Vitamin B\textsubscript{12}–photocatalyzed cyclopropanation of Michael acceptors using dichloromethane as the methylene source

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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\textsubscript{12}–photocatalyzed approach for the cyclopropanation of Michael acceptors using CH\textsubscript{2}Cl\textsubscript{2} as the methylene source. The reaction proceeds in good to excellent yields under mild conditions, has excellent functional group compatibility, and is highly regioselective. The scope could also be extended to the preparation of D2-cyclopropyl and methyl-substituted cyclopropyl adducts starting from CD\textsubscript{2}Cl\textsubscript{2} and 1,1-dichloroethane, respectively.

Introduction

The cyclopropyl group is among the most ubiquitous small ring system in medicinal chemistry and has been extensively exploited in pharmaceuticals since the 1960s.\textsuperscript{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.\textsuperscript{2–4} Consequently, they continue to be prevalent in recently approved or investigational drugs.\textsuperscript{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 a Michael acceptor lead to a significant improvement in the physicochemical properties of their lead compounds in the development of allosteric inhibitors of HCV (Figure 1A).\textsuperscript{6} Similar cyclopropyl moieties derived from Michael acceptors can also be found in FDA-approved drugs (Figure 1B).\textsuperscript{5} These examples demonstrate that synthetic strategies for the cyclopropanation of Michael acceptors are of great value as a tool for medicinal chemists to alter physicochemical properties of promising lead compounds, highlighting the importance of having reliable and efficient cyclopropanation methods that can tolerate the broad array of functional groups present in pharmaceutically active molecules.

Among the synthetic strategies for cyclopropanation of alkenes\textsuperscript{7,8}, the Simmons–Smith reaction (the formal cycloaddition of methylene and various alkenes by treatment of CH\textsubscript{2}I\textsubscript{2} with the zinc–copper couple) is the most established and widely utilized method in the literature.\textsuperscript{9,10} While this reaction is compatible with a wide scope of alkenes and proceeds with great stereospecificity, the tedious preparation of the zinc–copper couple, reproducibility problems, and the lack of broad functional group tolerance detracts from its synthetic utility. More recently, the groups of Suero and Molander, among others\textsuperscript{11,12}, demonstrated that visible-light photoredox catalysis could be leveraged to start addressing some of these problems.
Concerns. In this light, we envisioned that a visible-light-mediated cyclopropanation reaction using dichloromethane (CH$_2$Cl$_2$), 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, likely owing to difficulty of activating the strong C–Cl bond. Inspired by seminal contributions from Scheffold and Giese, and more recent reports from Carreira, Gryko, and Zultanski using nucleophilic square planar cobalt complexes like Vitamin B$_{12}$, we envisioned that nucleophilic activation of CH$_2$Cl$_2$ could provide a general radical polar-crossover approach for the cyclopropanation of alkenes (Figure 1C). Our mechanistic design 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$_{N}$2-type oxidative addition with CH$_2$Cl$_2$, generating Co(III)–CH$_2$Cl intermediate I. Intermediate I could then undergo facile photolysis (estimated BDE of 15 kcal/mol, see ESI) upon visible light irradiation to generate a *CH$_2$Cl radical and a persistent Co(II) radical. Giese addition followed by trapping of the carbon radical intermediate by Co(II) would yield intermediate II, which upon single-electron reduction could afford the cyclopropyl adduct after an S$_{N}$2-type cyclization.

**Scheme 1. Mechanistic design for the Vitamin B$_{12}$-photocatalyzed cyclopropanation of Michael acceptors.**

**Results and discussion**

We began our investigation of our Vitamin B$_{12}$-photocatalyzed cyclopropanation of Michael acceptors using benzyl acrylate (1) as a model system. After an extensive optimization of each reaction parameter (see ESI), we were successful in generating cyclopropyl adduct 2 in 70% yield using only 1.5 equivalents of CH$_2$Cl$_2$, 5 mol% of Vitamin B$_{12}$, and Zn/NH$_4$Cl as the reducing agent under green (525 nm) LED irradiation (Table 1, entry 1). Control reactions where Zn, NH$_4$Cl, or Vitamin B$_{12}$ were absent did not yield any of cycloadduct 2, indicating that each of these components is crucial for reactivity (entries 2-4). 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 5). Attempting the reaction at higher temperatures (without LED irradiation) did not result in any meaningful increases in yield. Finally, optimization of the photon flux led to a further increase in the yield, giving 2 in 78% yield (entry 6).

**Table 1. Optimization and control reactions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Modifications from standard conditions</th>
<th>Yield of 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>No Zn</td>
<td>N.R.</td>
</tr>
<tr>
<td>3</td>
<td>No NH$_4$Cl</td>
<td>N.R.</td>
</tr>
<tr>
<td>4</td>
<td>No Vitamin B$_{12}$</td>
<td>N.R.</td>
</tr>
<tr>
<td>5</td>
<td>No hv</td>
<td>29%</td>
</tr>
<tr>
<td>6</td>
<td>75% LED intensity</td>
<td>78%</td>
</tr>
</tbody>
</table>

[a] Standard Conditions: 1 (0.25 mmol, 1.0 equiv), CH$_2$Cl$_2$ (0.375 mmol, 1.5 equiv), Vitamin B$_{12}$ (0.0125 mmol, 5 mol%), activated Zn powder (0.75 mmol, 3.0 equiv), and NH$_4$Cl (0.25 mmol, 1 equiv) in DMF (2 ml) were irradiated under Ar with a Kessil PR-160L 525 nm LED (50% intensity) for 8 h. [b] Yields determined by $^1$H NMR using 1,1,3,3-trimethoxybenzene as an external standard. [c] Average of three trials.

With the optimized conditions identified, we examined the scope of the Vitamin B$_{12}$-photocatalyzed cyclopropanation of Michael acceptors (Scheme 2A). Using CH$_2$Cl$_2$ as the methylene source, cyclopropyl adducts from a series of acrylates (2-6), phenyl vinyl sulfone (7), and N-phenylacrylamide (8) were generated in good yields. Dehydroamino acids were also found to be suitable Michael acceptors under our reaction conditions (9-11), highlighting the potential utility of this method for generating unnatural amino acid derivatives. Of note, a methacrylate derivative with a pendant tertiary aliphatic amine (12) could be cyclopropanated in 72% 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 photocatalysed cyclopropanation methods, highlighting an advantage of employing our Vitamin B$_{12}$-photocatalyzed approach. Furthermore, cyclopropyl adduct 13 could also be generated in 84% yield as a single regiosomer, highlighting the selectivity afforded by the apparent nucleophilicity of the *CH$_2$Cl radical and its preference for the polarity-matched electrophilic alkene of the Michael acceptor.
Deuteration of small-molecule drugs has been shown to favourably affect their pharmacokinetic properties.\textsuperscript{37} Consequently, the metabolism of certain drugs may be positively influenced upon deuterium incorporation, resulting in improved safety, tolerability, or efficacy.\textsuperscript{38,39} Therefore, we envisioned that by starting with readily available CD\textsubscript{2}Cl\textsubscript{2}, our Vitamin B\textsubscript{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 D2-cyclopropyl adducts (14-18) in good to excellent yields upon switching to methylene source to CD\textsubscript{2}Cl\textsubscript{2}. Through modification of the reaction conditions (see ESI), we were also able to extend our protocol to the generation of methyl-substituted cyclopropanes (Scheme 2C).\textsuperscript{40} By switching the methylene source to 1,1-dichloroethane (CH(Me)Cl\textsubscript{2}), methyl-substituted cyclopropyl adducts 19-23 could be generated in good to excellent yields. Interestingly, these reactions produced a mixture of diastereomers, with adducts 19 and 21 even favouring the thermodynamically less stable cis cyclopropane. We hypothesize that this is because the diastereoselectivity of the cyclopropyl adduct is set prior to the S\textsubscript{N}2-type cyclization and instead during the formation of intermediate II (Scheme 1), allowing the steric environment of Vitamin B\textsubscript{12} to influence the diastereoselectivity. Finally, during our survey of the scope of our cyclopropanation reaction, we noted several limitations regarding the identity of the Michael acceptor (Scheme 2D). For example, Michael acceptors with substitution at the β-position were not compatible with our approach, likely owing to steric inhibiting the initial addition of the *CH\textsubscript{2}Cl radical, a commonly observed limitation of Giese reactions.\textsuperscript{41} Highly activated Michael acceptors, such as dimethyl furmarate and maleimides, were also not tolerated, as these were observed to undergo hydrogenation in the presence of Zn and NH\textsubscript{2}Cl\textsubscript{2}. As anticipated, more electron-rich alkenes, such as styrene, were also not compatible with our approach.\textsuperscript{31}

Having explored the synthetic scope, we next turned our attention to the key steps of the reaction mechanism, specifically, the feasibility of the S\textsubscript{N}2-type oxidative addition and the photolysis/*CH\textsubscript{2}Cl radical generation steps. To access the viability of the S\textsubscript{N}2-type oxidative addition, we performed a series of UV-vis studies, as shown in Scheme 3A. Upon addition of Zn and NH\textsubscript{2}Cl\textsubscript{2} to a sample of Vitamin B\textsubscript{12}, the appearance of a new λ\textsubscript{max} at ~390 nm, indicative of the formation of Co(II), was observed.\textsuperscript{42,43} Addition of CH\textsubscript{2}Cl\textsubscript{2} to the sample resulted in the immediate loss of the Co(II) 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.\textsuperscript{44} These data provide support for the formation of the Co(III) oxidation state of Vitamin B\textsubscript{12} and the subsequent S\textsubscript{N}2-type oxidative addition with CH\textsubscript{2}Cl\textsubscript{2} to form intermediate I under our reaction conditions. Next, we performed a control reaction with TEMPO to probe for the formation of the *CH\textsubscript{2}Cl 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). Furthermore, GS-MS analysis of the reaction mixture identified the formation of the TEMPO–CH\textsubscript{2}Cl adduct (see ESI), supporting the formation of *CH\textsubscript{2}Cl radicals under our reaction conditions.

Conclusions

A practical and efficient Vitamin B\textsubscript{12}-photocatalyzed approach for the cyclopropanation of Michael acceptors using CH\textsubscript{2}Cl\textsubscript{2} as the methylene source has been developed. The reaction works for a broad range of Michael acceptors, proceeds in high regioselectivity, and has increased functional group tolerance compared to other state-of-the-art methods. The reaction could also be extended to the preparation of D2-cyclopropyl and methyl-substituted cyclopropyl adducts starting from CD\textsubscript{2}Cl\textsubscript{2} and 1,1-dichloroethane, respectively. Mechanistic
studies indicate the reaction likely proceeds through an $S_\text{n}2$-type oxidative addition 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.

Notes and references

Author Contributions
J. H. G. Teye-Kau performed the scientific experimentation and data analysis. M. J. Ayodele aided in the experimentation and performed the computational studies. S. P. Pitre conceived and directed the project and wrote the original draft of the manuscript. All authors contributed to the revision of the manuscript and have given approval for publication.

Conflicts of interest
There are no conflicts to declare.

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