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Vanadium-photocatalyzed carbon–carbon bond cleavage of aliphatic alcohols

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Summary (50 words limit)

In this issue of *Chem Catalysis*, Ramalingam and Soo *et al.* describe aliphatic carbon-carbon bond cleavage and functionalization of unactivated alcohols using a visible-light-active vanadium photocatalyst under ambient reaction conditions. This photoredox catalysis provides effective ways to functionalize various substrates selectively ranging from simple alcohols to natural products.

Main text (1500 words limit)

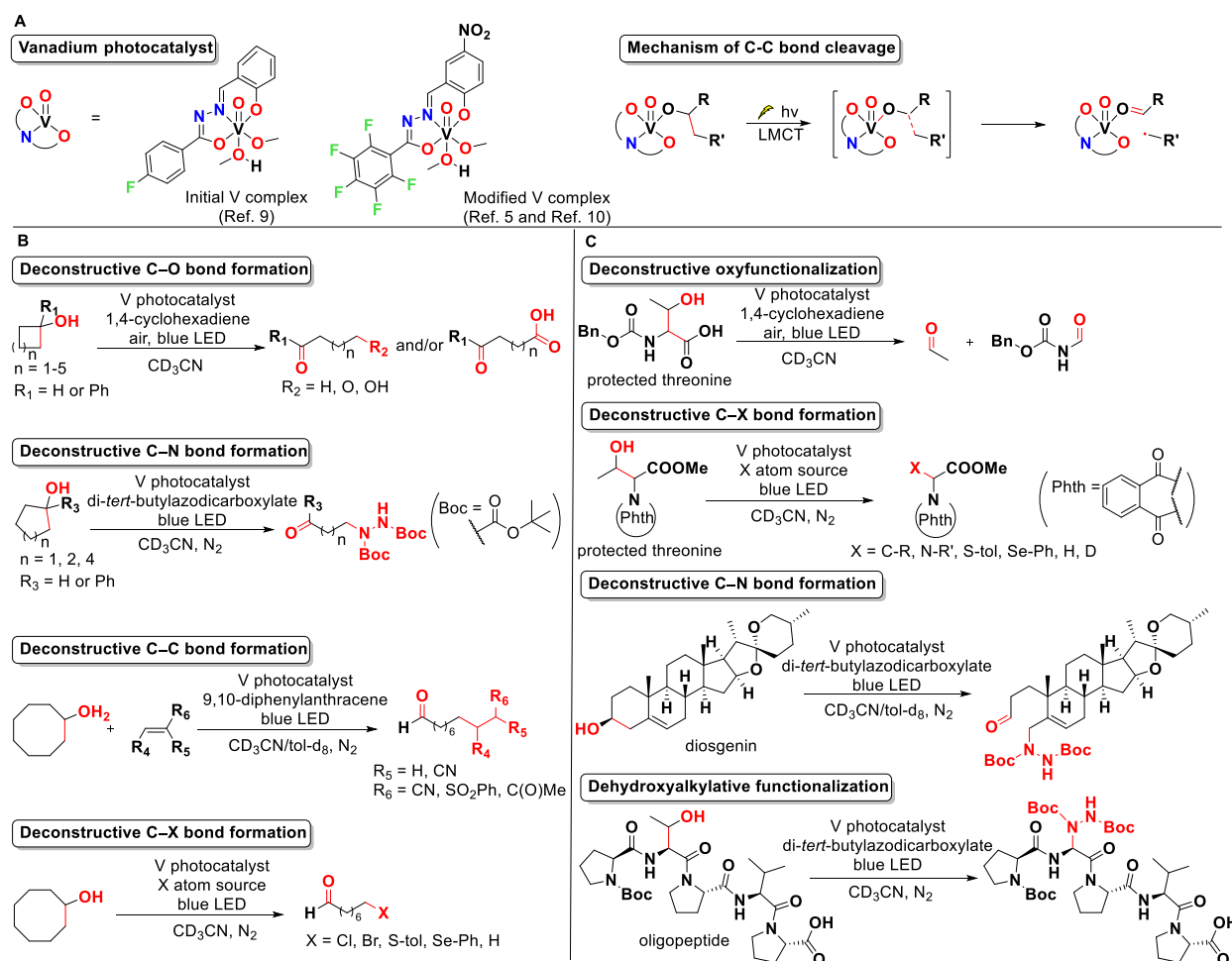
Organic chemistry has conventionally focused on the development of synthetic methods that can build complex molecules from simple starting materials via bond constructions. Most strategies established to date form new connectivity between carbon and carbon/heteroatoms to assemble molecules with desired functional groups. Although many synthetic pathways have been available, many molecular structures still remain inaccessible or require multiple synthetic steps with harsh reaction conditions. Therefore, deconstructive approaches through selective carbon-carbon (C–C) bond cleavage and subsequent functionalization should be good alternatives allowing facile access to structurally diverse and novel compounds with desired complexity and functionality.¹ While many methods such as ozonolysis and olefin metathesis have been developed for C(sp²)–C(sp²) bond cleavage, the inherent inertness of the C(sp³)–C(sp³) bond makes it challenging to activate or cleave resulting in a rather small number of reported examples.²

The chemistry of C(sp³)–C(sp³) bond cleavage was pioneered in 1952 by Eschenmoser, who reported the transformation of β -hydroxy ketone (2-(hydroxymethyl)-2-methylcyclopentan-1-one) into the corresponding tertiary alcohol (2,6-dimethylhept-6-en-2-ol) via a heterolytic fragmentation of C–C bonds.³ Since then, efforts have focused on transition metal-catalyzed C–C bond cleavage in strained molecules as a main strategy. Despite the improvements in this field, highly selective and efficient methods, particularly for deconstructive cleavage and functionalization of unstrained C–C bonds, have been lacking because the previous strategies suffer from the use of expensive heavy metal catalysts, the competition of C–H activation with C–C bond cleavage, and limited functionalization.¹

Photoredox catalysis has emerged as a versatile tool to mediate organic reactions under mild reaction conditions for the synthesis of complex molecules, including unusual products conventionally inaccessible.⁴ In particular, photoredox C–C bond formation can be achieved in a selective manner by employing transition metals and photosensitizers to generate highly reactive radical species. In contrast, although photoredox catalysis provides beneficial features for organic synthesis, the application in aliphatic C–C bond cleavage has remained largely unstudied. In this issue of *Chem Catalysis*, Ramalingam and Soo *et al.* report pioneering work on visible-light-assisted photocatalytic cleavage of aliphatic C–C bonds adjacent to a hydroxyl group with subsequent difunctionalization of alcohols.⁵ Their rationally designed vanadium(V)

oxo complex achieves various new bond formations selectively after C–C bond cleavage at atmospheric pressure and room temperature regardless of the type of alcohol (Scheme 1A).

The hydroxyl group is not only an abundant functional group in many organic substrates but also a useful precursor of alkoxy radicals that can allow C–C bond cleavage via β -scission. The first example of photocatalytic hydrogenative C–C bond cleavage in unstrained alcohols enabled by proton-coupled electron transfer was reported by Knowles and co-workers in 2016.⁶ In addition, Zuo and co-workers showed the deconstructive amination and alkylation of alcohols through a ligand to metal charge transfer (LMCT) process by utilizing a cerium photocatalyst.⁷ Recently, an iron-photocatalyzed deconstructive hydrogenation of alcohols through an LMCT process was also developed by Hu and co-workers.⁸ These works made significant contributions to photoredox catalysis for deconstructive C–C bond cleavage and functionalization of alcohols; however, current protocols either require expensive photocatalysts or have a restricted range of alcohol substrates. Furthermore, unstable and reactive alkoxy radical intermediates generated in the reactions become unsuitable for a wide range of applications including the late-stage transformation of natural products and pharmaceuticals requiring a high level of functional group tolerance.



Scheme 1. Vanadium-photocatalyzed aliphatic carbon-carbon bond cleavage and functionalization of unactivated alcohols under ambient reaction conditions; (A) Vanadium(V) complexes supported by hydrazone-imidate ligands and mechanism for the inner-sphere LMCT-induced homolytic C–C bond

cleavage of alcohols, and the deconstructive aliphatic carbon-carbon bond cleavage and functionalization of (B) simple alcohols and (C) hydroxyl-group-containing biomolecules.

Ramalingam and Soo *et al.* employ inner-sphere LMCT-induced homolytic C–C bond cleavage to generate the nucleophilic alkyl radicals directly instead of electrophilic alkoxy radicals while the alcohol substrates are coordinated to vanadium centers (Scheme 1A). In an initial work, it was found that a vanadium(V) complex supported by a redox noninnocent conjugated hydrazone-imidate ligand is able to absorb visible light via LMCT and catalyze the cleavage of the C–C bond next to the hydroxyl group selectively under mild reaction conditions.⁹ Since this discovery, the vanadium(V) photocatalyst has been modified to increase oxidative strength by introducing strong electron-withdrawing groups such as NO₂ and F on the aryl rings of the ligand framework.¹⁰ The new vanadium(V) photocatalyst indeed shows much higher activity (up to 7 times) than that of the initial vanadium(V) photocatalyst. In addition to aldehyde products, this C–C bond cleavage of alcohols produces other oxygenated products such as formate, resulting from the reaction of the generated alkyl radical and O₂. With these results, Ramalingam and Soo *et al.* significantly expand the scope of alcohol substrates and demonstrate a variety of bond formations after homolytic C–C bond cleavage.

The deconstructive C–O bond formation in cyclic aliphatic alcohols with different ring sizes is carried out under air at room temperature (Scheme 1B). The highly selective C–C bond cleavage is achieved regardless of ring size resulting in the formation of desired carbonyl products with high conversion. Moreover, a deconstructive C–N bond formation is realized by introducing an electrophilic radical trapping reagent, di-*tert*-butylazodicarboxylate, to cyclic and acyclic alcohols (Scheme 1B). The C–N coupled products are obtained with good yields under O₂-free conditions. The reaction with cyclic alcohols affords only one C–N coupled product whereas acyclic alcohols are transformed into ketones and C–N coupled products formed from the alcohol substrates and the C–N coupling of the alkyl radical, respectively. Changing the radical trapping reagent to electron-deficient alkenes allows the deconstructive C–C bond formation of cyclooctanol with a co-photocatalyst (9,10-diphenylanthracene) oxidizing V(IV) back to V(V) (Scheme 1B). Various C–C coupled products containing –CN and –SO₂Ph groups are prepared by the generated cyanomethanide radicals. Finally, the deconstructive C–X (X = Cl, Br, S, Se, H, D) bond formation of cyclooctanol or cyclobutanol is shown in a similar manner by using each atom source (Scheme 1B). These results suggest that this method can be applied to a broad range of transformations with excellent functional group tolerance.

The photocatalytic deconstructive functionalization method is further examined for valuable and complicated biomolecules such as amino acids, peptide chains, and pharmaceuticals. For example, threonine protected by a carboxybenzyl group to increase its solubility in acetonitrile undergoes a C–C bond oxyfunctionalization to give acetaldehyde with high yield and benzyl formylcarbamate from a second C–C bond cleavage and decarboxylation of the initial product (Scheme 1C). This vanadium(V) photocatalyst system is also compatible with oligopeptides consisting of proline-threonine-proline-valine-proline to induce multiple fragmentations successfully under ambient reaction conditions showing its functional group tolerance to secondary amine, amide, and carboxylate groups. In addition, a bioactive pharmaceutical ingredient, chloramphenicol (antibiotic), bearing many functional groups sensitive to oxidation can be treated for the selective deconstructive C–C bond cleavage and functionalization to obtain 4-nitrobenzaldehyde and 2,2-dichloro-*N*-formylacetamide, which could be used as an antiprotozoal drug.

In addition to oxygenation, the deconstructive C–X (X = C, N, S, Se, H, D) functionalization of biomolecules is demonstrated using the protected threonine and each atom source (Scheme 1C). In particular, the successful dehydroxyethylative thiolation and selenylation also imply excellent tolerance to

electron-rich sulfide and selenide groups that could undergo side reactions with alkoxy radicals. These transformations of the amino acid, including a selective deuteration, open the door to the development of a variety of previously unknown unnatural amino acids from abundant natural amino acids. Furthermore, diosgenin, a steroid precursor to several hormones, undergoes a selective deconstructive C–N bond formation even in the presence of alkene and acetal groups in their polycyclic structure (Scheme 1C). More complicated oligopeptides containing threonine undergo the dehydroxyalkylative functionalization through the deconstructive C–N bond formation under similar reaction conditions (Scheme 1C). The selective transformation at the threonine moiety is accomplished to create a new unnatural peptide without any side reactions with other functional groups such as amine, hydrazine, amide, and terminal carboxylate in the oligopeptide.

The study by Ramalingam and Soo *et al.* discloses a versatile vanadium photocatalyst system for the deconstructive aliphatic carbon-carbon bond cleavage and subsequent functionalization of unactivated alcohols under ambient reaction conditions. The rationally designed vanadium(V) oxo complex supported by a redox noninnocent conjugated hydrazone-imidate ligand absorbs visible-light, and inner-sphere LMCT induced the homolytic cleavage of the C–C bond next to the hydroxyl group followed by functionalization is accomplished with high selectivity. The major difference between this system and previous protocols is the direct generation of nucleophilic alkyl radicals instead of electrophilic alkoxy radicals to achieve a high level of selectivity and functional group tolerance. The vanadium photocatalyst system demonstrates ten different deconstructive bond formations with forty-four alcohol substrates ranging from simple acyclic alcohols to complicated biomolecules such as oligopeptides and pharmaceutical ingredients. These reactions underline that this photoredox catalysis protocol has great potential to access valuable and novel molecules that were not possible to synthesize before or required specific and cumbersome synthetic steps.

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