheme 4



compound **10** was subjected to the reaction conditions. We have previously shown that trichloroalkenes undergo vitamin B_{12}-catalyzed dechlorination that is initiated by electron transfer from Co(I) to the electron-deficient trichloroalkene.[78] The radical anion so produced is unstable and eliminates chloride anion, generating a vinyl radical.[79] Compound **10** contains both a trichloroalkene and a 1,1-disubstituted arylalkene and thus can serve as a probe for the relative rates of dimerization and dechlorination. In the event, dimerized product **11** was detected as the major[80] product as a 1:1 mixture of diastereomers (eq 4), and only traces of dechlorinated



(4)

products were produced. Whereas this does not prove that the dimerization reaction does not involve an electron transfer from Co(I) to the arylalkene, it is suggestive because the trichloroalkene should be significantly more electron-deficient. Another piece of indirect evidence against an outer-sphere electron-transfer mechanism involves the lack of reactivity of 1,2-di- and trisubstituted alkenes (Chart 1), which would not be expected to have significantly different redox potentials compared to mono- and 1,1-disubstituted alkenes. If an inner-sphere et or covalent process were responsible for radical generation, however, the difference in reactivity can be readily explained by unfavorable steric interactions between the side chains at the β-face of the corrin ring and the alkene substituents for 1,2-substituted olefins (see below).

Several mechanisms can be considered for the formation of benzylcobalamins from cob(I)alamin and styrenes. As shown in Scheme 4, alkylcobalamins (as well as other 18-electron 6-coordinate organocobalt macrocycles)[81−85]

(75) Torii, S.; Inokuchi, T.; Yukawa, T. *J. Org. Chem.* **1985**, *50*, 5875−5877.

(76) A transient species detected in electrochemical experiments has been tentatively assigned to *tert*-butylcobalamin. See ref 69.

(77) For instance, in ref 41 the BDE of *tert*-butylcobalamin was computed at 3 kcal/mol.

(78) Shey, J.; van der Donk, W. A. *J. Am. Chem. Soc.* **2000**, *122*, 12403−12404.

(79) Nonnenberg, C.; van der Donk, W. A.; Zipse, H., submitted for publication.

(80) In addition to 60% α,α,-dimer, about 30% of an α,*p*-dimer was produced. See ref 47 for literature precedent.

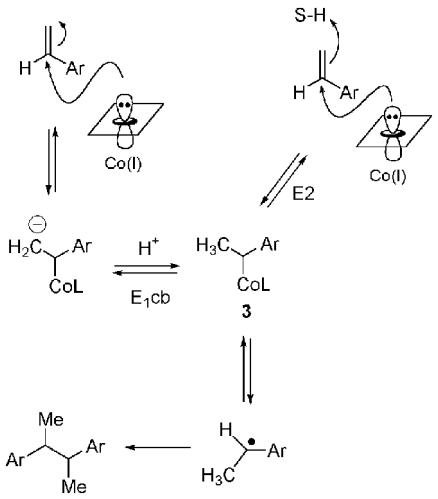
(81) Ng, F. T. T.; Rempel, G. L.; Mancuso, C.; Halpern, J. *Organometallics* **1990**, *9*, 2762−2772.

(82) Gridnev, A. A.; Ittel, S. D.; Fryd, M.; Wayland, B. B. *Organometallics* **1993**, *12*, 4871−4880.

are known to undergo β-hydride elimination to generate alkenes. The mechanism of these reactions have been investigated,[9,81,86] and most reports favor homolytic scission of the Co−C bond to provide a [LCo(II)• •CH_2R] geminate radical pair followed by hydrogen atom abstraction from the organic radical by the Co(II)-complex to give an alkene and a protonated Co(I) complex (Scheme 4).[87] For cobaloximes the resulting metal hydride ("hydridocobaloxime") has a reported pK_a of around 10.5.[88] Thus, according to the principle of microscopic reversibility, the reverse reaction, the formation of alkylcobaloximes from cob(I)aloxime and alkenes, can be formulated as a two-step addition of a cobalt-hydride (i.e. step $-b$, followed by step $-c$, Scheme 4). Such hydrocobaltation has been used to prepare primary alkylcobaloximes from alkenes.[89] A similar route can also be proposed for the formation of α-substituted benzylcobalamins from substituted styrenes. However, the combination of cob(II)alamin with the tertiary radical formed by hydrogen atom transfer might be difficult, leading to either return to the alkene or collapse of the solvent cage and diffusion of the benzylic radical to give dimers. In this mechanism, the unstable tertiary alkylcobalamins are either formed only transiently or not at all. One problem with this mechanism involves the pK_a of "hydridocobalamin",[90] which has been reported to be significantly lower, ∼1,[91] than that of hydridocobaloxime. Thus, under the conditions used for the dimerization of alkenes (pH = 8) the concentration of protonated cob(I)alamin is extremely low.

One other indirect piece of support favors the mechanism in Scheme 4. X-ray and NMR analysis of primary alkylcobalamins has shown that the rotation around the Co−C bond is restricted because of steric interactions with the side chains on the β-face of the equatorial corrin ligand.[1,92−96] The preferred orientation of the alkyl ligand places its β-carbon between rings C and D where the steric interaction is most favorable (Figure 3). Even alkyl ligands that are trisubstituted at the β-carbon, such as a neopentyl group ($-CH_2CMe_3$), can be accommodated.[37−39,97] Thus, hydrogen atom transfer from a cobalt-hydride to the terminal carbon in mono- and 1,1-disubstituted olefins is sterically feasible and produces a resonance stabilized benzyl radical (Figure 3B). On the other hand, 1,2-di- and trisubstituted alkenes may not show reactivity (Chart 1) because highly unfavorable interactions would develop between the alkene and the β-side chains of the corrin during the approach trajectory.

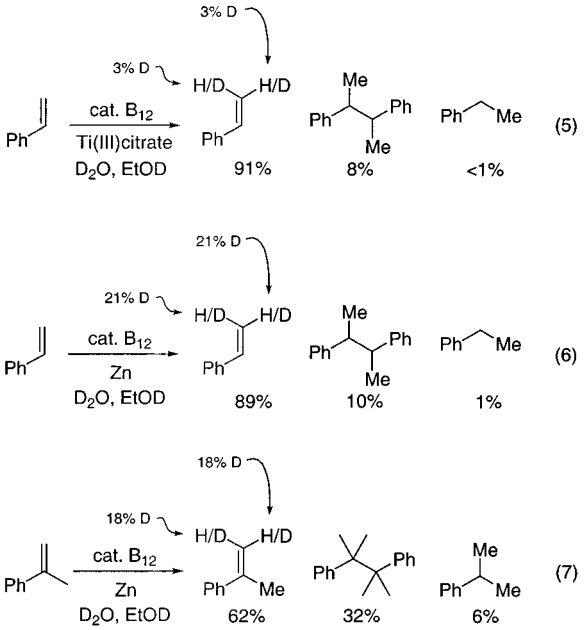
Scheme 5



Deuterium Labeling Studies. An alternative pathway to alkylcobalamins in the reaction between alkenes and cob(I)alamin involves nucleophilic attack followed by or concomitant with protonation by solvent (Scheme 5). In the former case, the reverse reaction would consist of an E_1cb mechanism, which would be significantly uphill given the expected low acidity of the methyl protons in **3**, and thus the reaction would not be readily reversible.

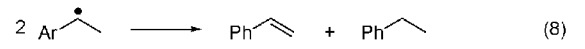
To test for any reversibility, we performed the dimerizations in D_2O and terminated the process before complete conversion of the starting alkene. ^1H and ^2H NMR analysis of the recovered alkenes clearly demonstrated deuterium incorporation at both terminal positions of the olefin in equal amounts (eqs 5−7). Furthermore, with α-methylstyrene the ^2H NMR spectrum displayed signals for the two terminal vinyl positions as well as the methyl group (integration ratio 1:1:3). Mass spectrometric analysis indicated that the recovered alkenes contained both mono- and dideuterated molecules, and as expected, deuterium was also present in the methyl groups of the products. Interestingly, the level of deuterium incorporation in the starting alkenes at similar conversion was dependent on the reductant (eqs 5 and 6), with a larger extent of labeling observed with Zn. In a separate experiment it was found that qualitatively, reduction of cob(II)alamin is much faster with Ti(III)-citrate than with Zn powder under the reaction conditions used. This difference can explain the higher extent of labeling in the presence of Zn according to the mechanism

(83) Ng, F. T. T.; Rempel, G. L. *J. Am. Chem. Soc.* **1982**, *104*, 621−623.
(84) Schrauzer, G. N.; Windgassen, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 1999−2007.
(85) Nguyen Van Duong, K.; Ahond, A.; Merienne, C.; Gaudemer, A. *J. Organomet. Chem.* **1973**, *55*, 375−82.
(86) Garr, C. D.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 10440−10445.
(87) This mechanism stands in contrast to a concerted four-center process that is preferred for other late transition metal complexes. Such a concerted pathway has also been proposed for B_{12} (ref 105), but several studies have provided experimental evidence against this mechanism. See refs 9, 81, and 86.
(88) Schrauzer, G. N.; Holland, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 1505−1506.
(89) (a) Bhandal, H.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1988**, 1110−1112. (b) Howell, A. R.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2715−2720.
(90) Hydridocobalamin is a rather ill-defined species altogether. It has been described as cob(I)alamin protonated on the electron pair in the d_{z2} orbital or as a Co(III) hydride. For a discussion of this species, see: (a) refs 29 and 91. (b) Chemaly, S. M.; Pratt, J. M. *J. Chem. Soc., Dalton Trans.* **1984**, 595−599. (c) Aleyunas, Y. W.; Fleming, P. E.; Finke R. G.; Pagano, T. C.; Marzilli, L. G. *J. Am. Chem. Soc.* **1991**, *113*, 3781.
(91) Lexa, D.; Savéant, J. *J. Chem. Soc., Chem. Commun.* **1975**, 872−874.
(92) Lenhert, P. G. *Proc. R. Soc. London, Ser. A* **1968**, *303*, 45−84.
(93) Alcock, N. W.; Dixon, R. M.; Golding, B. T. *J. Chem. Soc., Chem. Commun.* **1985**, 603−605.
(94) (a) Pagano, T. G.; Marzilli, L. G.; Flocco, M. M.; Tsai, C.; Carrell, H. L.; Glusker, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 531−542. (b) Wagner, T.; Afshar, C. E.; Carrell, H. L.; Glusker, J. P.; Englert, U.; Hogenkamp, H. P. C. *Inorg. Chem.* **1999**, *38*, 1785−1794.
(95) Deuterium incorporation into recovered alkene via hydrogen atom abstraction by cob(II)alamin from an intermediate radical inside a solvent cage has precedent in B_{12} chemistry. Garr and Finke showed the formation of a β-hydride elimination product from adenosylcobalamin (ref 86). For a detailed discussion of radical cage effects in organotransition metal chemistry, see: Koenig, T. W.; Hay, B. P.; Finke, R. G. *Polyhedron* **1988**, *7*, 1499−1516.
(96) Bax, A.; Marzilli, L. G.; Summers, M. F. *J. Am. Chem. Soc.* **1987**, *109*, 566−574.
(97) Mueller, S.; Wolleb, A.; Walder, L.; Keese, R. *Helv. Chim. Acta* **1990**, *73*, 1659−1668.



in Scheme 4. Removal of cob(II)alamin to give cob(I)alamin (k_{red}, Scheme 4) is less efficient with Zn and therefore is less competitive with the return of the radical intermediate to the starting alkene (k_b), leading to more deuterium incorporation into the alkene. In a semiquantitative analysis, comparison of the level of deuterium incorporation in the recovered alkene and the amounts of formation of product (one molecule of product is formed by two cage-escaped radicals) shows that regeneration of alkene is about 2-fold faster than product formation in eq 6.[95]

Aside from the mechanisms discussed, one other pathway could lead to label incorporation into starting material. Disproportionation of two radicals (eq 8) is well-



known and is likely to take place to some extent.[98] For every deuterated alkene regenerated by this pathway, one molecule of alkane is formed irreversibly. Hence, this pathway is relatively unimportant for the deuterium labeling studies discussed here since significantly larger amounts of deuterated alkenes than reduced products were present after partial conversions (eqs 5−7). With respect to the pathways in Scheme 5, collectively the deuterium labeling experiments disfavor a stepwise nucleophilic addition-protonation since the reverse reaction would be very unfavorable, inconsistent with the high extent of label incorporation via such a reverse reaction. On the other hand, the results of the deuterium labeling experiments are consistent with a reversible process up until the actual dimerization and support either hydrogen atom transfer from a hydridocobalamin species (Scheme 4) or a concerted nucleophilic attack and protonation (Scheme 5). In the latter mechanism, the reverse reaction that leads to deuterium incorporation would be an E2 pathway that may be more favorable than an E_1cb mechanism. As a working model, we favor the hydrogen atom transfer pathway as it can readily explain the chemoselectivity and regioselectivity of the reaction (see above), whereas a concerted nucleophilic addition at the benzylic carbon seems exceedingly difficult for 1,1-disubstituted alkenes given the steric requirements of the equatorial corrin ligand.

(98) For instance, radical disproportionation may well be a major route to the reduced products in Table 1.

Conclusion

In summary, we report a new multicomponent reaction that couples alkenes with defined regiochemistry under mild conditions in environmentally benign solvent systems such as ethanol/water. Our mechanistic studies indicate that organic free radicals are formed in this reaction. In the current process, the rate of combination of two radicals is increased by removing the persistent Co(II) radical with Ti(III) or Zn. This is in contrast to cobalt-catalyzed free-radical chain transfer and cobalt-mediated living radical polymerization in which the cobalt macrocycles function to reduce the steady-state concentration of free radicals. A disadvantage of the mechanism of dimerization from a synthetic perspective is the lack of diastereoselectivity that is inherent to radical combination.[13,58] The intramolecular reaction of dienes **6** and **7** suggests, however, that the transformation may find utility for the preparation of macrocycles. Further work along these lines is in progress.

Experimental Section

General. All NMR spectra were recorded on Varian U400, U500, or UI500NB spectrometers. ^1H spectra were referenced to $CHCl_3$ at 7.26 ppm, and ^{13}C spectra were referenced to $CDCl_3$ at 77.23 ppm unless otherwise indicated. Mass spectrometry was carried out by the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign (UIUC). Elemental analysis was performed by the Microanalysis Laboratory at UIUC. Infrared (IR) spectra were taken on a Mattson Galaxy Series FTIR 5000. GC and gas chromatography−mass spectrometry (GC−MS) data were collected on a Hewlett-Packard 5890A GC equipped with a 25 m HP-1 fused silica capillary column and a HP 5970 Series mass selective detector. The anaerobic chamber used was supplied by Coy Laboratory Products, Inc. The inside atmosphere was maintained at 6% H_2 and 94% N_2 and was deoxygenated with palladium catalysts. All dimerization reactions were performed in the Coy anaerobic chamber in vessels covered with aluminum foil and initiated in the dark under red light. Solvents used for dimerizations were deoxygenated under reduced pressure (10 min) and purged with N_2; this was repeated three times before storage in the anaerobic chamber. When possible, reactions were monitored by thin-layer chromatography on Merck silica gel 60 F_{254} plates. High performance liquid chromatography (HPLC) was performed on Rainin Dynamax SD-200 pumps equipped with a Dynamax UV-1 absorbance detector and a Supelcosil LC-PAH column. Compounds and solvents were obtained from Fisher, Aldrich, or Chemcycle at UIUC. Ti(III) chloride (Al-reduced) was purchased from Strem Chemical Company. Anhydrous $MgSO_4$ was used after workup for drying organic solutions. UV−vis studies were carried out using an Olis RSM 2000 instrument. No photolysis of samples was observed under the conditions of the spectroscopic analysis.

Typical Procedure for Dimerization. A flask covered with Al foil was charged with 0.01 mmol (10 mol %) of cyanocobalamin under a nitrogen atmosphere, followed by 7.0 mL of 50 mM aqueous Tris buffer (pH 8.0) and 5.5 mL of a 0.18 M aqueous Ti(III)citrate solution containing tetrabutylammonium hydroxide as phase transfer catalyst.[78] The substrate (0.1 mmol), dissolved in 12.5 mL of EtOH, was added to the B_{12} solution. After 1−24 h depending on the substrate, the reaction mixture was extracted with hexanes (3 × 20 mL), and the combined organic fractions were washed with water

(25 mL) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude products were analyzed by GC−MS and NMR to determine product ratios prior to purification.

Synthetic Route to 1-(3-Methyl-2-butenyl)-2-isopropenylpyrrole (6). For synthetic scheme with compound numbering and copies of ^{1}H NMR spectra, see Supporting Information.

1-(3-Methyl-2-butenyl)-2-acetylpyrrole (12). The procedure of Molander and Schmitt was followed using 2-acetylpyrrole and prenyl bromide.[99] The yield was 76% (clear oil) after purification by column chromatography eluting with 10% EtOAc in hexanes (R_f = 0.39). ^{1}H NMR (499.7 MHz) δ 1.74 (m, 3H), 1.75 (m, 3H), 2.43 (s, 3H), 4.95 (d, J = 7.0 Hz, 2H), 5.34 (m, 1H), 6.12 (m, 1H), 6.90 (m, 1H), 6.96 (m, 1H). ^{13}C NMR (125.7 MHz) δ 188.7 (Cq), 136.5 (Cq), 130.4 (Cq), 129.4 (CH), 120.7 (CH), 120.3 (CH), 108.2 (CH), 47.2 (CH_2), 27.5 (CH_3), 25.8 (CH_3), 18.2 (CH_3). IR (neat) 1650.2, 1406.8, 739.4, 1330.3, 1085.0, 1234.2, 943.6, 1468.5, 632.9, 1360.34. MS m/z (rel int, %) FI 177 (100), 178 (13). HRMS (EI) calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1156.

1-(3-Methyl-2-butenyl)-2-isopropenylpyrrole (6). To a 100 mL round-bottom flask was added 1.16 mmol (470 mg) CH_3PPh_3I. The flask was gently flame-dried and purged with Ar. After cooling to room temperature, dry, deoxygenated THF (4 mL) was added to the flask, which was then immersed into a −78 °C bath. A solution of n-BuLi in hexanes (0.97 mmol) was added, and the reaction mixture turned bright yellow. After 1 h, compound **12** (0.58 mmol) in 4 mL of dry, deoxygenated THF was added dropwise via cannula from a 15 mL conical flask. The reaction was incomplete by TLC after the addition, so it was allowed to warm to 0 °C. When the reaction did not proceed any further as judged by TLC, 25 mL of half saturated NH_4Cl was added, and the reaction was extracted with 3 × 25 mL of ether. The pooled organic layers were washed with 2 × 25 mL saturated NaCl, dried, and concentrated. The compound was purified by silica gel column chromatography using 5% EtOAc in hexanes (R_f 0.44). Yield 47% (light yellow oil). ^{1}H NMR (499.7 MHz) δ 1.75 (m, 3H), 1.78 (m, 3H), 2.11 (m, 3H), 4.59 (d, J = 6.6 Hz, 2H), 4.95 (q, J = 0.8 Hz, 1H), 5.13 (pentet, J = 1.5 Hz, 1H), 5.35 (m, 1H), 6.16 (m, 2H), 6.69 (m, 1H). ^{13}C NMR (125.7 MHz) δ 136.1 (Cq), 135.3 (Cq), 134.7 (Cq), 122.6 (CH), 121.7 (CH), 112.5 (CH_2), 108.3 (CH), 107.5 (CH), 45.8 (CH_2), 25.8 (CH_3), 24.3 (CH_3), 18.1 (CH_3). IR (neat) 712.4, 2920.3, 2970.2, 1445.6, 1376.0, 1311.4, 1472.8, 1077.4, 885.0, 1626.7. MS m/z (rel int, %) FI 175 (100), 176 (14). HRMS (EI) calcd for $C_{12}H_{17}N$ 175.1361, found 175.1359.

Reaction of 6 with Hydroxocobalamin and Ti(III)-citrate. The reaction using the general conditions described above provided cyclized products **8a** and **8b** in a 3:2 ratio (^{1}H NMR and GC−MS), which could not be separated by chromatography. The combined yield of both products was 70%. Cyclized product **8a**: ^{1}H NMR (499.7 MHz) δ 1.07 (s, 3H), 1.41 (s, 3H), 1.75 (s, 3H), 3.12 (t, J = 7.9 Hz, 1H), 4.01 (m, 2H), 4.79 (m, 1H), 4.95 (pentet, J = 1.5 Hz, 1H), 5.73 (dd, J = 3.6, 1.3 Hz, 1H), 6.19 (t, J = 2.9 Hz, 1H), 6.53 (dd, J = 2.6, 1.3 Hz, 1H). ^{13}C NMR (125.7 MHz) δ 143.0 (Cq), 113.6 (CH_2), 113.1 (CH), 111.5 (CH), 96.7 (CH), 60.5 (CH), 48.7 (CH_2), 41.1 (Cq), 28.6 (CH_3), 23.8 (CH_3), 23.0 (CH_3). HRMS (EI) calcd for $C_{12}H_{17}N$ 175.1361, found 175.1362. Cyclized and reduced product **8b**: ^{1}H NMR (499.7 MHz) δ 0.93 (d, J = 6.6 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 1.14 (s, 3H), 1.43 (s, 3H), 1.89 (m, 1H), 2.21 (td, J = 10.0, 7.8 Hz, 1H), 3.60 (t, J = 10.3 Hz, 1H), 4.03 (dd, J = 10.3, 7.4 Hz, 1H), 5.70 (dd, J = 3.4, 1.4 Hz, 1H), 6.17 (t, J = 2.7 Hz, 1H), 6.48 (dd, J = 2.5, 1.3 Hz, 1H). ^{13}C NMR (125.7 MHz) δ 112.8 (CH), 111.2 (CH), 96.2 (CH), 60.8 (CH), 50.1 (CH_2), 40.3 (Cq), 28.9 (CH or CH_3), 28.7 (CH or CH_3), 23.1 (CH_3), 22.5 (CH_3), 22.4 (CH_3). HRMS (EI) calcd for $C_{12}H_{19}N$ 177.1518, found 177.1517.

Synthetic Route to 1-(3,3-Diphenyl-2-propenyl)-2-isopropenylpyrrole (7). For synthetic scheme with compound numbering and copies of ^{1}H NMR spectra, see Supporting Information.

1-(3,3-Diphenyl-2-propenyl)-2-acetylpyrrole (13). 3-Bromo-1,1-diphenyl-1-propene was synthesized following literature procedures.[100,101] 2-Acetylpyrrole was reacted with 3-bromo-1,1-diphenyl-1-propene following the procedure of Molander and Schmitt, except only 1 equiv of the bromide was used.[99] After purification by column chromatography using 7% EtOAc in hexanes (R_f = 0.26), the desired product was obtained in 68% yield (viscous yellow oil). ^{1}H NMR (400.0 MHz) δ 2.46 (s, 3H), 5.02 (d, J = 6.9 Hz, 2H), 6.13 (dd, J = 3.0, 2.5 Hz, 1H), 6.29 (t, J = 7.0 Hz, 1H), 6.78 (dd, J = 2.4, 1.7 Hz, 1H), 6.98 (dd, J = 4.0, 1.7 Hz, 1H), 7.24 (m, 7H), 7.40 (m, 3H). ^{13}C NMR (100.6 MHz) δ 188.7 (Cq), 144.6 (Cq), 141.5 (Cq), 139.2 (Cq), 130.3 (Cq), 129.9 (CH), 129.7 (CH), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 124.8 (CH), 120.4 (CH), 108.5 (CH), 48.6 (CH_2), 27.5 (CH_3). IR (neat) 1649.4, 742.5, 1406.4, 761.9, 1328.1, 1234.2, 1087.8, 1363.0, 1443.8, 1466.8. MS m/z (rel int, %) FI 301 (100), 302 (24). HRMS (EI) calcd for $C_{21}H_{19}NO$ 301.1467, found 301.1473.

1-(3,3-Diphenyl-2-propenyl)-2-isopropenylpyrrole (7). The procedure described for the synthesis of **6** was followed using compound **13**. After purification by column chromatography eluting with 5% EtOAc in hexanes (R_f = 0.5 in 10% EtOAc in hexanes), **7** was obtained in 26% yield (clear oil). ^{1}H NMR (499.7 MHz) δ 2.06 (dd, J = 1.6, 0.9 Hz, 3H), 4.69 (d, J = 6.7 Hz, 2H), 4.86 (q, J = 0.7 Hz, 1H), 5.04 (quintet, J = 1.5 Hz, 1H), 6.16−6.19 (m, 2H), 6.20 (t, J = 6.8 Hz, 1H), 6.71 (dd, J = 2.5, 1.9 Hz, 1H), 7.22−7.45 (m, 10H). ^{13}C NMR (125.7 MHz) δ 144.1 (Cq), 141.7 (Cq), 139.0 (Cq), 135.9 (Cq), 134.9 (Cq), 129.9 (CH), 128.7 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 125.5 (CH), 122.8 (CH), 112.8 (CH_2), 108.5 (CH), 107.8 (CH), 47.1 (CH_2), 24.3 (CH_3). IR (neat) 733.6, 702.2, 716.4, 909.5, 759.8, 1444.2, 1493.8, 1312.7, 1248.5, 1472.8. MS m/z (rel int, %) FI 299 (100), 300 (44). HRMS (EI) calcd for $C_{22}H_{21}N$ 299.1674, found 299.1672.

Reaction of 7 with Vitamin B_{12} and Ti(III)citrate. The reaction provided exclusively the cyclized product **9** in 80% yield (R_f = 0.5 in 10% EtOAc in hexanes). ^{1}H NMR (499.7 MHz) δ 0.97 (s, 3H), 1.19 (s, 3H), 3.51 (t, J = 10.5 Hz, 1H), 3.65 (ddd, J = 11.9, 10.5, 7.4 Hz, 1H), 3.77 (dd, J = 10.5, 7.3 Hz, 1H), 4.07 (d, J = 11.7 Hz, 1H), 5.69 (dd, J = 3.5, 1.2 Hz, 1H), 6.15 (t, J = 3.0 Hz, 1H), 6.42 (dd, J = 2.6, 1.3 Hz, 1H), 7.17−7.46 (m, 10H). ^{13}C NMR (125.7 MHz) δ 147.7 (Cq), 144.3 (Cq), 143.2 (Cq), 129.1 (CH), 128.8 (CH), 128.5 (CH), 127.7 (CH), 126.94 (CH), 126.89 (CH), 113.1 (CH), 111.2 (CH), 96.5 (CH), 56.5 (CH), 53.0 (CH), 50.7 (CH_2), 40.8 (Cq), 28.2 (CH_3), 23.7 (CH_3). IR (neat) 704.3, 1493.2, 2959.4, 747.1, 1452.3, 2926.3, 1463.9, 738.2, 761.6, 1303.8. MS m/z (rel int, %) FI 301 (100), 302 (47). HRMS (EI) calcd for $C_{22}H_{23}N$ 301.1830, found 301.1826. The control reaction resulted in recovered starting material in 95%.

Synthetic Route to 1,1,2-Trichloro-5-phenyl-1,5-hexadiene (10). For synthetic scheme with compound numbering and copies of ^{1}H NMR spectra, see Supporting Information.

4-Pheny-4-penten-1-al Dimethyl Acetal (15). Compounds **14** and **16** were prepared following literature procedures.[102−104] In a 250 mL round-bottom flask, Ph_3PCH_3I (1.81 g, 4.5 mmol) and dry THF (54 mL) were combined and cooled to −78 °C. A 1.6 M solution of butyllithium (0.175 g, 3.44 mL) in hexane was added dropwise, and the resulting solution was allowed to stir for 30 min at −78 °C. Compound **14** (0.547 g, 2.6 mmol) in dry THF (54 mL) was added dropwise to the reaction solution. The solution was allowed to warm to 25 °C over 6 h. The solution was quenched with saturated NH_4Cl/

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H_2O (1:1; 50 mL) and combined with ether (50 mL). The organic layer was separated, washed with H_2O (100 mL) and brine (100 mL), and dried over $MgSO_4$. The product was purified by flash column chromatography eluting with hexane/ethyl acetate (38:1; $R_f = 0.25$) yielding a transparent oil (0.37 g, 70%). Characterization matched the previous literature data[102] for this compound obtained via a different procedure.

1,1,1-Trichloro-5-phenyl-5-hexen-2-ol (17). In a 25 mL round-bottom flask, trichloroacetic acid (0.18 g, 1.1 mmol) and sodium trichloroacetate (0.204 g, 1.1 mmol) were combined with **16** (0.12 g, 0.74 mmol) in DMF (6 mL). After the mixture stirred for 2 h, hexane/ether (9:1; 100 mL) was added, and the solution was washed with saturated $NaHCO_3$ (3 × 50 mL) and brine (100 mL) and dried, yielding a light yellow oil (0.29 g, 96%). It was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (1 H, m), 2.21 (1 H, m), 2.66 (1 H, m), 2.92 (1 H, m), 4.06 (1 H, dd, J = 9.98, 1.65 Hz), 5.16 (1 H, bm), 5.36 (1H, bd), 7.29 (1 H, m), 7.35 (2 H, m), 7.42 (2 H, m). ^{13}C NMR (125 MHz, APT, $CDCl_3$ referenced to 77.00 ppm) δ 29.9 (CH_2), 31.4 (CH_2), 82.2 (CH), 113.4 (CH_2), 126.1 (CH), 127.6 (CH), 128.4 (CH), 140.5 (Cq), 147.1 (Cq). FT-IR (CCl_4) 3588, 3055, 2986, 749, 732 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{13}O_1Cl_3$ 278.003198, found 278.002871.

1,1,2-Trichloro-5-phenyl-1,5-hexadiene (10). In a 100 mL round-bottom flask, PPh_3 (0.302 g, 1.15 mmol) was added to dry CCl_4 (22 mL) containing **17** (0.29 g, 1.05 mmol). The system was heated to reflux for 3 d. After the CCl_4 was removed under reduced pressure, the reaction material was passed through a silica plug eluting with hexane followed by purification by HPLC. To the light yellow oil was added an ethanolic NaOH solution (4 mg, 0.1 mmol in 0.5 mL), and the solution was stirred for 20 h. Ether (50 mL) was added, and the organic layer was separated, washed with saturated NH_4-Cl (50 mL) and brine (50 mL), and dried with $MgSO_4$. The product was purified by silica gel column chromatography eluting with hexane followed by HPLC purification yielding a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (2 H, m), 2.78 (2 H, m), 5.12 (1 H, d, J = 1.17 Hz), 5.35 (1 H, d, J = 1.17 Hz), 7.30 (1 H, m), 7.34 (2 H, m), 7.41 (2 H, m). ^{13}C NMR (125 MHz, APT, $CDCl_3$ referenced to 77.00 ppm) δ 32.4 (CH_2), 35.3 (CH_2), 113.6 (CH_2), 117.6 (Cq), 126.1 (CH), 127.7 (CH), 128.4 (CH), 132.2 (CCl_2), 140.1 (Cq), 146.1 (Cq). IR (CCl_4) 3084, 3055, 2985, 2943, 1629, 1495, 1445, 1265, 896, 725, 707 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{11}Cl_3$ 259.992634, found 259.992677.

Reaction of 10 with Vitamin B_{12} and Ti(III)citrate. The general procedure described above was followed and provided both diastereomers of **11** in 60% yield, which were purified together using HPLC; R_f 0.21 in hexanes. Diastereomer A: ^{1}H NMR δ 7.2 (m, 6H), 6.99 (br d, J = 6.6 Hz, 4H), 2.32 (m, 4H), 2.15 (m, 2H), 1.87 (m, 2H), 1.30 (s, 6H). Diastereomer B: ^{1}H NMR δ 7.2 (m, 6H), 6.89 (br s, 4H), 2.42 (td, J = 12.5, 3.2 Hz, 2H), 2.32 (m, 2H), 2.12 (m, 2H), 1.79 (td, J = 12.6, 4.6 Hz, 2H), 1.35 (s, 6H). HRMS (CI) calcd for $C_{24}H_{23}Cl_5$37Cl 522.9901, found 522.9896.

Synthesis and Reduction of Benzylcobalamin. All solvents were thoroughly degassed by five freeze−pump−thaw cycles and stored under argon. Benzylcobalamin was prepared as described previously,[38,105] and was characterized by UV−visible and ^{1}H NMR spectroscopy. A description of its reduction at one specific Ti(III)citrate concentration follows. In an anaerobic glovebox, two airtight Starna UV cell were charged with 1.5 mL of 0.2 mM aqueous benzylcobalamin in 0.05 M Tris buffer, pH 8.0. To one cell was added 10 μL of 0.175 M Ti(III)citrate, whereas the second cell served as control. The UV absorption spectra of both samples were monitored over 60 min, with the cell removed from the spectrophotometer and stored in the dark between scans.

General Procedure for Deuterium Labeling Studies Using Ti(III)citrate. In an anaerobic chamber, a flask was charged with vitamin B_{12} (135 mg, 0.10 mmol), 10 mL of EtOD, 5 mL of Tris buffer in D_2O (pD 7.9), and 7.5 mL of 0.26 M Ti(III)citrate in D_2O. The reaction mixture was stirred for 10 min prior to the addition by gastight syringe of styrene or α-methylstyrene (0.44 mmol). After 20 min, the aqueous solution was extracted with hexanes (3 × 30 mL), and the combined organic layers were washed with water (3 × 40 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure while maintaining the flask in an ice bath to avoid loss of volatile products. The deuterium incorporation was measured using both ^{1}H and ^{2}H NMR and MS. Deuterium incorporation at the vinyl positions of styrene or α-methylstyrene caused chemical shifts in the vinyl protons in the ^{1}H NMR. Thus, integration of the signals of vinyl protons in nondeuterated and monodeuterated products in the crude reaction mixture were used to provide the ratios of these products. Note that products containing two vinylic deuteriums will not give vinylic proton resonances and hence cannot be quantitated this way. Multiply deuterated products were in fact detected by mass spectrometry, but evaluation of several available ionization techniques did not result in reproducible quantitation of product ratios. Therefore, the percentages deuterium incorporation shown in eqs 5−7 are based only on NMR data and present an underestimate of the total deuterium incorporation. Incorporation into the products and methyl group of α-methyl styrene was quantitated by ^{2}H NMR before and after purification. In the case of the methyl group of α-methyl styrene the deuterium incorporation was integrated and quantitated in comparison to the integration of the vinylic deuterium resonances.

General Procedure for Deuterium Labeling Studies Using Zinc. A flask containing vitamin B_{12} (135 mg, 0.10 mmol) and Zn dust (1.25 g, 19.25 mmol) was introduced into the anaerobic chamber. To this was added 10 mL of EtOD and 10 mL of 0.05 M Tris buffer in D_2O. The suspension was stirred in the dark for 6 h prior to the addition of styrene or α-methylstyrene (0.87 mmol) via syringe. The reaction was worked up after 6 h as described for reactions in which Ti(III)citrate was used as the reducing agent.

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Supporting Information Available: ^{1}H NMR of compounds **6**−**13** and **17** and schemes for the synthesis of substrates **6**, **7**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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