JOC*Article*

Vitamin B_{12} Derivatives as Natural Asymmetric Catalysts: Enantioselective Cyclopropanation of Alkenes

Ying Chen and X. Peter Zhang*

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37996-1600

pzhang@utk.edu

Received January 22, 2004

Vitamin B_{12} derivatives were found for the first time to be general and efficient catalysts for asymmetric cyclopropanation of alkenes with ethyl diazoacetate (EDA). Among several common derivatives, aquocobalamin (B_{12a}) was shown to be the most effective catalyst for a variety of alkenes, providing *cis*-dominant cyclopropanes in excellent yields and moderate enantioselectivity. Reactivity studies under different conditions suggest that the active species in the proposed catalytic cycle is the base-on cob(II)alamin (B_{12r}) that is generated possibly via in situ reduction of B_{12a} by EDA.

Introduction

The vitamin B_{12} and its derivatives are the first known naturally occurring organometallic compounds that play a number of essential roles in biological systems.[1] They share the common cobalamin structure (Figure 1), the core of which is a low-spin Co(III) complex of corrin macrocycle that is highly substituted by methyl and amide groups in the periphery. In addition to the four equatorial nitrogen atoms of the corrin ring, the metal center is further coordinated by an intramolecularly bound 5,6-dimethylbenzimidazole at the lower axial site and a sixth ligand R at the upper axial site. The nature of the ligand R gives rise to the different derivatives of vitamin B_{12} such as cyanocobalamin (CNCbl, R = CN), methylcobalamin (MeCbl, R = CH_3), coenzyme B_{12} (AdoCbl, R = 5′-deoxyadenosyl), aquocobalamin (B_{12a}, R = HO·HCl), and the reduced form cob(II)alamin (B_{12r}, R = e) (Figure 1). Among a number of essential functions in biological systems, the vitamin B_{12}-dependent enzymes are notably known for mediating diverse isomerization reactions that correspond to intramolecular 1,2-shift between an H atom and an O, N, or C group on vicinal carbons and for promoting ribonucleotide reductase (RR) in the reduction of the ribose to the deoxyribose moiety during the first step of the biosynthesis of DNA.[1] The fascinating structures, the unique catalytic activities, and their intriguing mechanisms[2] have attracted the growing interest of scientists from numerous disciplines ever since the landmark establishment of the structure of vitamin B_{12} half a century ago.[3]

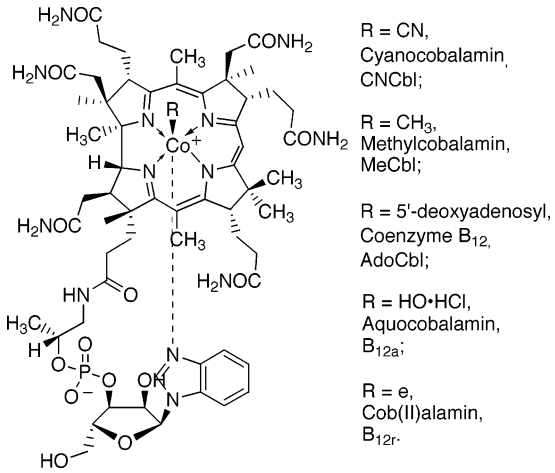


FIGURE 1. Structures of vitamin B_{12} derivatives.

Inspired by the extraordinary catalytic abilities of the natural organometallic system, there have been continuous searches for new catalytic reactions of vitamin B_{12} derivatives in nonbiological environments. As a result, a number of vitamin B_{12}-mediated chemical transformations that are unknown for vitamin B_{12}-dependent enzymes have been discovered, including new carbon−carbon bond formation reactions.[4] Of special interest in organic synthesis is the possibility that vitamin B_{12}

* To whom correspondence should be addressed. Fax: 865-974-3454.

(1) (a) *Chemistry and Biochemistry of B_{12}*; Banerjee, R., Ed.; Wiley-Interscience: New York, 1999. (b) *Vitamin B_{12} and B_{12} Proteins*; Krautler, B., Arigoni, D., Golding, B. T., Eds.; Wiley-VCH: Weinheim, 1998. (c) Schneider, Z.; Stroinski, A. *Comprehensive B_{12}*; W. de Gruyter: Berlin, 1987. (d) *B_{12}*; Dolphin, D., Ed.; Wiley-Interscience: New York, 1982. (e) Pratt, J. M. *Inorganic Chemistry of Vitamin B_{12}*; Academic Press: London, 1972.

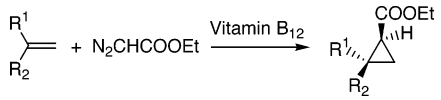
(2) (a) Halpern, J. *Science* **1985**, *227*, 869. (b) Pratt, J. M. *Pure Appl. Chem.* **1993**, *65*, 1513.

(3) (a) Hodgkin, D. C., Pickworth, J.; Robertson, J. H.; Trueblood, K. N.; Prosen, R. J.; White, J. G. *Nature* **1956**, *176*, 325. (b) Lenhert, P. G.; Hodgkin, D. C. *Nature* **1961**, *192*, 937. (c) Hodgkin, D. C. *Science* **1965**, *150*, 979.

(4) (a) Branchaud, B. P.; Friestad, G. K. In *Encyclopedia of Reagents for Organic Synthesis*; Paguette, L., Ed.; Wiley: New York, 1995; pp 5511−5514. (b) Pattenden, G. *Chem. Soc. Rev.* **1988**, *17*, 361. (c) Scheffold, R.; Abrecht, S.; Orlinski, R.; Ruf, H.-R.; Stamouli, P.; Tinembart, O.; Walder, L.; Weymuth, C. *Pure Appl. Chem.* **1987**, *59*, 363. (d) Scheffold, R.; Rytz, G.; Walder, L., In *Modern Synthetic Methods*; Scheffold, R., Ed.; Wiley: New York, 1983; Vol. 3, pp 355−440. (e) Shey, J.; McGinley, C. M.; McCauley, K. M.; Dearth, A. S.; Young, B. T.; van der Donk, W. A. *J. Org. Chem.* **2002**, *67*, 837 and references therein. (f) Njue, C. K.; Nuthakki, B.; Vaze, A.; Bobbitt, J. M.; Rusling, J. F. *Electrochem. Commun.* **2001**, *3*, 733.

10.1021/jo049870f CCC: $27.50
Published on Web 03/03/2004

SCHEME 1. Cyclopropanation of Alkenes Catalyzed by Vitamin B_{12} Derivatives



derivatives can be used as asymmetric catalysts in view of the natural existence of multiple stereogenic centers surrounding the metal center.[5] Demonstrated examples of vitamin B_{12}-mediated enantioselective processes are presently limited to conjugate reduction of α,β-unsaturated carbonyl compounds[6] and isomerization reactions of cyclic compounds such as epoxides, aziridines, and cyclopropanes.[7] As part of our research program of metalloporphyrin-based catalysis[8] and considering the close structural relationship between porphyrin and corrin macrocycles, we became interested in exploring the application of vitamin B_{12} derivatives as natural asymmetric catalysts for important organic transformations such as carbon−carbon bond formation reactions. We reveal herein that vitamin B_{12} derivatives are general and efficient catalysts for asymmetric cyclopropanation of alkenes with ethyl diazoacetate (EDA), producing *cis*-dominant cyclopropanes in excellent yields and moderate enantioselectivity (Scheme 1). This represents the first example of a vitamin B_{12} system that is effective for mediating this class of important reactions.[9]

Results and Discussion

The catalytic activities of the four common vitamin B_{12} derivatives CNCbl, MeCbl, AdoCbl, and B_{12a} (Figure 1) were investigated for cyclopropanation reaction using styrene as a model substrate and ethyl diazoacetate (EDA) as a carbene source. The reactions were carried out under a nitrogen atmosphere for 24 h at room temperature or 80 °C in trifluoroethanol (TFE), the most effective solvent found for the system (vide infra), with 1.2 equiv of EDA, using 2 mol % vitamin B_{12} derivative per styrene. As shown in Table 1, all of the derivatives were capable of catalyzing the reaction to give *cis*-dominant cyclopropanes with observed asymmetric inductions for both the diasteromers. An elevated reaction temperature was needed for high-yielding reactions, as the reaction rates were slow at room temperature.

TABLE 1. Cyclopropanation of Styrene with EDA-Catalyzed by Vitamine B_{12} Derivatives[a]

entry	cobalamin[b]	temp (°C)	yield[c]	*cis*:*trans*[c]	ee(%)[d]
1	CNCbl	23	1		−(−)
2	CNCbl	80	34	56:44	47(29)
3	MeCbl	23	3	57:43	63(35)
4	MeCbl	80	86	61:39	62(52)
5	AdoCbl	23	7	56:44	59(32)
6	AdoCbl	80	82	61:39	61(51)
7	B_{12a}	23	13	67:33	78(59)
8	B_{12a}	80	98	61:39	64(54)

[a] Carried out in TFE for 24 h under N_2 with 1.0 equiv of styrene, 1.2 equiv of EDA, and 2 mol % vitamin B_{12} derivative. Concentration: 0.5 mmol styrene/2 mL TFE. [b] See Figure 1. [c] Determined by GC. [d] Determined by chiral GC: *cis*(*trans*).

Although all the reactions were operated with styrene as the limiting reagent, the dimerization products of EDA, ethyl maleate, and fumarate were not observed or observed in a very small amount. This desirable feature is atypical for most of known cyclopropanation catalytic systems[9,10] as large excesses of alkenes have to be applied to minimize the common side products. Among the vitamin B_{12} derivatives, the catalytic efficiency varied from moderate for CNCbl to high for MeCbl and AdoCbl to excellent for B_{12a}. This reactivity trend can be readily explained by the relative lability of the ligand R of the vitamin B_{12} derivatives (Figure 1).[4e,11] At 80 °C, the use of B_{12a} as the catalyst resulted in the quantitative formation of the *cis*-dominant cyclopropanes (*cis*:*trans* = 61:39) in moderate enantioselectivities (*cis* 64% ee; *trans* 54% ee) (Table 1, entry 8). Although the yield was much lower, the enantioselectivity of B_{12a} could be further improved when the reaction was performed at room temperature (*cis* 78% ee; *trans* 59% ee) (Table 1, entry 7).

The finding of TFE as the most effective solvent resulted from a detailed study of solvent effect on the catalytic reaction. As indicated in Table 2, the catalytic activity of B_{12a} has a remarkable solvent dependence. The initial use of common organic solvents such as toluene and chlorobenzene resulted in low yields and low selectivities (Table 2, entries 1 and 2). Improvements were obtained when more polar solvents such as tetrahydrofuran, acetonitrile, dimethylformamide, and dimethyl sulfoxide were employed (Table 2, entries 3−6). This led to the attempts of using alcohols as reaction solvents, as they are known to well solubilize vitamin B_{12} derivatives including B_{12a}. Although both methanol and ethanol gave poor results (Table 2, entries 7 and 8), further improvements in both yields and selectivities were noted when higher alcohols such as 2-propanol, 1-butanol, and 1-hexanol were utilized (Table 2, entries 9−11). Among all solvents tested, the fluorinated ethanol TFE was found to afford the desired product in the best yield and selectivity, suggesting factors besides solubility may play important roles in the catalytic process (Table 2, entry 12).

(5) Pfaltz, A. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springler-Verlag: Berlin, 1989; Vol. 5, pp 199−248.

(6) (a) Fischli, A.; Suss, D. *Helv. Chim. Acta* **1979**, *62*, 48. (b) Fischli, A.; Suss, D. *Helv. Chim. Acta* **1979**, *62*, 2361. (c) Fischli, A.; Daly, J. J. *Helv. Chim. Acta* **1980**, *63*, 1628. (d) Fischli, A. *Helv. Chim. Acta* **1982**, *65*, 2697.

(7) (a) Su, H.; Waldler, L.; Zhang, Z.-D.; Scheffold, R. *Helv. Chim. Acta* **1988**, *71*, 1073. (b) Busato, S.; Tinembart, O.; Zhang, Z.-D.; Scheffold, R. *Tetrahedron* **1990**, *46*, 3155. (c) Bonhote, P.; Scheffold, R. *Helv. Chim. Acta* **1991**, *74*, 1425. (d) Zhang, Z.-D.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 2602. (e) Troxler, T.; Scheffold, R. *Helv. Chim. Acta* **1994**, *77*, 1193.

(8) (a) Chen, Y.; Huang, L.; Ranade, M. A.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 3714. (b) Chen, Y.; Huang, L.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 5925. (c) Chen, Y.; Huang, L.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 2493. (d) Huang, L.; Chen, Y.; Gao, G.-Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 8179. (e) Lee, M.-Y.; Chen, Y.; Zhang, X. P. *Organometallics* **2003**, *22*, 4905.

(9) (a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (b) Doyle, M. P.; Ren, T. *Prog. Inorg. Chem.* **2001**, *49*, 113. (c) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (e) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (f) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385−5453. (g) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247.

(10) Ikeno, T.; Iwakura, I.; Yamada, T. *J. Am. Chem. Soc.* **2002**, *124*, 15152.

(11) (a) Hamza, M. S. A.; Zou, X.; Brown, K. L.; van Eldik, R. *J. Chem. Soc., Dalton Trans.* **2002**, 3832. (b) Hamza, M. S. A.; Zou, X.; Brown, K. L.; van Eldik, R. *Inorg. Chem.* **2001**, *40*, 5440. (c) Marques, H. M.; Bradley, J. C.; Brown, K. L.; Brooks, H. *Inorg. Chim. Acta* **1993**, *209*, 161. (d) Brown, K. L.; Satyanarayana, S. *Inorg. Chim. Acta* **1992**, *201*, 113.

TABLE 2. Solvent Effect on Cyclopropanation of Styrene with EDA by B_{12a}[a]

entry	solvent	yield[b]	*cis*:*trans*[b]	ee(%)[c]
1	toluene	35	39:61	7(1)
2	chlorobenzene	39	52:48	34(7)
3	tetrahydrofuran	55	43:57	17(5)
4	acetonitrile	55	64:46	34(21)
5	dimethylformamide	52	68:32	48(28)
6	dimethylsulfoxide	59	62:38	47(31)
7	methanol	45	65:35	53(41)
8	ethanol	49	64:36	49(34)
9	2-propanol	66	63:37	45(32)
10	1-butanol	63	65:35	48(35)
11	1-hexanol	72	64:36	48(36)
12	trifluoroethanol	98	61:39	64(54)

[a] Carried out at 80 °C for 24 h under N_2 with 1.0 equiv of styrene, 1.2 equiv of EDA, and 2 mol % B_{12a}. Concentration: 0.5 mmol styrene/2 mL solvent. [b] Determined by GC. [c] Determined by chiral GC: *cis*(*trans*).

TABLE 3. Cyclopropanation of Styrene with EDA by B_{12a} under Different Conditions[a]

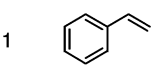
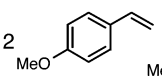
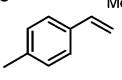
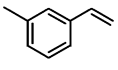
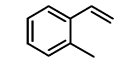
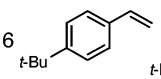
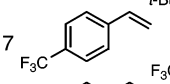
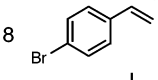
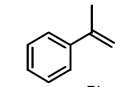
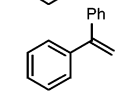
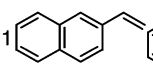
entry	B_{12a} (mol%)	temp (°C)	time (h)	yield (%)[b]	*cis*:*trans*[b]	ee(%)[c]
1	2	80	24	98	61:39	64(54)
2	2	80	13	93	61:39	64(54)
3	2	80	4	83	61:39	64(55)
4	5	80	24	95	60:40	64(55)
5	10	80	24	99	60:40	65(54)
6	1	80	24	89	61:39	62(54)
7	0.5	80	24	57	61:39	59(50)
8	2	50	24	61	65:35	72(57)
9	5	50	24	72	65:35	73(62)
10	10	50	24	78	65:35	73(61)
11	2	23	24	13	67:33	78(59)
12	5	23	24	19	67:33	78(66)
13	10	23	24	34	67:33	77(65)

[a] Carried out in TFE under N_2 with 1.0 equiv of styrene, 1.2 equiv of EDA, and catalytic amount of B_{12a}. Concentration: 0.5 mmol styrene/2 mL TFE. [b] Determined by GC. [c] Determined by chiral GC: *cis*(*trans*).

In addition to the solvent effect, the catalytic reaction by B_{12a} in TFE was evaluated under various conditions, including catalyst loading, reaction temperature, and reaction time (Table 3). At 80 °C using 2 mol % B_{12a}, the reaction time could be shortened from 24 to 13 h without significantly affecting the yield and selectivity, although a lower yield was observed when the reaction was stopped within 4 h (Table 3, entries 1−3). Although increase in catalyst loading had no obvious improvement in selectivity (Table 3, entries 4 and 5), reduction in catalyst loadings resulted in lower yields (Table 3, entries 6 and 7). The reaction could proceed at 50 °C and even at room temperature, but in slower rates that resulted in incomplete conversions within 24 h (Table 3, entries 8 and 11). The lower yields could be improved when higher catalyst loadings were employed (Table 3, entries 9, 10, 12, and 13). In all cases, lower reaction temperatures gave better diastereoselectivity and enantioselectivity.

Under the current optimized reaction conditions for styrene (using 2 mol % B_{12a} at 80 °C for 12−15 h in TFE), the substrate scope of the cyclopropanation reaction by B_{12a} was further explored with a variety of alkenes. The results obtained with a series of styrene derivatives are given in Table 4. Similar to styrene (Table 4, entry 1), alkyl-substituted derivatives such as those having a methyl group at the *para*, *meta*, or *ortho* postion or a *tert*-butyl group at the *para* position were suitable substrates, giving the corresponding *cis*-dominant cyclopropanes in excellent isolated yields and moderate enantioselectivities (Table 4, entries 3−6). Whereas styrene derivatives with electron-withdrawing substituents such as trifluoromethyl and bromo groups gave relatively lower isolated yields, the cyclopropanation of the electron-rich styrene 4-methoxystyrene proceeded in excellent isolated yield. High-yielding cyclopropanation reactions were also achieved for α-substituted styrenes with both aliphatic and aromatic groups (Table 4, entries 9 and 10). In addition, 2-vinylnaphthalene could be effectively cyclopropanated. For all styrene derivatives, the diastereoselectivity and enantioselectivity were found similar to those of styrene substrate.

TABLE 4. Cyclopropanation of Alkenes with EDA Catalyzed by B_{12a}[a]

entry	substrate	product	yield (%)[b]	*cis*:*trans*[c]	ee(%)[d]
1			88	61:39	64(54)
2			92	63:37	64(50[e])
3			86	64:36	64(54[e])
4			94	60:40	66(58)
5			88	61:39	NR[f](57[e])
6			95	62:38	66(51[e])
7			84	65:35	64(48[e])
8			70	62:38	65(47[e])
9			84	64:36	68(58)
10			95	—[g]	55[e,g](–[g])
11			75	58:42	64(NR[f])

[a] Carried out at 80 °C in TFE for 12−15 h under N_2 with 1.0 equiv of alkene, 1.2 equiv of EDA, and 2 mol % of B_{12a}. Concentration: 0.5 mmol alkene/2 mL TFE. [b] Isolated yields. [c] Determined by GC. [d] Determined by chiral GC: *cis*(*trans*). [e] Determined by ^1H NMR using Eu(hfc)$_3$ as a chiral shift reagent. [f] Not resolved. [g] No diastereomer.

The catalytic cyclopropanation by vitamin B_{12} derivatives is assumed to proceed via a carbene transfer mechanism similar to that proposed for other metal-mediated cyclopropanation systems (Scheme 2).[9] The Co(III) center of vitamin B_{12} is presumably reduced in situ by EDA to the catalytically active Co(II) form B_{12r},[12] which reacts with EDA to afford the cobalt-carbene

(12) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.

SCHEME 2. Proposed Cyclopropanation Mechanism by Vitamin B_{12}.

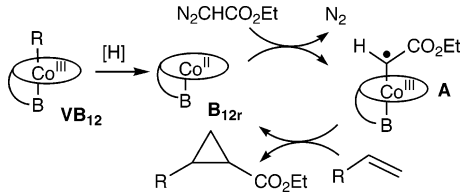


TABLE 5. Additive Effects on Cyclopropanation of Styrene with EDA Catalyzed by B_{12a}[a]

entry	additive (equiv)	temp (°C)	yield (%)[b]	*cis*:*trans*[b]	ee(%)[c]
1	HCO_2Na (0.1)	80	99	62:38	67(57)
2	$NaBH_4$ (0.2)	80	99	66:34	67(50)
3	HCO_2Na (0.2)	23	10	66:34	75(64)
4	$NaBH_4$ (0.3)	23	18	67:33	77(63)
5	*N*-methylimidazole (0.5)	80	98	61:39	62(63)

[a] Carried out in TFE for 24 h under N_2 with 1.0 equiv of styrene, 1.2 equiv of EDA, and 2 mol % of B_{12a}. Concentration: 0.5 mmol styrene/2 mL TFE. [b] Determined by GC. [c] Determined by chiral GC: *cis*(*trans*).

intermediate **A** with concomitant release of nitrogen. Carbene transfer from intermediate **A** to alkene substrate yields the cyclopropane product and regenerates the active B_{12r} to turn over the catalytic cycle. UV−vis studies on the reaction of B_{12a} with EDA showed the formation of the Co(II) form B_{12r} but not the Co(I) form B_{12s}.[13] Reactivity studies in the presence of external reducing agents such as sodium formate and sodium borohydride, which are known to reduce B_{12a} to B_{12r},[14] are also consistent with the proposed Co(II) active species. For example, nearly identical results were obtained between styrene reactions in the presence (Table 5, entries 1−4) and absence (Table 1, 7 and 8) of the reducing agents. Indistinguishable results were also attained between reactions with (Table 5, entry 5) and without (Table 1, entry 8) the addition of potential coordinating ligands such as *N*-methylimidazole,[15] suggesting that the Co centers in the catalytic cycle are in base-on forms. Attempts to reveal the nature of intermediate **A** have so far been inconclusive. Among several possible structures, the intermediate **A** could be considered as a cobalt(III)-carbene complex having a Co−C single bond with carbon-based radical character, an unusual metal-carbene structure that was recently proposed for 3-oxobutylideneaminato- and salen-cobalt-based cyclopropanation systems.[10]

Conclusions

In summary, we have demonstrated for the first time that vitamin B_{12} derivatives efficiently catalyze asymmetric cyclopropanation of alkenes, an important class of carbon−carbon bond formation reaction that is unknown for vitamin B_{12}-dependent enzymes. The catalytic system operates with alkenes as limiting reagents and requires no slow addition of diazo compounds. In view of these attractive characteristics together with their commercial availability from natural resources and industrial fermentation at relatively low costs, vitamin B_{12} derivatives may prove to be useful asymmetric catalysts for the efficient synthesis of cyclopropanes from alkenes. Efforts are underway to further improve its enantioselectivity and to elucidate the underlying mechanism.

Experimental Section

General Considerations. All reactions were carried out in oven-dried glassware using standard Schlenk techniques. All solvents were of liquid chromatography grade quality. Alkenes, vitamin B_{12}, B_{12a} and methylcobalamin were purchased and used without further purification. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a 300 MHz spectrometer and referenced with respect to internal TMS standard or residual solvent. Thin-layer chromatography was carried out on silica gel 60 F-254 TLC plates.

General Procedures for Cyclopropanation Reaction. Catalyst (2 mol %) was placed in an oven-dried, resealable Schlenk tube. The tube was capped with a Teflon screwcap, evacuated, and backfilled with nitrogen. The screwcap was replaced with a rubber septum, and 1.0 equiv of alkene (0.5 mmol) was added via syringe, followed by solvent (1 mL), 1.2 equiv of EDA, and solvent again (1 mL). The tube was purged with nitrogen for 1 min, and its contents were stirred at constant temperature in an oil bath. After the reaction finished, the resulting mixture was cooled to room temperature and concentrated. The residue was purified by flash silica gel chromatography to give the product.

Ethyl 2-phenylcyclopropane-1-carboxylate[16] was synthesized from styrene. ^{1}H NMR (300 MHz, $CDC1_3$) *trans*-isomer: δ 7.09−7.31 (m, 5H), 4.17 (q, J = 7.2 Hz, 2H), 2.52 (ddd, J = 9.3, 6.6, 4.2 Hz, 1H), 1.90 (ddd, J = 8.7, 5.4, 4.5 Hz, 1H), 1.60 (ddd, J = 9.0, 5.1, 4.2 Hz, 1H), 1.30 (ddd, J = 8.4, 6.6, 4.8 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 173.4, 140.1, 128.4, 126.4, 126.1, 60.7, 26.2, 24.2, 17.1, 14.3. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 7.18−7.28 (m, 5H), 3.88 (q, J = 7.2 Hz, 2H), 2.59 (m, 1H), 2.08 (ddd, J = 9.0, 7.8, 5.6 Hz, 1H), 1.72 (ddd, J = 6.3, 4.9, 4.4 Hz, 1H), 1.32 (ddd, J = 8.9, 7.9, 5.0 Hz, 1H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 170.9, 136.5, 129.2, 127.8, 126.6, 60.1, 25.4, 21.7, 14.0, 11.1.

Ethyl 2-(4-methoxyphenyl)cyclopropane-1-carboxylate[17] was synthesized from 4-methoxystyrene. ^{1}H NMR (300 MHz, $CDC1_3$) *trans*-isomer: δ 7.03 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 2.48 (ddd, J = 9.2, 6.6, 4.2 Hz, 1H), 1.82 (ddd, J = 8.7, 5.4, 4.2 Hz, 1H), 1.55 (ddd, J = 9.6, 5.1, 4.2 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.25 (m, 1H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 173.5, 158.3, 132.0, 127.3, 113.8, 60.6, 55.3, 25.6, 23.8, 16.7, 14.2. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 7.18 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 8.1 Hz, 2H), 3.89 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 2.52 (m, 1H), 2.03 (ddd, J = 9.3, 7.8, 5.7 Hz, 1H), 1.64 (m, 1H), 1.29 (ddd, J = 9.3, 8.1, 5.4 Hz, 1H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 171.0, 158.2, 130.2, 128.5, 113.2, 60.1, 55.1, 24.8, 21.6, 14.0, 11.2.

Ethyl 2-(4-trifluoromethylphenyl)cyclopropane-1-carboxylate[17] was synthesized from 4-trifluoromethylstyrene. ^{1}H NMR (300 MHz, $CDC1_3$) *trans*-isomer: δ 7.53 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 2.56 (ddd, J = 9.0, 6.0, 4.2 Hz, 1H), 1.90 (ddd, J = 8.7, 5.4, 4.2 Hz,

(13) Pratt, J. M. *Inorganic Chemistry of Vitamin B_{12}*; Academic Press: London, 1972; Chapter 7, pp 96−113.

(14) Wolak, M.; Zahl, A.; Schneppensieper, T.; Stochel, G.; van Eldik, R. *J. Am. Chem. Soc.* **2001**, *123*, 9780.

(15) (a) Marques, H. M.; Marsh, J. H.; Mellor, J. R.; Munro, O. Q. *Inorg. Chim. Acta* **1990**, *170*, 259. (b) Sirovatka, J. M.; Finke, R. G. *J. Am. Chem. Soc.* **1997**, *119*, 3057. (c) Sirovatka, J. M.; Finke, R. G. *Inorg. Chem.* **1999**, *38*, 1697. (d) Cregan, A. G.; Brasch, N. E.; van Eldik, R. *Inorg. Chem.* **2001**, *40*, 1430.

(16) Sanders, C. J.; Gillrspie, K. M.; Scott, P. *Tetrahedron Asymmetry* **2001**, *12*, 1055.

(17) Bachmann, S.; Mezzetti, A. *Helv. Chim. Acta* **2001**, *84*, 3063.

1H), 1.66 (ddd, J = 9.3, 5.7, 4.5 Hz, 1H), 1.30 (ddd, J = 8.4, 6.0, 4.8 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 172.9, 144.4, 128.9, 126.4, 125.4, 60.9, 25.7, 24.5, 17.1, 14.2. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 7.53 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 3.89 (q, J = 7.2 Hz, 2H), 2.59 (m, 1H), 2.14 (ddd, J = 9.3, 8.1, 5.7 Hz, 1H), 1.74 (m, 1H), 1.39 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 170.9, 141.0, 129.9, 126.4, 125.0, 60.6, 25.3, 22.2, 14.2, 11.6.

Ethyl 2-methyl-2-phenylcyclopropane-1-carboxylate[17] was synthesized from α-methylstyrene. ^{1}H NMR (300 MHz, $CDC1_3$): *trans*-isomer: δ 7.18−7.30 (m, 5H), 4.19 (q, J = 7.2 Hz, 2H), 1.96 (dd, J = 8.1, 5.7 Hz, 1H), 1.52 (s, 3H), 1.42 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 172.2, 145.9, 128.4, 127.3, 126.4, 60.5, 30.5, 27.8, 20.7, 19.8, 14.4. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 7.17−7.28 (m, 5H), 3.84 (m, 2H), 1.90 (dd, J = 7.8, 5.4 Hz, 1H), 1.78 (m, 1H), 1.46(s, 3H), 1.14 (dd, J = 7.8, 4.2 Hz, 1H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 171.2, 141.8, 128.7, 128.1, 126.6, 60.0, 32.0, 28.5, 28.4, 19.4, 13.9.

Ethyl 2-(4-methylphenyl)cyclopropane-1-carboxylate[18] was synthesized from 4-methylstyrene. ^{1}H NMR (300 MHz, $CDC1_3$) *trans*-isomer: δ 7.08 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 8.1 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.56 (ddd, J = 9.0, 6.3, 3.9 Hz, 1H), 2.31 (s, 3H), 1.86 (ddd, J = 8.4, 5.1, 4.2 Hz, 1H), 1.57 (m, 1H), 1.28 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 173.5, 137.0, 136.0, 129.1, 126.1, 60.6, 25.9, 24.0, 20.9, 16.9, 14.2. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 7.15 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 3.89 (q, J = 7.2 Hz, 2H), 2.53 (m, 1H), 2.29(s, 3H), 2.04 (ddd, J = 9.0, 8.1, 5.7 Hz, 1H), 1.67 (m, 1H), 1.30 (m, 1H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 171.1, 136.1, 133.4, 129.1, 128.6, 60.1, 25.2, 21.6, 21.0, 14.0, 11.2.

Ethyl 2-(2-methylphenyl)cyclopropane-1-carboxylate was synthesized from 2-methylstyrene. ^{1}H NMR (300 MHz, $CDC1_3$) *trans*-isomer: δ 6.98−7.17 (m, 4H), 4.20 (q, J = 7.2 Hz, 2H), 2.51 (ddd, J = 9.0, 6.6, 4.2 Hz, 1H), 2.38 (s, 3H), 1.78 (m, 1H), 1.57 (m, 1H), 1.31 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 173.9, 138.0, 137.8, 129.8, 126.7, 125.8, 60.6, 24.6, 22.3, 19.5, 15.3, 14.3. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 7.10−7.22 (m, 4H), 3.84 (q, J = 7.2 Hz, 2H), 2.44 (q, J = 8.4 Hz, 1H), 2.34 (s, 3H), 2.15 (ddd, J = 9.0, 8.1, 5.4 Hz, 1H), 1.74 (m, 1H), 1.34 (m, 1H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 171.1, 138.1, 134.8, 129.3, 129.1, 126.7, 125.3, 60.0, 24.4, 21.1, 19.3, 13.9, 11.2.

Ethyl 2-(3-methylphenyl)cyclopropane-1-carboxylate[19] was synthesized from 3-methylstyrene. ^{1}H NMR (300 MHz, $CDC1_3$) *trans*-isomer: δ 6.88−7.19 (m, 4H), 4.16 (q, J = 7.2 Hz, 2H), 2.48 (ddd, J = 9.3, 6.6, 4.2 Hz, 1H), 2.32 (s, 3H), 1.89 (m, 1H), 1.58 (m, 1H), 1.29 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 173.4, 140.0, 138.1, 128.3, 127.2, 126.9, 123.1, 60.6, 26.1, 24.1, 21.3, 17.0, 14.2. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 6.99−7.17 (m, 4H), 3.88 (q, J = 7.2 Hz, 2H), 2.54 (m, 1H), 2.31(s, 3H), 2.05 (ddd, J = 9.6, 8.1, 5.7 Hz, 1H), 1.68 (m, 1H), 1.29 (ddd, J = 8.7, 7.8, 4.8 Hz, 1H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 171.0, 137.2, 136.4, 130.1, 127.7, 127.3, 126.2, 60.1, 25.3, 21.6, 21.3, 14.0, 11.0.

Ethyl 2-[4-(*tert*-butyl)phenyl]cyclopropane-1-carboxylate[17] was synthesized from 4-*tert*-butylstyrene. ^{1}H NMR (300 MHz, $CDC1_3$) *trans*-isomer: δ 7.31 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 8.1 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.49 (ddd, J = 9.6, 6.6, 4.2 Hz, 1H), 1.88 (m, 1H), 1.58 (m, 1H), 1.30 (m, 1H), 1.30 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 173.5, 149.4, 137.1, 125.8, 125.3, 60.6, 34.4, 31.3, 25.8, 24.1, 16.9, 14.2. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 7.28 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 3.87 (q, J = 7.2 Hz, 2H), 2.53 (m, 1H), 2.04 (ddd, J = 9.6, 8.1, 5.7 Hz, 1H), 1.69 (m, 1H), 1.30 (m, 1H), 1.29 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 171.3, 149.6, 133.7, 129.2, 125.0, 60.3, 34.6, 31.6, 25.3, 22.1, 14.2, 11.4.

Ethyl 2,2-diphenylcyclopropane-1-carboxylate[17] was synthesized from 1,1-diphenylethylene. ^{1}H NMR ($CDC1_3$): δ 7.13−7.35 (m, 10H), 3.90 (m, 2H), 2.53 (dd, J = 8.1, 6.3 Hz, 1H), 2.16 (dd, J = 5.7, 4.8, 1H), 1.56 (dd, J = 8.1, 4.8 Hz, 1H), 0.99 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$): δ 170.5, 144.8, 140.2, 129.7, 128.3, 128.2, 127.5, 126.9, 126.4, 60.3, 39.7, 28.9, 20.0, 13.9.

Ethyl 2-(4-bromophenyl)cyclopropane-1-carboxylate[19] was synthesized from 4-bromostyrene. ^{1}H NMR (300 MHz, $CDC1_3$) *trans*-isomer: δ 7.39 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 2.47 (ddd, J = 9.6, 6.9, 4.5 Hz, 1H), 1.87 (m, 1H), 1.60 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.26 (m, 1H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 173.1, 139.1, 131.5, 127.9, 120.1, 60.8, 25.5, 24.1, 17.0, 14.2. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 7.38 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 3.90 (q, J = 6.9 Hz, 2H), 2.50 (m, 1H), 2.08 (ddd, J = 9.3, 8.1, 5.7 Hz, 1H), 1.67 (m, 1H), 1.34 (ddd, J = 8.4, 7.5, 5.1 Hz, 1H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 170.7, 135.6, 131.0, 130.9, 120.5, 60.3, 24.9, 21.8, 14.9, 11.3.

Ethyl 2-(2-naphthalenyl)cyclopropane-1-carboxylate[20] was synthesized from 2-vinylnaphthalene. ^{1}H NMR (300 MHz, $CDC1_3$) *trans*-isomer: δ 7.79 (m, 3H), 7.56 (s, 1H), 7.43 (m, 2H), 7.20(dd, J = 8.4, 2,4 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 2.69 (ddd, J = 9.6, 6.9, 4.5 Hz, 1H), 1.68 (m, 1H), 1.60 (m, 1H), 1.42 (ddd, J = 8.4, 6.6, 4.5 Hz, 1H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *trans*-isomer: δ 173.4, 137.5, 133.3, 132.2, 128.1, 127.6, 127.4, 126.2, 125.4, 124.7, 124.5, 60.7, 26.4, 24.1, 17.0, 14.2. ^{1}H NMR (300 MHz, $CDC1_3$) *cis*-isomer: δ 7.75 (m, 4H), 7.41 (m, 3H), 3.82 (q, J = 6.9 Hz, 2H), 2.71 (q, J = 8.1 Hz, 1H), 2.14 (ddd, J = 9.6, 8.1, 5.7 Hz, 1H), 1.84 (m, 1H), 1.40 (m, 1H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDC1_3$) *cis*-isomer: δ 170.9, 134.0, 133.1, 132.3, 127.9, 127.6, 127.5, 127.3, 125.8, 125.4, 60.1, 25.6, 21.9, 14.0, 11.3.

Acknowledgment. We are grateful for financial support of this work from the Department of Chemistry of the University of Tennessee. We thank Dr. Lingyu Huang for initial investigation on this project.

Note Added after ASAP Posting. Reference 4f was not included in the version posted ASAP March 3, 2004; the corrected version was posted March 10, 2004.

JO049870F

(18) Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem.* **2001**, *66*, 8260.

(19) Hixson, S. S.; Franke, L. A.; Gere, J. A.; Xing, Y. *J. Am. Chem. Soc.* **1988**, *110*, 3601.

(20) Solladie-Cavallo, A.; Isarno, T. *Tetrahedron Lett.* **1999**, *40*, 1579.