Vitamin B_{12}-Photocatalyzed Cyclopropanation of Electron-Deficient Alkenes Using Dichloromethane as the Methylene Source

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Abstract: The cyclopropyl group is of great importance in medicinal chemistry, as it can be leveraged to influence a range of pharmaceutical properties in drug molecules. This report describes a Vitamin B_{12}-photocatalyzed approach for the cyclopropanation of electron-deficient alkenes using CH_2Cl_2 as the methylene source. The reaction proceeds in good to excellent yields under mild conditions, has excellent functional group compatibility, and is highly chemoselective. The scope could also be extended to the preparation of D_2-cyclopropyl and methyl-substituted cyclopropyl adducts starting from CD_2Cl_2 and 1,1-dichloroethane, respectively.

The cyclopropyl group is among the most ubiquitous small ring system in medicinal chemistry and has been extensively exploited in pharmaceuticals since the 1960s.[1] Cyclopropanes have proven to be invaluable isosteres for small alkyl groups, aromatic groups, and alkenes, as they can influence important pharmaceutical properties such as lipophilicity, metabolic stability, conformational stability, and pharmacokinetics, among others.[2–4] Consequently, they continue to be prevalent in recently approved or investigational drugs.[5] Another emerging use of cyclopropanes in drug development has been to block potentially reactive Michael acceptors. In 2014, Bristol-Myers Squibb demonstrated that the introduction of a cyclopropyl group as an isostere for an electron-deficient alkene led to a significant improvement in the physicochemical properties of their lead compounds in the development of allosteric inhibitors of HCV (Figure 1A).[6] Similar cyclopropyl moieties derived from electron-deficient alkenes can also be found in FDA-approved drugs (Figure 1B).[5] These examples demonstrate that synthetic strategies for the cyclopropanation of electron-deficient alkenes are of great value as a tool for medicinal chemists to alter physicochemical properties of promising lead compounds. Cyclopropanes are also invaluable building blocks in organic synthesis owing to their unique structural and electronic properties,[7,8] further highlighting the importance of having reliable, efficient, and chemoselective cyclopropanation methods with good functional group compatibility.

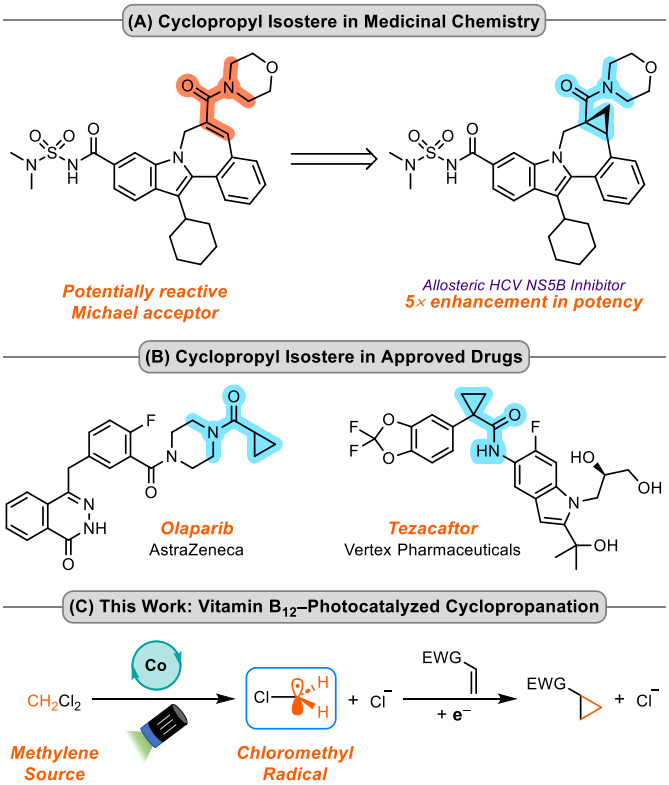
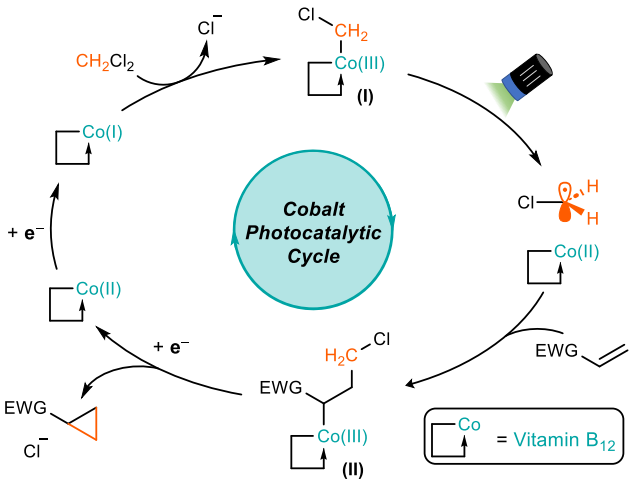


Figure 1. (A) Example of the cyclopropyl group as an isostere for potentially reactive electron-deficient alkenes in the pursuit of lead compounds for allosteric HCV NS5B inhibitors (Bristol-Myers Squibb, reference 6). (B) Examples of the cyclopropyl isostere to block potentially reactive electron-deficient alkenes in approved drugs. (C) This work: Vitamin B_{12}-photocatalyzed cyclopropanation of electron-deficient alkenes.

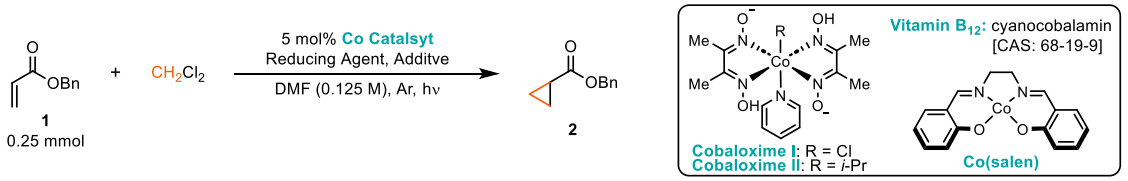
Among the synthetic strategies for cyclopropanation of alkenes[9,10], the Simmons–Smith and the Corey–Chaykovsky cyclopropanation reactions are the most established and widely utilized methods in the literature.[11–17] In contrast, radical-based methodologies are still less well-developed. One notable advancement in this area is alkene cyclopropanations via Co(II)–based metalloradical catalysis.[18–24] While the associated methods are broad in scope and have enabled the preparation of

cyclopropyl adducts in high diastereo- and enantioselectivities, they rely on the use of diazo compounds to generate the key metalloradical intermediate. Recently, the groups of Suero and Molander, among others[25], have demonstrated that visible-light photoredox catalysis can be leveraged for the preparation of cyclopropanes from CH_2I_2 and borosilicate salts, respectively.[26–28] In this light, we envisioned that a visible-light-mediated cyclopropanation reaction using dichloromethane (CH_2Cl_2), a low-cost organic solvent, as the methylene source would be an ideal approach for the installation of cyclopropyl groups. Catalytic cyclopropanation protocols employing 1,1-dichloroalkanes are extremely rare[29–34], likely owing to difficulty of activating the strong C–Cl bond. Inspired by seminal contributions from Scheffold[35] and Giese[36], and more recent reports from Carreira[37], Gryko[38–40], and Zultanski[41] using nucleophilic square planar cobalt complexes like Vitamin B_{12} for the generation of radicals from alkyl halides, we envisioned that nucleophilic activation of CH_2Cl_2, followed by $^{\bullet}CH_2Cl$ radical generation, could provide a general radical polar-crossover approach for the cyclopropanation of alkenes (Figure 1C). Furthermore, Rusling and coworker have observed the formation of cyclopropylbenzene from styrene using Vitamin B_{12} in the presence of CH_2Cl_2 under electrochemical conditions, albeit in low yields (<10%).[42] Our mechanistic design for our photocatalytic cyclopropanation using CH_2Cl_2 as the methylene source is outlined in Scheme 1. We anticipated that generation of the highly nucleophilic Co(I) oxidation state of Vitamin B_{12} would enable an S_N2-type nucleophilic substitution with CH_2Cl_2[43–45], generating Co(III)–CH_2Cl intermediate **I**. Intermediate I could then undergo facile photolysis (estimated BDE of 15 kcal/mol, see Supporting Information) upon visible light irradiation to generate a $^{\bullet}CH_2Cl$ radical and a persistent Co(II) radical.[46] Giese addition followed by trapping of the carbon radical intermediate by Co(II) would yield intermediate **II**, which upon single-electron reduction could afford the cyclopropyl adduct after a polar 3-*exo-tet* cyclization of the resulting carbanion.[42]



Scheme 1. Mechanistic design for the Vitamin B_{12}-photocatalyzed cyclopropanation of electron-deficient alkenes.

Table 1. Optimization of reaction conditions and control reactions.[a]



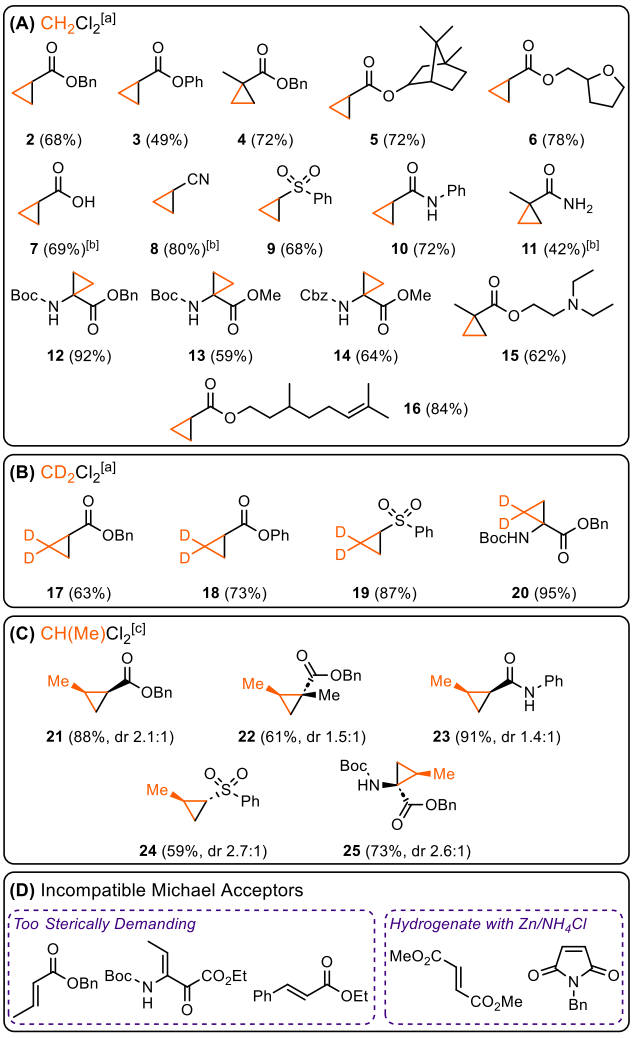
Entry	CH_2Cl_2	Co Catalyst	Reducing Agent	Additive	LED λ (Intensity)	Yield of **2**[b]
1	2.0 equiv	Vitamin B_{12}	Zn (3 equiv)	NEt_3•HCl (1.4 equiv)	456 nm (100%)	37%
2	2.0 equiv	Vitamin B_{12}	Zn (3 equiv)	NEt_3•HCl (1.4 equiv)	525 nm (100%)	56%
3	3.0 equiv	Vitamin B_{12}	Zn (3 equiv)	NEt_3•HCl (1.4 equiv)	525 nm (100%)	61%
4	4.0 equiv	Vitamin B_{12}	Zn (3 equiv)	NEt_3•HCl (1.4 equiv)	525 nm (100%)	38%
5	3.0 equiv	Vitamin B_{12}	Zn (2 equiv)	NEt_3•HCl (1.4 equiv)	525 nm (100%)	44%
6	3.0 equiv	Vitamin B_{12}	Mn (2-4 equiv)	NEt_3•HCl (1.4 equiv)	525 nm (100%)	24-42%
7	3.0 equiv	Vitamin B_{12}	Zn (3 equiv)	NH_4Cl (1.0 equiv)	525 nm (100%)	65%
8	3.0 equiv	Co(salen)	Zn (3 equiv)	NH_4Cl (1.0 equiv)	525 nm (100%)	7%
9	3.0 equiv	Cobaloxime I or II	Zn (3 equiv)	NH_4Cl (1.0 equiv)	525 nm (100%)	< 5%
10	1.5 equiv	Vitamin B_{12}	Zn (3 equiv)	NH_4Cl (1.0 equiv)	525 nm (100%)	62%
11	1.5 equiv	Vitamin B_{12}	Zn (3 equiv)	NH_4Cl (1.0 equiv)	525 nm (75%)	78%[c]
12	1.5 equiv	-	Zn (3 equiv)	NH_4Cl (1.0 equiv)	525 nm (75%)	N.R.
13	1.5 equiv	Vitamin B_{12}	-	NH_4Cl (1.0 equiv)	525 nm (75%)	N.R.
14	1.5 equiv	Vitamin B_{12}	Zn (3 equiv)	-	525 nm (75%)	N.R.
15	1.5 equiv	Vitamin B_{12}	Zn (3 equiv)	NH_4Cl (1.0 equiv)	No hv	29%

[a] Standard Conditions: **1** (0.25 mmol, 1.0 equiv), CH_2Cl_2, Co catalyst (5 mol%), reducing agent, and the additive in DMF (2 mL) were irradiated under Ar with a Kessil PR-160L LED (40 W maximum output power) for 8-18 h. [b] Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as the external standard. [c] Average of three trials. N.R.: no reaction.

We began our investigation of our Vitamin B_{12}-photocatalyzed cyclopropanation of electron-deficient alkenes using benzyl acrylate (**1**) as a model system (see Supporting Information for full optimization). In an initial attempt, we were able to successfully generate cyclopropyl adduct **2** in 37% yield using only 2.0 equivalents of CH_2Cl_2, 5 mol% of Vitamin B_{12}, and Zn/NEt_3•HCl as the reducing agent under blue (456 nm) LED irradiation (Table 1, entry 1). Switching the irradiation wavelength to 525 nm resulted in a significant increase in yield (entry 2), likely a result of greater spectral overlap with the absorption of the Co(III)–CH_2Cl ligand-to-metal charge-transfer (LMCT) band (*vide infra*). More than 3.0 equiv of CH_2Cl_2 was found to be detrimental

to the yield of **2** (entries 3,4), and Zn (3.0 equiv) and NH_4Cl (1.0 equiv) were determined to be the optimal reducing agent and additive, respectively (entries 5-7). Other square planar cobalt complexes were tested but displayed minimal to no catalytic activities (entries 8,9). Gratifyingly, the amount of CH_2Cl_2 could be decreased to 1.5 equiv without negatively impacting the yield (entry 10). Finally, optimization of the photon flux led to a further increase in the yield, giving **2** in 78% yield (entry 11). Control reactions where Zn, NH_4Cl, or Vitamin B_{12} were absent did not yield any of cycloadduct **2**, indicating that each of these components is crucial for reactivity (entries 12-44). 29% yield of **2** could be obtained in the absence of irradiation, likely resulting from thermolysis of the weak Co(III)–C bond of intermediate **I** (~15 kcal/mol) at room temperature (entry 15). Attempting the reaction at higher temperatures (without LED irradiation) did not result in any meaningful increases in yield.

With the optimized conditions identified, we examined the scope of the Vitamin B_{12}-photocatalyzed cyclopropanation of electron-deficient alkenes (Scheme 2A). Using CH_2Cl_2 as the methylene source, cyclopropyl adducts from a series of acrylates (**2**-**6**), acrylic acid (**7**), acrylonitrile (**8**), phenyl vinyl sulfone (**9**), *N*-phenylacrylamide (**10**) and methacrylamide (**11**) were generated in moderate to good yields. Our method's tolerance to protic functional groups (**7**, **11**) is particularly noteworthy, as such functionality is generally not compatible with established methods such as the Corey–Chaykovsky cyclopropanation reaction.[17] Dehydroamino acid esters were also found to be suitable substrates under our reaction conditions (**12**-**14**), highlighting the potential utility of this method for generating unnatural amino acid derivatives.[47–49] Of note, a methacrylate derivative with a pendant tertiary aliphatic amine (**15**) could be cyclopropanated in 62% yield. As tertiary aliphatic amines are potent excited state quenchers of many common photocatalysts, such functionality would not be tolerated in the aforementioned state-of-the-art photoredox-catalyzed cyclopropanation methods[50,51], highlighting an advantage of employing our Vitamin B_{12}-photocatalyzed approach. Furthermore, **16** could also be generated in 84% yield as the sole cyclopropanated product, a remarkable improvement compared to known methods which produce a 2:1 ratio of mono- to bis-cyclopropyl adducts.[52] This result highlights the chemoselectivity of our method that is afforded by the apparent nucleophilicity of the $^{\bullet}CH_2Cl$ radical and its preference for the polarity-matched electron-deficient alkene.[53]

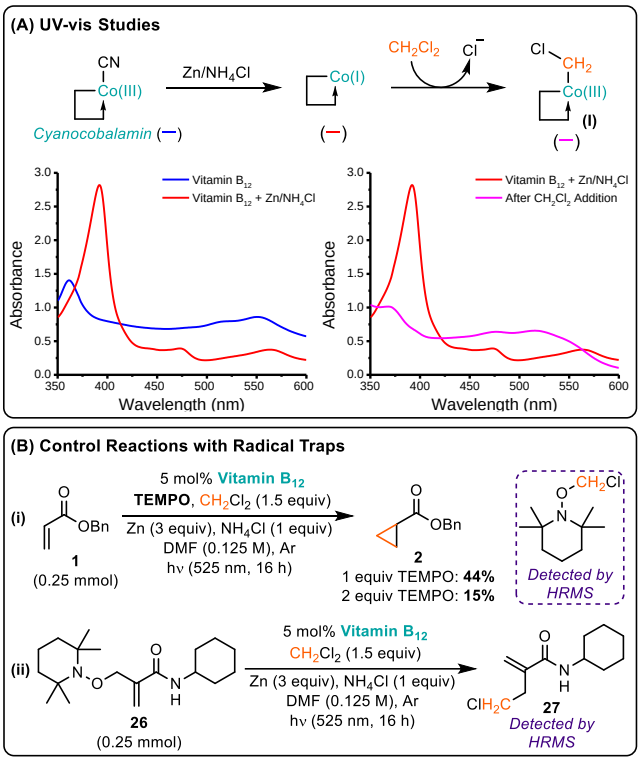


Scheme 2. Reaction scope. Yields reported as isolated yields of purified products. [a] Reaction conditions: Alkene (0.25 mmol), CH_2Cl_2/CD_2Cl_2 (1.5 equiv), Vitamin B_{12} (5 mol%), Zn (3 equiv), NH_4Cl (1 equiv), and DMF (2 mL) were irradiated at 525 nm under Ar for 16 h. [b] Reaction performed in DMF-d_7 and the yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction conditions: Alkene (0.25 mmol), $CH(Me)Cl_2$ (1.5 equiv), Vitamin B_{12} (20 mol%), Zn (5 equiv), NH_4Cl (1 equiv), and DMF (2 mL) were irradiated at 525 nm under Ar for 16 h. Diastereomeric ratios (dr) were determined by ^1H NMR analysis of the isolated purified products.

Deuteration of small-molecule drugs has been shown to favorably affect their pharmacokinetic properties.[54] Consequently, the metabolism of certain drugs may be positively influenced upon deuterium incorporation, resulting in improved safety, tolerability, or efficacy.[55,56] Therefore, we envisioned that by starting with readily available CD_2Cl_2, our Vitamin B_{12}-photocatalyzed cyclopropanation could offer a facile and inexpensive means for late-stage deuterium incorporation into pharmaceutically active compounds. Gratifyingly, as shown in Scheme 2B, our optimized reaction conditions were able to afford a variety of D_2-cyclopropyl adducts (**17**-**20**) in good to excellent yields upon switching the methylene source to CD_2Cl_2. Through modification of the reaction conditions (see Supporting Information), we were also able to extend our protocol to the generation of methyl-substituted

cyclopropanes (Scheme 2C).[57] By switching the methylene source to 1,1-dichloroethane ($CH(Me)Cl_2$), methyl-substituted cyclopropyl adducts **21**-**25** could be generated in good to excellent yields, albeit with increased catalyst loadings being required. It should be noted, however, that moderate yields can still be obtained using 5 mol% of Vitamin B_{12} (see Supporting Information). Interestingly, these reactions produced a mixture of diastereomers, with adducts **21** and **23** even favoring the thermodynamically less stable *cis* cyclopropane. The observed diastereoselectivities are comparable with those previously reported by Zhang and coworkers for the Vitamin B_{12}-catalyzed cyclopropanation of styrenes using ethyl diazoacetate.[58] Finally, during our survey of the scope of our cyclopropanation reaction, we noted several limitations regarding the identity of the electron-deficient alkene (Scheme 2D). For example, alkenes with substitution at the β-position were not compatible with our approach, likely owing to sterics inhibiting the initial addition of the $^{\bullet}CH_2Cl$ radical, a commonly observed limitation of Giese reactions.[59] Highly activated alkenes, such as dimethyl fumarate and maleimides, were also not tolerated, as these were observed to undergo hydrogenation in the presence of Zn and NH_4Cl. As anticipated, more electron-rich alkenes, such as styrene, were also not compatible with our approach (see Supporting Information).[42]

Having explored the synthetic scope, we next turned our attention to the key steps of the reaction mechanism, specifically, the feasibility of the S_N2-type nucleophilic substitution and the photolysis/$^{\bullet}CH_2Cl$ radical generation steps. To access the viability of the S_N2-type nucleophilic substitution, we performed a series of UV-vis studies, as shown in Scheme 3A. Upon addition of Zn and NH_4Cl to a sample of Vitamin B_{12}, the appearance of a new λ_{max} at ~390 nm, indicative of the formation of Co(I), was observed.[60,61] Addition of CH_2Cl_2 to the sample resulted in the immediate loss of the Co(I) band, accompanied by the growth of a new charge-transfer band between 450-600 nm, characteristic of the formation of a Co(III)–R species.[62] These data provide support for the formation of the Co(I) oxidation state of Vitamin B_{12} and the subsequent S_N2-type nucleophilic substitution with CH_2Cl_2 to form intermediate **I** under our reaction conditions. Next, we performed a control reaction with TEMPO to probe for the formation of the $^{\bullet}CH_2Cl$ radical that would be generated upon photolysis of intermediate **I**. For our model system of the cyclopropanation of benzyl acrylate (**1**), increasing concentrations of TEMPO decreased the formation of cyclopropyl adduct **2** (Scheme 3B), and both GC-MS and HRMS analysis of the reaction mixture identified the formation of the TEMPO–CH_2Cl adduct (see Supporting Information). Additionally, by employing the recently reported allyl–TEMPO radical trap CHANT (**26**) under our standard conditions,[63] the expected CHANT–CH_2Cl product (**27**) was identified using HRMS analysis (see Supporting Information), further supporting the formation of $^{\bullet}CH_2Cl$ radicals under our reaction conditions.



Scheme 3. (A) UV-vis studies investigating the feasibility of the S_N2-type nucleophilic substitution step. [Vitamin B_{12}] = 0.11 mM, Zn = 25 mg, [NH_4Cl] = 69 mM, and [CH_2Cl_2] = 0.05 mM in 3 mL DMF. (B) Control reactions in the presence of radical traps.

In summary, a practical and efficient Vitamin B_{12}-photocatalyzed approach for the cyclopropanation of electron-deficient alkenes using CH_2Cl_2 as the methylene source has been developed. The reaction works for a broad range of electron-deficient alkenes, proceeds in high chemoselectivity, and has increased functional group tolerance compared to other state-of-the-art methods. The reaction could also be extended to the preparation of D_2-cyclopropyl and methyl-substituted cyclopropyl adducts starting from CD_2Cl_2 and 1,1-dichloroethane, respectively. Mechanistic studies indicate the reaction likely proceeds through an S_N2-type nucleophilic substitution between the Co(I) oxidation state of Vitamin B_{12} and the 1,1-dichloroalkane, followed by photolysis under visible-light irradiation. We anticipate that our approach will be of great value to medicinal chemists for the late-stage incorporation of cyclopropyl isosteres in pharmaceutically active compounds. Furthermore, the biocompatibility and water solubility of Vitamin B_{12} may enable opportunities for the direct cyclopropanation of biomolecules, like peptides and proteins, in aqueous, physiological media.[64]

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Keywords: Cyclopropanation • Vitamin B_{12} • Photocatalysis • Visible Light • Radicals

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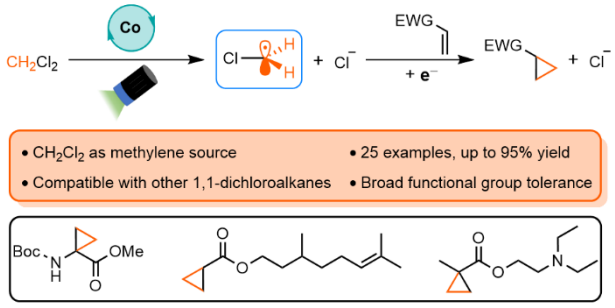

We report a Vitamin B_{12}-photocatalyzed strategy for the cyclopropanation of electron-deficient alkenes is presented using dichloromethane (CH_2Cl_2) as the methylene source. The reaction has excellent functional group tolerance, is highly chemoselective, and the scope can be extended to other 1,1-dichloroalkanes for the preparation of D_2-cyclopropyl and methyl-substituted cyclopropyl adducts, all of which are important isosteres in medical chemistry.

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