Radical-Promoted C−C Bond Cleavage: A Deconstructive Approach for Selective Functionalization

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A DECONSTRUCTIVE APPROACH FOR SELECTIVE FUNCTIONALIZATION
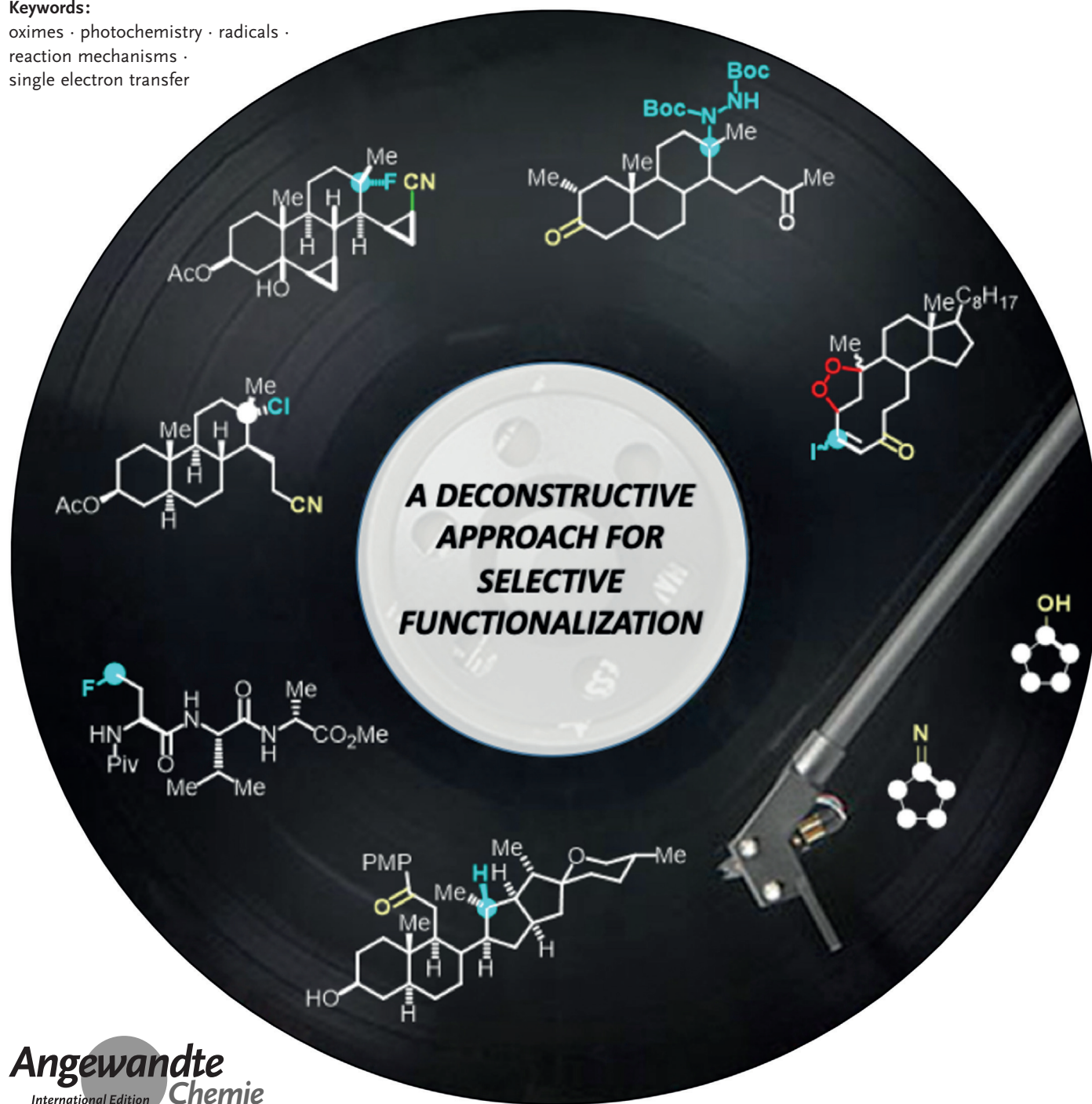
Just as "Deconstructivism" appeared as a novel movement in architecture in the 1980s, deconstructive approaches have recently emerged as excellent strategies for scaffold hopping modifications in chemistry. The deconstruction and functionalization of cyclic molecules mainly involves the cleavage of the carbon–carbon (C−C) bond followed by the construction of new bonds. The cleavage of inert C−C single bonds, especially in unstrained cycles, and their subsequent functionalization is still one of the most sought-after challenges in chemistry. In this vein, radical-mediated strategies provide an excellent approach for achieving this aim. This minireview is an outline of the history of homolytic cleavage and highlights the recent advances in exploring new chemical space by deconstructive functionalization.

1. Introduction

Since the very beginning of the study of chemistry, the art of making and breaking bonds has been the main driver of innovation for chemists. A common target for organic and synthetic chemists lies in the creation of new C−C bonds and C–heteroatom bonds, delivering novel molecules in more convenient ways. Great progress has led to the design and development of strategies to address this purpose. However, the current tendency is an increasing interest in the question "What molecules to make?".[1] In this context, both the academic and the industrial medicinal chemistry communities have moved from the preparation of classical aromatic-based small molecules to the utilization of recent methodologies aimed at exploring new chemical space by direct $C(sp^3)$ functionalization.[2] The selective functionalization of inert sp^3-carbon centers in structurally complex and densely functionalized molecules is still one of the major challenges for chemists.[3] From a structural-diversification standpoint, the transformation of C−H bonds into C−X bonds (Scheme 1) is an important process that can give rise to changes in chemical and biological properties. However, sometimes these modifications are not enough to find novel active

compounds with desirable properties. In 2018, the group of Sarpong[65] extrapolated the concept "scaffold hopping" from medicinal chemistry to synthetic chemistry, the aims of which are "to discover structurally novel compounds starting from known active compounds by modifying the central core structure of the molecule". This concept lies at the base of recent drug-discovery campaigns to make structurally novel compounds with improved properties.

The breaking open of rings, existing at the core of biomolecules, followed by selective functionalization appears to be a good strategy for scaffold hopping. The key step relies on the selective cleavage of inert C−C bonds, and has recently come to be known as "strategies to selectively deconstruct and functionalize".[4] An important feature in ring fragmentations is that they are particularly useful reactions for modifying compounds since they have the ability to unmask dormant functional groups. This aspect is in contrast to selective functionalization of C−H bonds. Let us say that the value of deconstructive strategies comes from the creation of two new functional groups which are tethered at a predefined distance determined by the ring size (Scheme 1). The selective C−C bond cleavage is a formidable challenge for the chemistry community to resolve as a way to make hybrid druglike molecules for fast and efficient exploration of chemical space.

Historically, heterolytic fragmentations were the pioneering approaches to cleaving $C(sp^3)−C(sp^3)$ bonds.[5] This chemistry was started in the 1950s by Eschenmoser,[6] and later followed by Grob.[7] Over the last three decades, efforts have been focused on transition-metal catalysts for realizing C−C cleavage in strained rings.[8] In this approach the C−C bond scission can occur 1) through C−C bond activation by direct oxidative addition or 2) by β-carbon elimination (Scheme 2). In spite of the progress in this area, reactions involving a selective deconstructive functionalization remain extremely challenging, mainly because 1) of limitations with functionalizations and 2) the selective C−C bond cleavage competes with the C−H bond activation. To address this concern, homolytic fragmentation has recently appeared to be an attractive strategy for achieving selective C−C bond cleavage.

In this review, the key discoveries in deconstructive functionalization strategies by homolytic C−C bond cleavage are highlighted. The main goal is to describe the pioneering
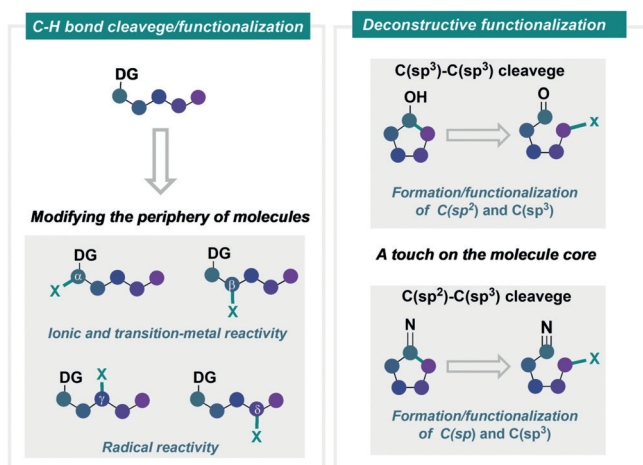
Scheme 1. Strategies for the selective functionalization of inert sp^3 carbon centers. DG = directing group.

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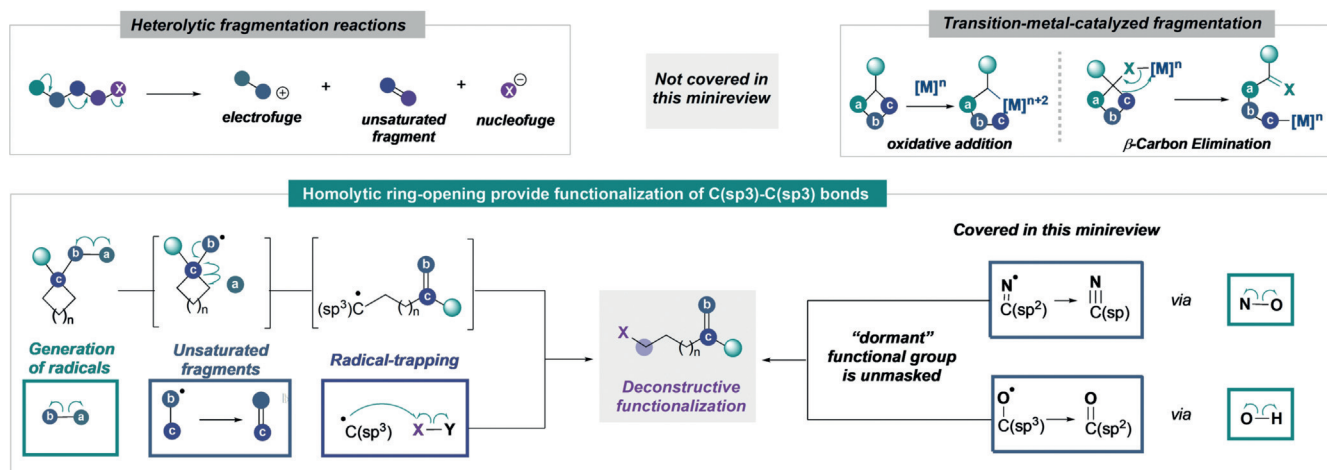
Scheme 2. Fundamental concepts of fragmentation reactions.

works and those leading up to the more recent contributions in this area, as well as to summarize the challenges and opportunities that lie ahead. Functionalizations can be classified on the basis of: a) the radical generated to promote β-C−C bond cleavage, b) the unsaturated fragment formed, and c) the deconstructive functionalization accomplished. A set of elementary concepts are summarized (Scheme 2) to familiarize the reader with the fundamental aspects in this area, followed by the most notable examples presented in chronological order.

Radical Generated: The first step in setting up C−C bond cleavage relies on the radical generated. Historically, the formation of cyclopropylcarbinyl radicals has been an excellent example for the ring opening of strained cycles (radical clock). However, carbon-centered radicals have been extensively reviewed elsewhere.[9] Hence, we will focus on heteroatom-centered radicals, which enable the deconstruction of the more challenging unstrained rings.

Unsaturated fragments: Recently, the chemistry of iminyl and alkoxy radicals has arisen as a powerful strategy because of their ability to break into an alkyl radical species and an unsaturated fragment. This process is commonly called β-scission or β-fragmentation. During this process, a dormant functional group is unmasked through oxidation, forming an unsaturated fragment. Although nitriles (from iminyl radicals) and ketones (from alkoxy radicals) are the typical

unsaturated fragments formed, formamides have been attained.

Deconstructive functionalization: Here, to transform cyclic compounds into versatile functionalized structures plays a crucial role in the design. The key strategy in this step lies in the use of commercially available reagents, which enable the construction of valued bonds. Therefore, to introduce functional groups such as halogens, azides, amines, or even a new C−C bond, is typically a good strategy. These functional groups may affect the properties of the product, and are of great interest in either drug–target interactions or the search for phenotypic changes.

2. Deconstructive Functionalization of Cyclic Alcohols

Alkoxy radical driven deconstructive functionalization of cyclic alcohols by β-fragmentation of C−C bonds will be discussed in this section. These processes are mainly governed by 1) the thermodynamic stability of alkyl radical generated, 2) a favourable relief of ring strain (strain energy release), 3) reversibility of the *exo*-cyclization reaction of alkyl radicals versus functionalization by means of competitive kinetics, and 4) the way in which the alcohol is activated to provide an alkoxy radical.

The earliest strategies were based on the prefunctionalization of alcohols to achieve weak O−X bonds, since the pronounced homolytic stability of the alcoholic O−H bond (BDFE ≈ 105 kcal mol^{-1}) would not make it possible to attain direct homolysis.[10] Later, a one-electron oxidation using stoichiometric amounts of strong oxidants were used to provide alkoxy radicals. However, recently the chemistry community has focused its attention on catalytic methods for the selective and direct homolysis of O−H bonds.

2.1. Pioneering Examples of Modifying Steroidal Skeletons

Synthetic applications of deconstructive functionalization emerged in 1961 to modify the core of steroid derivatives.
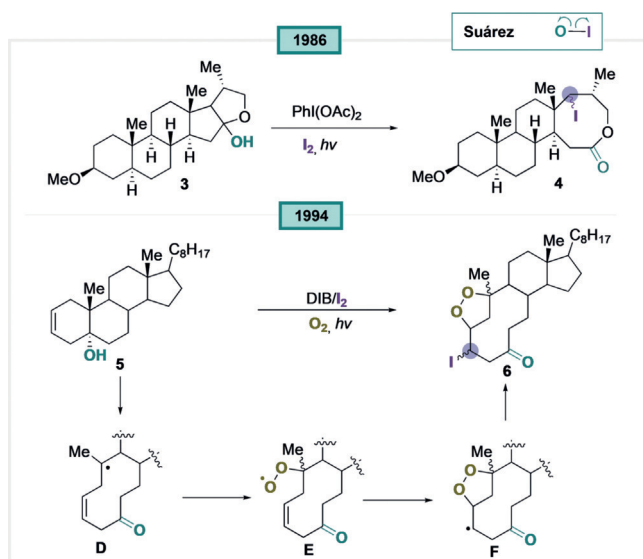
Sara P. Morcillo was awarded a Ph.D. in 2014 under the supervision of Prof. Cuerva and Dr. Justicia at the University of Granada (UGR). During her Ph.D. studies, she spent a short period in the group of Prof. A. Gansäuer at the University of Bonn. Afterwards, she joined the group of Prof. V. Gandon (University of Paris-Saclay). In 2016, she joined the group of Prof. D. Leonori as a researcher (University of Manchester). In 2018, she returned to UGR as a research fellow and has recently been awarded a "Juan de la Cierva Incorporación" grant.

Barton et al. published an elegant solution for generating alkoxy radicals by using a precursor having a weak O−NO bond (BDE ≈ O−NO 37 Kcal mol^{-1}).[11] The mechanism relies on photolytic homolysis of nitrite into nitric oxide and an alkoxy radical (**A**), which undergoes β-fragmentation (Scheme 3).[12] The formed tertiary alkyl radical **B** then captures the nitric oxide to furnish the nitroso aldehyde **C**, which leads to hydroxamic acid after cyclization.
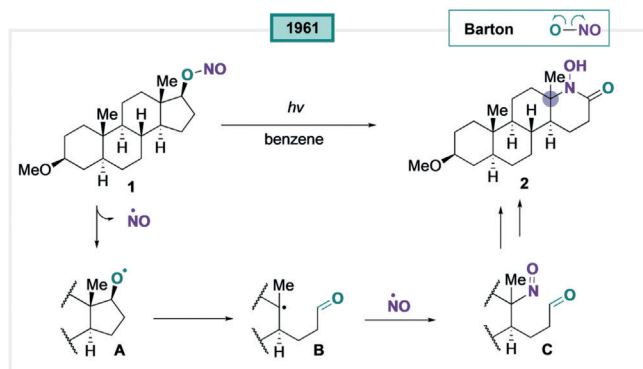
Scheme 3. Deconstructive functionalization by homolysis of O−NO bonds.

A few years later, the group of Suárez developed a method for the deconstruction of steroidal lactols by using iodobenzene diacetate (IBDA) and iodine.[13] Suárez's reagent has the ability to generate weak O−I bonds in situ, which can be homolysed by visible light to generate alkoxy radicals (Scheme 4). The beauty of this approach is that after ring-opening a seven-membered-ring iodo-lactone (**4**) is achieved in the steroidal core. Probably one of the most remarkable results is the deconstruction/functionalization of cholesterol derivatives attained by using this strategy. Suárez's group achieved a tandem β-fragmentation/cycloperoxyiodination of several steroidal alcohols.[14] The key step was to the irradiate homoallylic alcohol **5** with visible light in the presence of molecular oxygen, which enabled the formation of the peroxyl radicals **E** by peroxidation of the alkyl radical **D**. Then, the radical added to the double bond, generating the second alkyl radical **F**, which was trapped with iodine to give **6**.

2.2. One-Electron Oxidation of Alcohols

As previously mentioned, the selective homolysis of the O−H bonds is thermodynamically and synthetically difficult since these bonds are stronger than the C−H bonds in the same molecule.[15] Despite this challenge, in the 1960s, Schaafsma and co-workers[16] found that Cu^{II}- and Fe^{III}-promoted one-electron oxidization of cyclopropanol to give a ring-opened free-radical intermediate. In 1972, Rocek disclosed that metals such as Mn^{III}, V^{V} and Ce^{IV} are excellent for one-electron oxidation to achieve the deconstruction of cyclobutanols towards C−C bond cleavage.[17] The reaction by one-electron oxidation is strongly assisted by the strain energy relief, which is a favourable processes against C−H cleavage, and should lead to ketones and proceed by two-electron oxidations. Twenty years later, by using the same strategy the group of Narasaka reported a Mn^{III}-mediated oxidative cleavage of cyclopropanol for the generation of alkyl radicals, which were added to silyl enol ethers.[18]

In the following decades, researchers focused their efforts on promoting catalytic reactions.[19] It was found that by using a sub-stoichiometric amount of a Ag^{I}, Mn^{III}, or Cu^{I} catalyst, O−H bonds could be homolysed to generate alkoxy radicals. The earliest studies suggested that the metal–catalyst turnover should depend on its ability to be oxidized at the same time as the X-ligand exchange occurs (Scheme 5). Conse-

Scheme 4. Deconstructive functionalization by homolysis of O−I bonds.
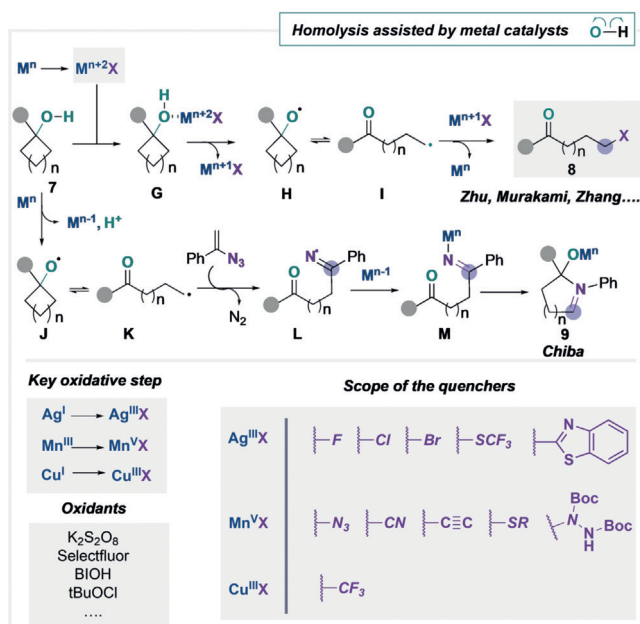
Scheme 5. Homolysis assisted by metal catalysis. Boc = *tert*-butoxycarbonyl.

quently, the M^n–**X** species are oxidized under strong oxidative conditions into the high-oxidative M^{n+2}–**X** species. Upon single-electron transfer (SET) an alkoxy radical (**H**) is achieved at the same time as the release of M^{n+1}–**X**. Well-designed strategies combining metal catalysts, **X**–**Y** reagents, and oxidants have enabled the groups of Narasaka,[20] Murakami,[21] Zhu,[22] Loh,[23] Duan,[24] Zhang,[25] Lopp,[26] and Orellana,[27] to achieve a wide range of deconstructive functionalizations of cycloalkanols. An alternative protocol was reported by Chiba,[28] where an alkoxy radical (**J**) was added to a vinyl azide.

Despite the outcomes achieved, most of the C–C bond cleavages are accompanied by the relief of strain. Moreover, intramolecular dehydration to give a ketone through α-C–H bond cleavage may compete in the middle of the reaction when either secondary alcohols are used or strong oxidants are used to achieve two-electron oxidation.

2.3. Photoinduced Synthetic Approaches

Photocatalyzed processes have recently emerged as an alternative for the generation of alkoxy radicals by using milder reaction conditions, thus avoiding undesired side-reactions.[29] In 2015, the group of Leckta[30] disclosed the first deconstruction/fluorination of cyclopropanols in the presence of a photooxidant (PO). The radical cation generated under these conditions is able to induce a C–C bond elongation (Scheme 6), the thermodynamic driving force for the photolytic homolysis. In 2016, the group of Chen[31] developed a complementary strategy to generate alkoxy radicals by using cyclic iodine(III) reagent (CIR) catalysis. The elementary step of this transformation resembles Suárez's chemistry, but here the authors used a CIR/photoredox dual-catalytic system for the generation of an alkoxy radical under milder reaction conditions. Despite these achievements, these catalytic photoinduced approaches are only used with strained cycloalkanols.

A few months later, Knowles and co-workers developed the first proton-coupled electron transfer (PCET) activation of unstrained cycloalkanols, and it enabled them to address
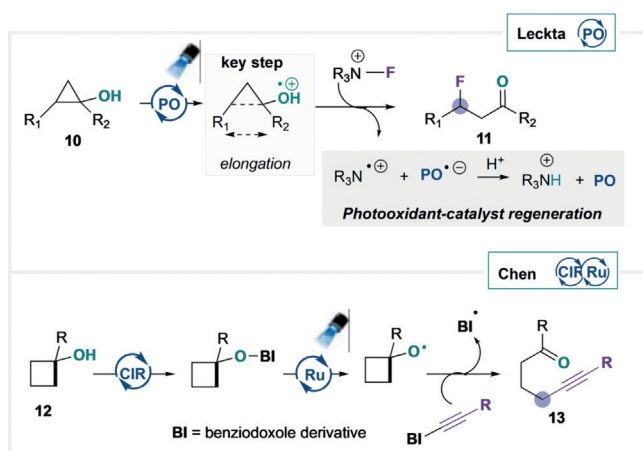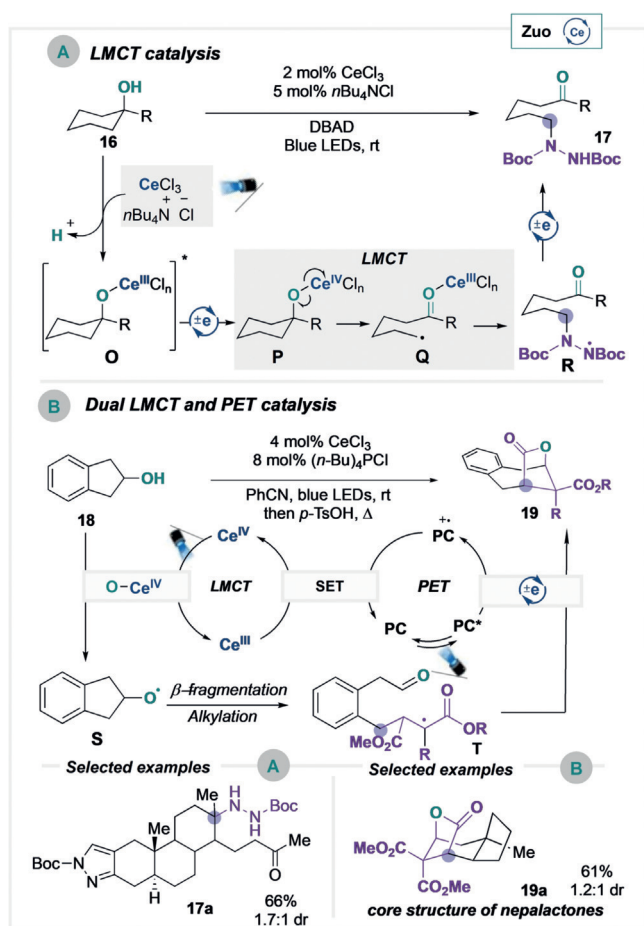

Scheme 6. Photoinduced approaches.

the limitation of the previously described methods to strained cycloalkanols (Scheme 7).[32] The key to this elegant solution relies on the formation of the arene radical cation **N**, which serves as internal oxidant of a proximal O–H bond. The
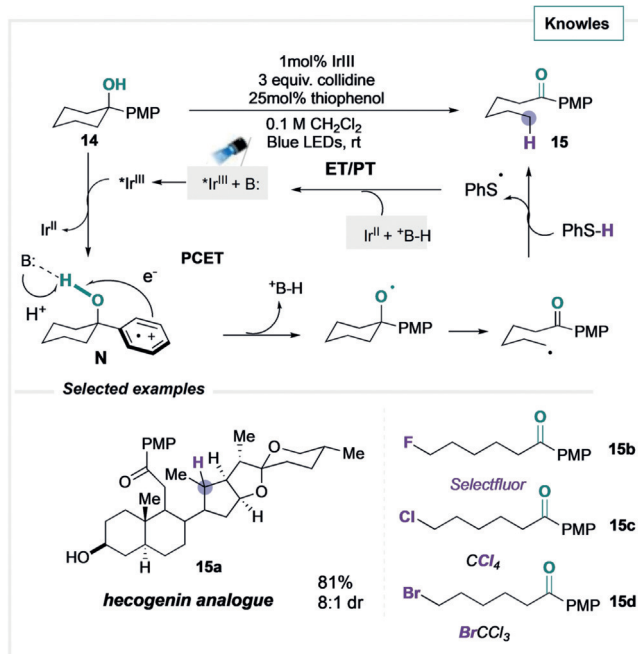
Scheme 7. Proton-coupled electron transfer (PCET) activation of unstrained cycloalkanols. PMP = *para*-methoxyphenyl.

radical cation intermediate is rapidly (if not simultaneously) followed by deprotonation of the hydroxy group by collidine involving the formation of an alkoxy radical and a one-electron reduction of the radical cation. Under these reaction conditions, the ring-strain energy is not a prerequisite to furnishing an efficient β-fragmentation that leads to fragmentation of several ring sizes. The synthetic utility of this strategy is clear since the deconstruction/hydrogenation of complex natural product derivatives such as the hecogenin analogue **15a**, can be attained. Moreover, deconstruction/halogenation by using halogen-atoms donors (**15b** and **15c**) were sustainable with the PCET system. Xia and co-workers also reported a similar methodology by using white light to achieve either deconstruction/allylation or deconstruction/formylation.[33]

Seeking to overcome some of the limitations, Zuo and co-workers reported a strategy for the fragmentation of unstrained cycloalkanols, including secondary alcohols.[34] The key point in this strategy lies in the use of a cerium(III) chloride complex as a photoredox catalyst, which behaves as an efficient ligand-to-metal charge transfer (LMCT).[35] In contrast to photoinduced electron-transfer (PET) processes, photoinduced LMCT undergoes a direct and more selective homolysis of a metal–ligand bond by a formal reduction of the metal, enabling the oxidation to occur exclusively at the coordinated functional group (O–Ce^{IV}), thus circumventing an over-oxidation (see section 2.2). By applying this method the deconstruction/amination of complex steroid-derived cycloalkanols were achieved (Scheme 8). However, electron
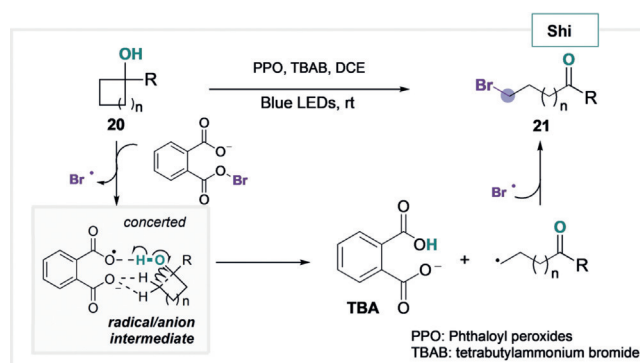
Scheme 8. C−C bond cleavage and functionalization by using a Ce[III] photocatalyst.

Scheme 9. Hydrogen-atom transfer/electron transfer (HAT-ET) for the homolysis of O−H bonds.

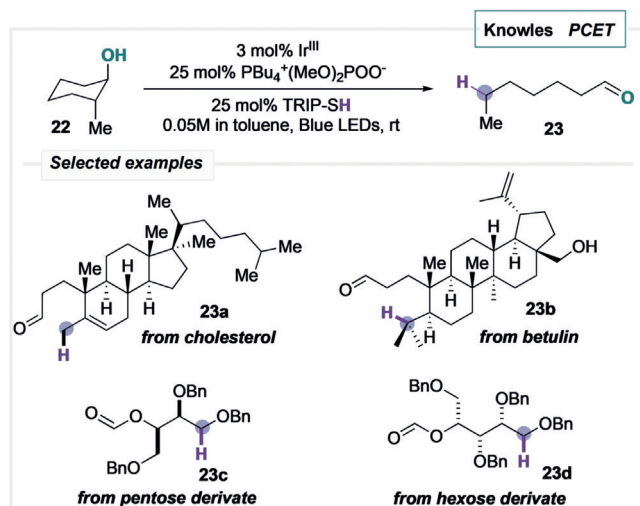**Scheme 10.** Deconstruction/hydrogenation of secondary cyclic alcohols by PCET.

acceptors with low redox potential cannot be used to facilitate the turnover cerium catalytic cycle because of the narrow redox window of cerium ($E_{1/2}$ (Ce[III]/Ce[IV]) = 0.4 V vs. SCE in MeCN). To address this concern, the authors reported a new dual photocatalytic protocol.[36] The methodology has allowed a radical cross-coupling with electron-deficient alkenes, which falls outside of the redox window of Ce[III] to be achieved, thus the strongly reducing photoexcited anthracene catalyst may reduce the alkyl radical. Final SET between the radical cation of anthracene and Ce[III] enables the closure of both catalytic cycles.

In 2018, Zhu and co-workers developed a PCET methodology for the deconstructive bromination of unstrained cycloalcohols.[37] Later, Shi and co-workers[38] disclosed an induced hydrogen-atom transfer/electron transfer (HAT-ET) as an alternative to the above methods. Here, a radical/anion intermediate enhances the ability to promote HAT to accomplish the homolytic cleavage of the O−H bond. The alkyl radicals formed react with the bromine radical, forming brominated ketones **21** (Scheme 9).

In 2019, the group of Knowles[39] demonstrated that PCET processes can lead to homolytic activation of O−H bonds in secondary cycloalkanols, thereby circumventing the use of substrate-based aromatic groups (Scheme 10). This new approach can be harnessed in the deconstruction/hydrogena-

tion of complex polycyclic structures, including derivatives of cholesterol (**23a**), betulin (**23b**) etc. This method certainly sets an example for exploring new chemical space by modifying the core of small bioactive molecules.

3. Deconstructive Functionalization of Cycloketone Oximes Derivatives.

Iminyl radicals exhibit a complementary reactivity to alkoxy radicals to modify the core of small biomolecules by deconstruction/functionalization. Iminyl radicals mainly require the use of oxime derivatives to achieve an easier homolysis through their weak N−O bond (BDE ≈ 50 kcal mol⁻¹).[40] Unlike alkoxy radicals, the homolysis of N−O bonds to achieve iminyl radicals mainly occurs by a SET reduction, although SET oxidation can be applied, but this has been less explored.

3.1. Earliest Examples

Pioneering studies were reported by the group of Zard in the 1990s.[41] The authors disclosed the homolysis of the N−S

bonds in sulphenylimines (Scheme 11), by using stannyl radicals as the driving force for producing iminyl radicals. However, the use of the toxic reagent Bu₃SnH/AIBN, which may act as hydrogen-atom donor and therefore reduce the
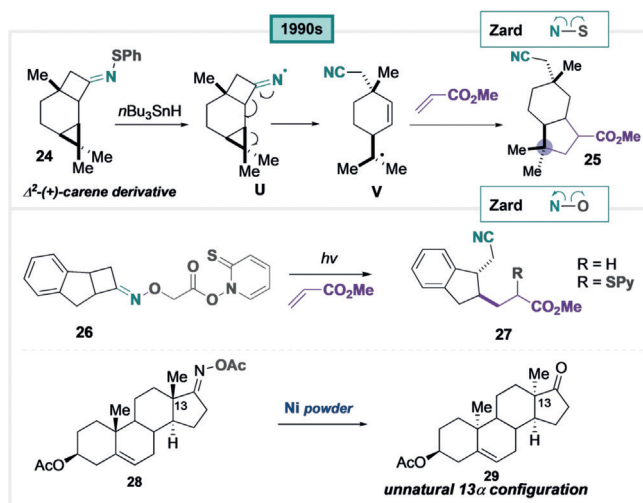
Scheme 11. Pioneering examples for the generation of iminyl radicals.

alkyl radical, could preclude further functionalizations. To address this limitation, the authors, inspired by Forrester's research,[42] reported a strategy based on O-carboxymethyl oxime derivatives (N–O bonds).[43] This seminal study showed that iminyl radicals could be generated by photolytic homolysis through a modification of Barton's decarboxylation.[44] Upon β-fragmentation, the alkyl radical was captured by electrophilic olefins to give **27**.[45]

In 1992, the group of Zard reported an alternative for the reduction of the oxime acetates **28** by using nickel powder (Scheme 11).[46] On the other hand, in 2005 the Uemura and co-workers found that the use of an iridium complex gave rise to iminyl radicals.[47]

3.2. Transition Metal Catalysed Reductive Fragmentation

It was not until 2017 when a considerable boom occurred in using transition-metal catalysis (mostly iron and copper catalysts) for the formation of iminyl radicals. These transition metals mainly involved radical species and SETs necessary for the fragmentation processes, in contrast to precious metals, which are typically involved in two-electron oxidative addition.

In 2016, the group of Selander[48] reported a C–C bond cleavage via the formation of an iminyl radical, where cyclobutanone-derived O-acyl oximes underwent a selective fragmentation process catalysed by FeII complexes. The first example using Cu complexes as a catalyst was reported in 2017 by Zhao and Shi.[49] Here, the authors showed that a Cu salt behaves as a redox catalyst for the Heck-like coupling of cyclobutanone oximes. In 2018, Guo and co-workers reported the first Ni-catalysed cyanopropylation etherification of cyclobutanones oxime esters.[50] In the following months, the

groups of Liu, Guo, and Yu focused their efforts on developing strategies for the fragmentation of unstrained cyclopentanone or cyclohexanone oxime derivatives. In this vein, metal catalysts such as copper[51] and iron[52] have successfully been used to achieve this aim (Scheme 12).
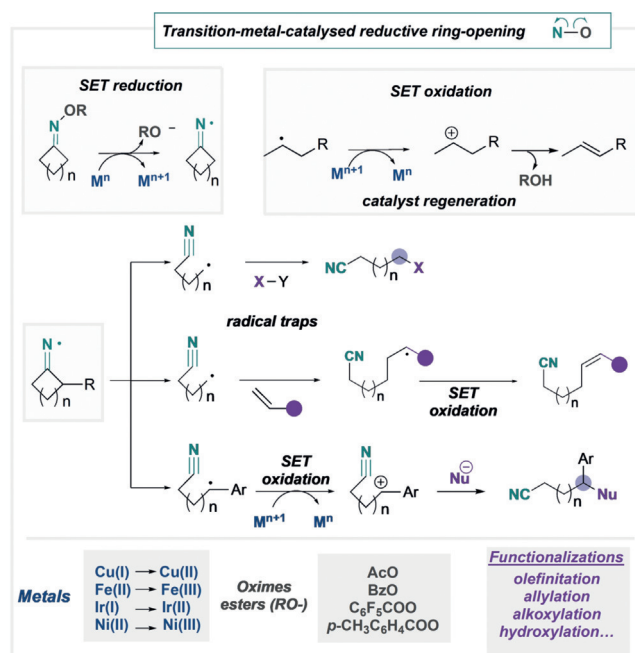
Scheme 12. Homolysis of N–O bonds by transition-metal catalysis.

In 2018, the group of Wang group developed the first deconstruction-based C–C bond cleavage/cross-electrophile coupling strategy by using Ni catalysis (Scheme 13).[53] In this
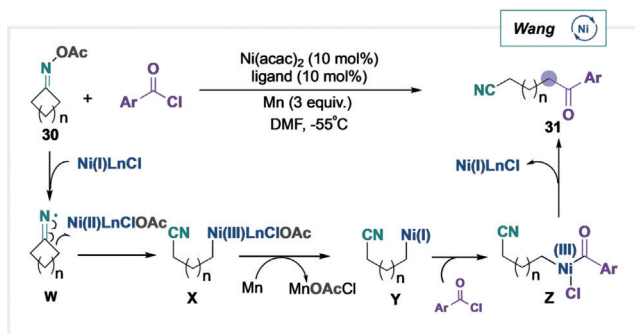
Scheme 13. Ni-catalysed C–C bond cleavage/cross-electrophile coupling. acac = acetylacetonate, DMF = N,N-dimethylformamide.

approach, a NiI complex, generated in situ, is able to catalyse a reductive cleavage to give the NiII complex, which can recombine with the alkyl radical to give the NiIII intermediate **X**. In the presence of Mn, the NiIII intermediate is reduced to NiI (**Y**), and is thus able to provide an oxidative addition to aroyl chlorides. Afterwards, the generated NiIII complex **Z** undergoes reductive elimination to achieve cyanoketones, thereby ensuring the turnover of the NiI catalyst.

3.3. Photoredox Catalysed Methods

During the past decade, visible-light photoredox catalysis has emerged as a powerful catalytic platform for the selective generation of nitrogen-centered radicals by SET processes.[54] Unlike transition metal catalysed processes, photoredox catalysis can use either reductive SET or oxidative SET approaches for N−O bond homolysis, thus enabling access to a broad range of products.

During the last two years, Chen, Xiao and co-workers[55] as well as the group of Zhou group,[56] have reported a number of studies on the photoinduced reductive fragmentation of O-acyl oxime derivatives. Despite the extraordinary advances achieved in reductive approaches, fragmentation of unstrained rings has so far been significantly overlooked. Jiao, Shi, and co-workers reported a photoinduced deconstruction/oxidation of unstrained cycloketoxime esters (**33**).[57] It was suggested that, upon the β-fragmentation process, the generated alkyl radical would be able to reduce the photocatalyst, thus forming a carbocation intermediate (**AI**; Scheme 14),
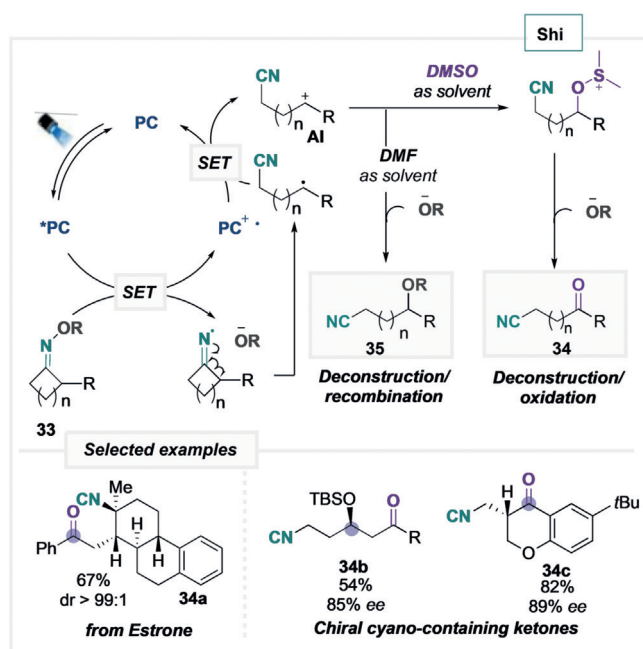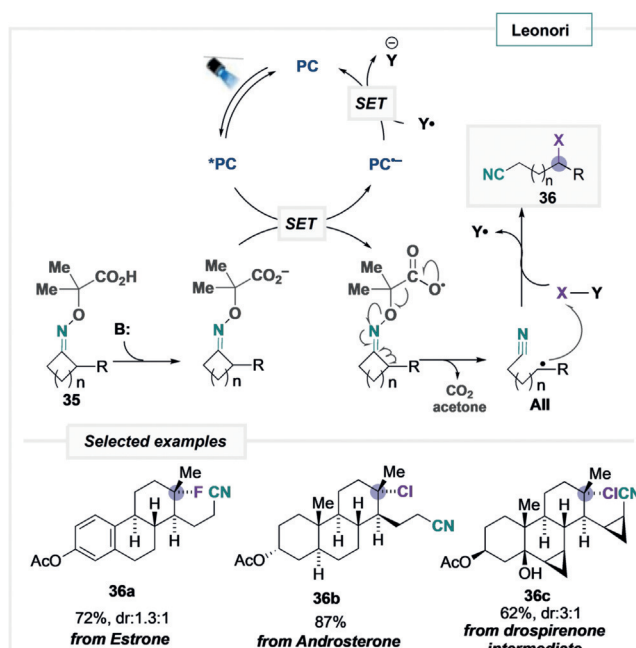

Scheme 14. Reductive fragmentation of unstrained cycloketoxime esters. DMSO = dimethylsulfoxide, TBS = *tert*-butyldimethylsilyl.

which should undergo oxidation with DMSO to give the ketone product **34**. As an illustration of its synthetic utility, the method was applied for the selective deconstruction/oxidation of the estrone-derived product **34a**, and the synthesis of enantiopure cyano-containing ketone products (**34b** and **34c**). Later, it was discovered that by using DMF as a solvent instead of DMSO, a fragmentation/rearrangement took place involving the "leaving group" in an intermolecular recombination to give **35** (Scheme 14).[58]

Inspired by the earliest studies of Zard, Leonori and co-workers,[59] reported an original method for the oxidative generation of iminyl radicals by using carboxylic acids

containing oximes as a precursor. With the oxidative SET the carboxylate undergoes a double β-scission to form an iminyl radical (Scheme 15). The oxidative SET mechanism should evolve similarly to reductive approaches to deliver the functional group nitrile and an alkyl radical (**AII**; Scheme 15).


Scheme 15. Oxidative fragmentation of unstrained cycloketoxime esters.

The key reaction is a homolytic substitution (S$_H$2), involving a radicophile (X-Y) and the alkyl radical **AII** (Scheme 15). In this particular case, **AII** is expected to be a nucleophilic radical, which reacts with a polarised radicophile (X-Y) to generate a Y· radical. The key point in this oxidative strategy is that Y· becomes a net electron-poor radical and, thus, is considered electrophilic, making the final SET reduction highly exergonic and enabling the regeneration of the ground-state photocatalyst. This process is in contrast to reductive approaches where the final SET oxidation is expected to be endergonic. The authors used this method for the selective deconstruction/fluorination, deconstruction/chlorination, and deconstruction/azidation of strained and unstrained (from five- to seven-membered ring) cycloketoxime esters. Most importantly, they applied the strategy for the structural modification and functionalization of small biomolecules, such as prasterone, estrone, a precursor of drospirenone (which is an active ingredient in birth control pills), and isosteviol. This application represents a clear example of directly modifying the core of small bioactive molecules, and could serve to simplify the preparation of molecular libraries used for biological screening. In 2018, Waser and co-workers[60] reported a related method, wherein a C−C formation was achieved by using ethynylbenziodoxolones (EBX) reagents as the radicophile.

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3.4. Miscellaneous

Alongside transition-metal or photoredox catalysis, alternative strategies enabling fragmentation of cycloketoxime derivatives have been developed in recent years. For example, the group of Castle developed the first microwave-promoted deconstruction/functionalization of unstrained cycloketoxime ethers. The authors found that O-phenyl ketoxime ethers undergo selective N−O homolysis upon microwave heating (MW, $T \approx 90\,°C$).[61] Recently, the group of Guo[62] developed a transition metal free strategy for the deconstruction/borylation of cycloketoxime esters. The author suggested that a dimethylacetamide (DMA) solvent molecule binds to the boron atoms of $B_2(OH)_4$, forming an heteroleptic ternary complex (**AIII**; Scheme 16). This species leads to the thermal cleavage of the B−B bond, thus forming two equivalents of the DMA-stabilized boryl radical **AIV**, which subsequently undergoes N−O homolysis to produce the iminyl radical. Upon β-fragmentation, the alkyl radical reacts with DMA-ligated $B_2(OH)_4$, thus generating the desired boronic ester and **AIV**. Finally, the resulting boryl radical might propagate a radical chain reaction.
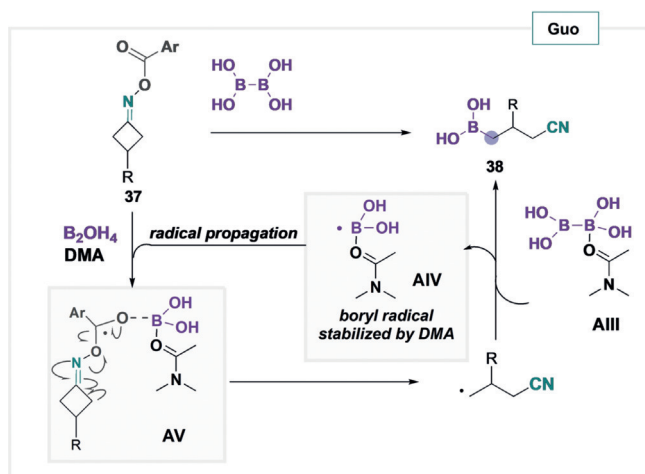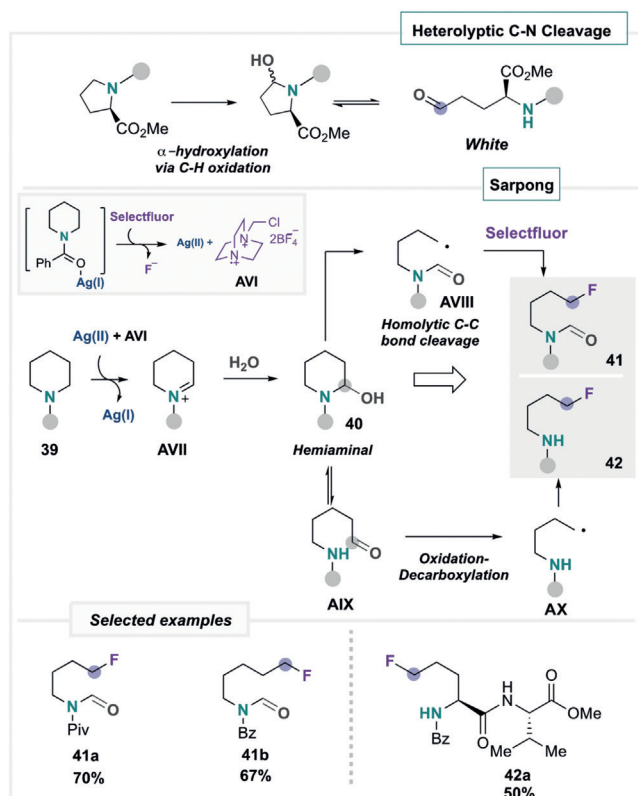

Scheme 16. Deconstruction/borylation of cycloketoxime esters. DMA = dimethylacetamide.

4. Deconstructive Functionalization of Cyclic Amines.

The development of deconstructive functionalization of cyclic amines is less intuitive than cyclic alcohols or cycloketoxime derivatives. The strategies are mainly based on C−H oxidations of amino acids. In particular, α-amine hydroxylation can undergo C−N bond fragmentation by the well-established equilibrium with the hemiaminal that is formed.[63] However, these approaches belong to heterolytic C−N bond cleavage methods, which are not covered in this section. Here, we focus on C−C cleavage, however, methods able to distinguish between the cleavage of C−C bonds versus C−N bonds remain a challenge.

In 2018, the group of Sarpong[64] developed the first homolytic C−C bond cleavage method for the deconstruction/

fluorination of unstrained cyclic amines. The significance of this chemistry is that the functional group (alcohol in this case), which is indispensable for the cleavage, is installed in situ during the reaction. This aspect is in contrast to all the other methods discussed so far for C−C bond cleavage. This method involves two key steps, each mediated by a silver salt. In the first step, a cyclic amine is oxidized to the corresponding iminium ion **AVII**, which is trapped by H_2O to form the hemiaminal **40** (Scheme 17). The authors proposed that an

Scheme 17. Deconstructive fluorination of cyclic amines. Bz = benzoyl, Piv = pivaloyl.

initial coordination of Ag^{I} to the cyclic amine leads to the formation of Ag^{II} and the radical dication **AVI** through a single-electron oxidation by Selectfluor. The process to form **AVII** proceeds by single-electron transfer between **39** and Ag^{II}, followed by hydrogen-atom abstraction by **AVI**. The second step is the key transformation in this reaction, since **40** could lead to either **AVIII** by homolytic C−C bond cleavage or to the intermediate **AIX** by heterolytic C−N cleavage. It was proposed by the authors that the formation of an alkoxy Ag^{II} intermediate was responsible for the fragmentation and the subsequent generation of **AVIII**, which gives rise to fluorination product **41** in the presence of Selectfluor.

As mentioned above, the challenge in this transformation lies in the competition between the homolytic versus heterolytic cleavage. It was found that the selectivity may be governed by the steric hindrance at the α-position of the cyclic amines. The authors reported the deconstruction/fluorination of several cyclic amines either by homolytic C−C bond

cleavage (**41 a** and **41 b**) or by heterolytic C−N bond cleavage (**42**). In spite of the unprecedented results achieved, the deconstructive fluorination by heterolytic cleavage (**AIX**) followed by oxidation and decarboxylation (**AX**) gave rise to the most impressive results. By applying this methodology, the deconstruction/fluorination of synthetic peptides was achieved (**42 a**) through C−N bond cleavage. Moreover, a similar strategy for the deconstruction/chlorination and deconstruction/bromination was also reported by the authors to achieve a broad product diversification.[65] As a result, both strategies established a powerful protocol for the direct diversification of complex molecules, amino acids, and peptides, and should benefit small-peptide therapeutics since they enable access to a wide range of structural diversity for the rapid exploration of key physical properties.

5. Summary and Outlook

Radical-mediated β-fragmentation reactions hold a unique position in organic synthesis thanks to their ability to form two new chemical bonds through the disconnection of inert bonds and their subsequent functionalization. The successful combination of various modes of catalysis, including metal-catalysis or photoredox catalysis amongst others, have made the cleavage of many challenging C−C bonds possible. As new methods for mild radical generation are under permanent development, the challenges that remain maybe resolved in the coming years. For example, the development of enantioselective variants, by making use of dual catalysis, the design of new strategies enabling the generation of unsaturated fragments other than ketones and nitriles, or the development of creative designs enabling functionalization of carboxylic acids by circumventing the decarboxylation reaction, could be some important challenges to address. Deconstructive chemistry will have a direct impact on the future exploration of new chemical space for drug discovery.

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Conflict of interest

The authors declare no conflict of interest.

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