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Dealkenylative Functionalizations: Conversion of Alkene C(sp³)–C(sp²) Bonds into C(sp³)–X Bonds via Redox-Based Radical Processes

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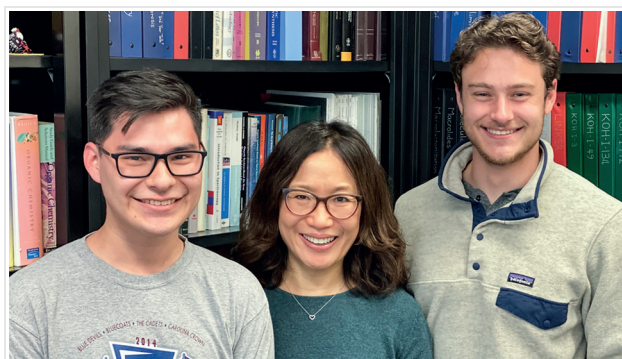*Advances in Skeletal Editing and Rearrangement Reactions*
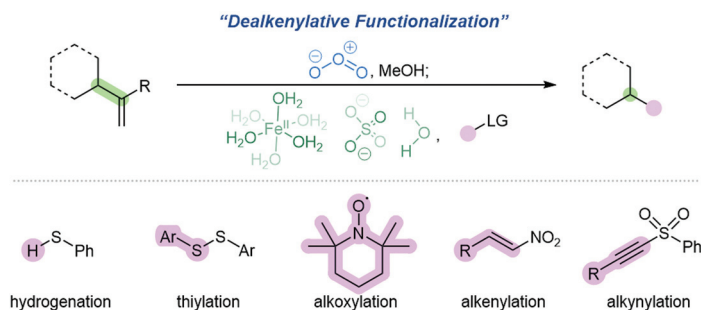
Abstract   This review highlights the history and recent advances in dealkenylative functionalization. Through this deconstructive strategy, radical functionalizations occur under mild, robust conditions. The reactions described proceed with high efficiency, good stereoselectivity, tolerate many functional groups, and are completed within a matter of minutes. By cleaving the C(sp³)–C(sp²) bond of terpenes and terpenoid-derived precursors, rapid diversification of natural products is possible.

Key words hydroperoxide, radical, iron(II), dealkenylation, β-scission, terpenes

Ohyun Kwon   (middle) is a Professor of Chemistry and Biochemistry at UCLA. She received her B.S. and M.S. degrees from Seoul National University in 1991 and 1993, respectively. After obtaining her Ph.D. from Columbia University in 1998, and a postdoctoral stint at Harvard University, Kwon began her independent career at UCLA in 2001. Her research involves the development of defunctionalative C–C activation chemistry and phosphorus organocatalysis processes, and their application in the synthesis of compounds of biological significance. She has played key roles in establishing nucleophilic phosphine catalysis as one of the main areas of organocatalysis, and is recognized as one of the leaders in the field. **Brady W. Dehnert** (left) received his B.S. in chemistry from the University of Oklahoma in 2021. **Jeremy. H Dworkin** (right) received his B.S. in chemical biology from the University of California, Berkeley in 2021.

1   Introduction

Within the broad scope of natural products, alkenes are abundant functional groups that are seemingly quintessential to organic chemistry. Recent analysis based on a dataset of 13 million structures has estimated that 39.85% of natural products contain olefinic units, and that they are the second most encountered functionality.[1] Their wide availability and synthetic versatility have guided many prominent chemists to seek synthetic transformations for building, cleaving, and functionalizing olefins. Over the years, numerous reactions have been devised to cleave the C(sp²)–C(sp²) π-bonds of alkenes, including traditional ozonolysis or oxidative cleavage using osmium tetroxide and sodium periodate or potassium permanganate. Relatively recently, transition-metal-catalyzed alkene cleavage reactions (e.g.,

olefin metathesis) have become popular synthetic strategies. There have been, however, few literature precedents of C(sp³)–C(sp²) σ-bond fissions of alkenes,[2–7] despite the abundance of olefinic units in natural products and commodity/feedstock chemicals. Gratifyingly, methods have been developed recently to strategically cleave alkenyl C(sp³)–C(sp²) σ-bonds to expand the existing potential of olefinic compounds. Indeed, several examples of fragmenting these 'inert' bonds and installing useful synthetic motifs in their wake—including C(sp³)–H,[8,9] C(sp³)–S,[10] C(sp³)–O,[11]

C(sp³)=O,[11] C(sp³)–C(sp²),[12] and C(sp³)–C(sp)[13] functionalities—have been explored since 2018.

While there are plenty of methods to cleave C–C bonds through radical, heterolytic, or transition-metal-mediated means,[14] the functionalizations that we present herein stem from iron(II)-mediated single-electron reductions of the α-alkoxyhydroperoxides that originate from alcohol-intercepted ozonolysis of alkenes, thereby producing fleeting alkyl radicals that are trapped by radical acceptors. The utility of ozone-mediated oxidation and iron(II)-mediated fragmentation–radical functionalization arises from their ease of operation and applications to natural products synthesis. These dump-and-stir, open-to-the-air reactions are usually complete within minutes, enabling quick and robust functionalization. Using terpenes and terpenoids from Nature's chiral pool allows the rapid derivatization of feedstock olefins into enantiopure terpene derivatives that are relevant synthetically. For example, many natural products[3,9,12,15,16] and chiral phosphine catalysts[8] have been synthesized efficiently and selectively using this approach. Overall, dealkenylative functionalization is a powerful method that allows synthetic chemists to take advantage of ubiquitous alkenes and provides access to unprecedented building blocks from Nature.
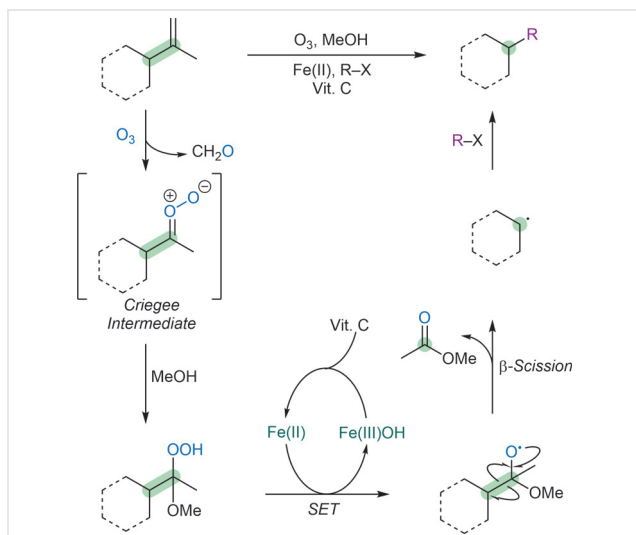
2   Mechanism

Criegee ozonolysis and metal-mediated peroxide cleavage form the basis for dealkenylative functionalization (Scheme 1). In this one-pot process, a solution of an alkene substrate in methanol is cooled to –78 °C and bubbled with ozone. In a matter of minutes, the alkene is transformed into an α-methoxyhydroperoxide. First, a (3+2) cycloaddi-

Scheme 1 Mechanism for ozone-mediated peroxidation and iron(II) reduction of feedstock olefins

tion forms a molozonide that rapidly engages in a retro-(3+2) cycloaddition to form a carbonyl oxide—the so-called 'Criegee intermediate.' The methanol charge-ablates to form a neutral α-methoxyhydroperoxide. After the excess ozone is removed through an argon sparge, the radical acceptor, reductant (if applicable), and iron(II) sulfate heptahydrate are added directly into the reaction mixture. While the mixture is warmed to room temperature, iron(II) sulfate heptahydrate dissolves completely, enabling a single-electron transfer (SET) event to reduce the hydroperoxide. This process forms an alkoxy radical, a hydroxide anion, and iron(III). Rapid β-scission of the alkoxy radical generates an alkyl radical, expelling a methyl ester. Radical addition into a radical trap terminates the reaction cascade to yield the dealkenylated product. To make this method catalytic, a benign stoichiometric reductant can be used to turn over the iron(III) back to iron(II), which restarts the cycle. A variety of radical traps have been used to ensure hydrodealkenylation [C(sp³)–H], dealkenylative thiylation [C(sp³)–SPh], dealkenylative aminoxylation [C(sp³)–OR], oxodealkenylation [C=O], dealkenylative alkenylation [C(sp³)–C(sp²)], and dealkenylative alkynylation [C(sp³)–C(sp)].

3   History

Dealkenylative functionalization combines three ideas into one powerful methodology. First, ozone-mediated oxidation of an olefin generates a peroxide. Second, SET from an iron(II) salt to the peroxide initiates a radical cascade. Third, the resulting alkoxy radical undergoes β-scission to give an alkyl radical species that is immediately coupled with a desired functional group to yield the final product. Precedents for each of these processes have been developed over the course of the last century, with the discovery of various methods to synthesize peroxides, the elucidation of SET from metals to peroxides to form radicals, and a survey of the potential transformations available from these radicals.

Since their discovery, peroxides have served as attractive synthetic intermediates because of their unique interactions with metal salts (Figure 1). In 1862, Brodie provided preliminary results regarding the reactions of hydrogen peroxide with various metals.[17,18] In particular, he observed ferrocyanide oxidation mediated by hydrogen peroxide under acidic conditions and reduction under basic conditions, marking one of the first observations of the redox relationship between peroxide and iron. A few years later, Parnell published his findings on the reducibility of hydrogen peroxide with iron(II) sulfate, directly resulting in an iron(III) species.[19] Subsequently, in 1894, Fenton demonstrated the catalytic capability of iron(II) sulfate through the oxidation of tartaric acid with hydrogen peroxide.[20] The connection between ferrous species and peroxides was clarified in 1932 with contributions from Häber and Weiss. They pro-
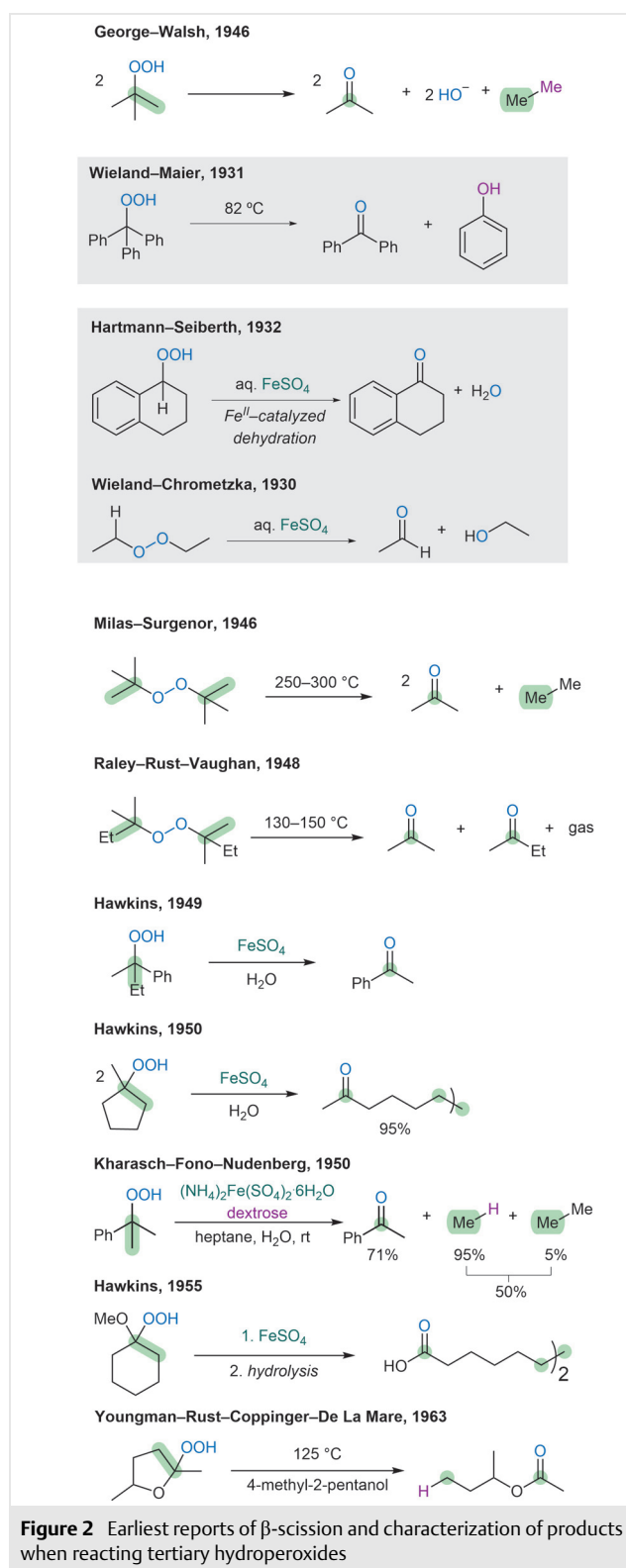
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posed a mechanism in which hydrogen peroxide, in the presence of iron(II), would be reduced to a hydroxide ion and a hydroxyl radical.[21] Thereafter, iron(II) salts and other low-valent transition metals were studied extensively in the context of organic peroxide fission.

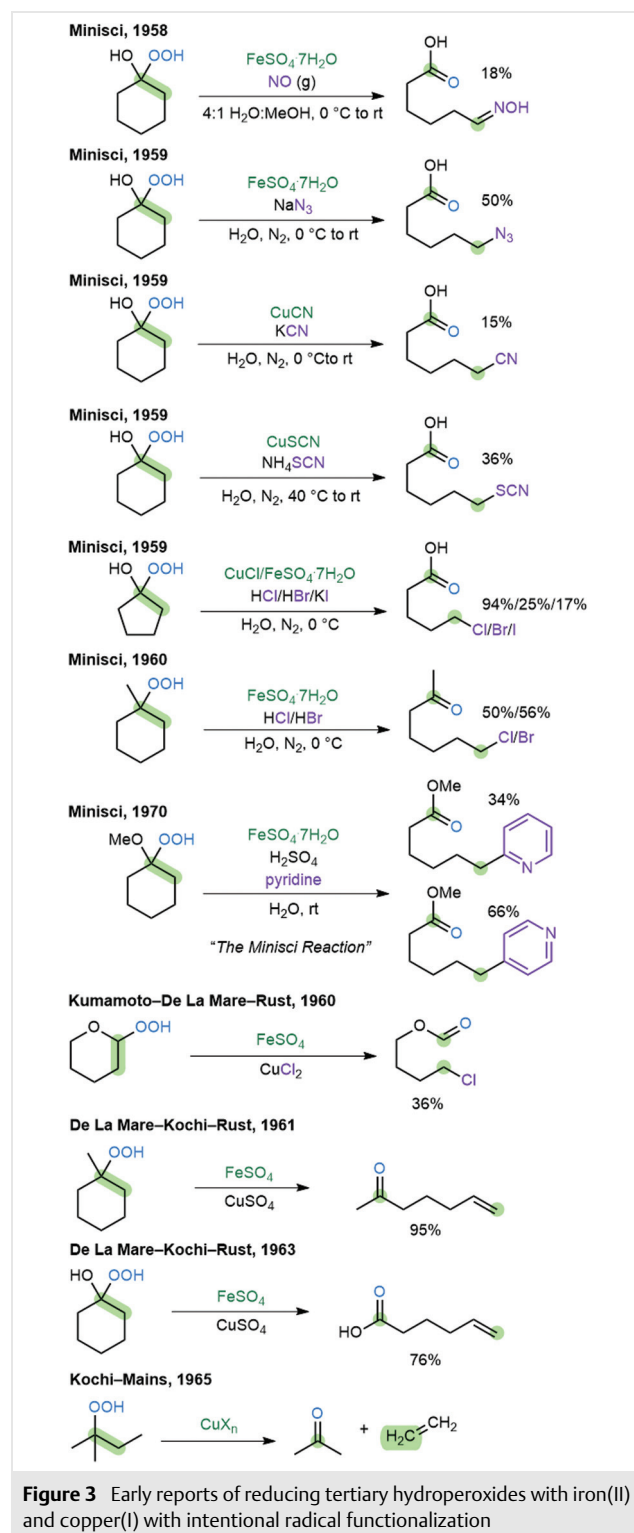**Figure 1** Initial studies on iron(II) reduction of hydrogen peroxide
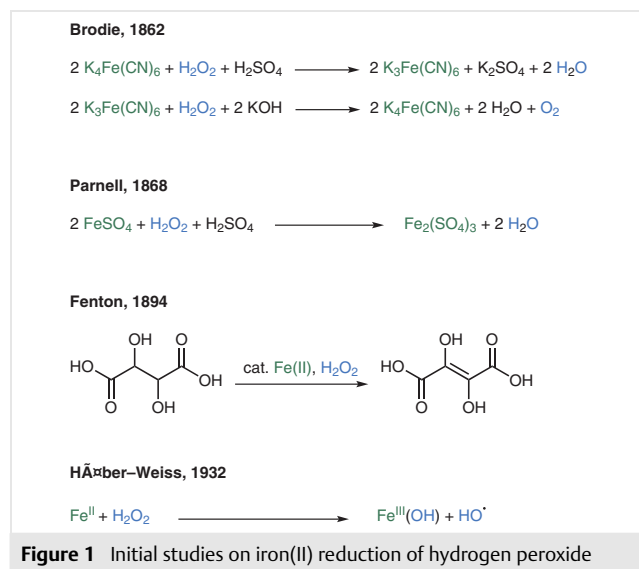
With the mechanism of peroxide decomposition mediated by metal salts revealed, prominent peroxide chemists from the 1940s and early 1950s began further investigations into alkyl hydroperoxide reduction (Figure 2). These chemists were primarily interested in the methods and mechanism of peroxide decomposition, with β-scission surfacing as the main mechanistic idea. George and Walsh, in their critical review from 1946, explicitly introduced the concept of β-scission for carbonyl bond (C=O) formation and concomitant scission of the weakest β-bond.[22] They made this claim based on their unpublished work into the degradation of *tert*-butyl hydroperoxide. The β-scission of alkyl hydroperoxides was, however, observed earlier, in 1931, by Wieland and Maier with the formation of acetophenone and phenol from the pyrolysis of trityl hydroperoxide.[23] Acyl peroxides, on the other hand, have been known to undergo β-scission through a decarboxylative degradation pathway, but they are not applicable intermediates for dealkenylative functionalization, so we have excluded them from the scope of this review.[24,25] Furthermore, secondary hydroperoxides tend to lead to dehydration reactions, often predominantly over scission, as observed by Hartmann and Seiberth in 1932 with the reduction of tetralin hydroperoxide to tetralone mediated by ferrous sulfate.[26] Similar reactivity was shown by Wieland and Chrometzka when they used iron(II) to reduce diethyl peroxide to acetaldehyde and ethanol.[27] Thus, only alkyl hydroperoxide scissions that result in C(sp³)–C(sp³) bond cleavage are considered within the scope of this review. The

Figure 2 Earliest reports of β-scission and characterization of products when reacting tertiary hydroperoxides

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idea of alkyl hydroperoxide β-scission-guided explorations of the decomposition process climaxed separately in series of papers released by Milas, Raley–Rust–Vaughan, Hawkins, Kharasch, Kochi, and Youngman–Rust–Coppinger–De La Mare (Figure 2). We have selected a few examples from each of these series as markers of the progress of this field and how they relate to dealkenylative functionalization. In 1946, Milas focused mainly on the synthesis of peroxides and the thermal decomposition of hydroperoxides.[28,29] After thermolytic cleavage of di-*tert*-butyl peroxide, analysis of the decomposition products revealed the production of acetone and ethane gas. Milas also suggested that the decomposition of hydroperoxides leads to 'formation of intermediate free radicals'—an important observation for future work. In 1948, Raley, Rust, and Vaughan examined the rates of di-*tert*-amyl peroxide decomposition and concluded that 'alkoxy and methyl radicals' were produced.[30] Then, in 1949, Hawkins demonstrated the reduction of 2-phenyl-2-butyl hydroperoxide with ferrous salt, but failed to mention a radical pathway.[31] A year later, however, Hawkins realized that radical intermediates were formed in a ferrous sulfate promoted dimerization from methylcyclopentyl hydroperoxide.[32] Kharasch also explored decomposition products during this time.[24g,33,34] In one of his reports, he used ferrous ammonium sulfate to reduce α-cumyl hydroperoxide and emphasized the ratio of decomposition products and the effects of additives.[35] Kharasch observed the formation of acetophenone in 71% yield, resulting from β-scission, and collected 50% of the expected mixed gas containing 5% ethane and 95% methane originating from the β-scission. The ethane gas arose through dimerization of two methyl radicals, and the methane gas from a methyl radical abstracting a hydrogen atom from dextrose, the hydrogen atom donor. In 1955, the first report emerged of the reduction of an α-alkoxyhydroperoxide to produce an alkyl radical that was trapped immediately. Hawkins used iron(II) sulfate to reduce methoxycyclohexyl hydroperoxide to induce a ring-opening cascade terminating in a dimethyl ester dimer, which yielded a diacid after immediate hydrolysis.[36] Finally, Youngman and co-workers identified a ring-opening product from the thermal fragmentation of 2,5-dimethyltetrahydrofuran-2-hydroperoxide, adding another example of an alkoxy hydroperoxide degradation that is relevant to dealkenylative functionalization.[37] The 1940s through 1960s was a tremendous era for peroxide decomposition chemistry, in which the patterns for β-scission were realized, the scission rates were first measured, and α-alkoxyhydroperoxides—the main intermediates in dealkenylative functionalization—were first used in this context.

The ability to reliably generate alkyl radicals from alkyl peroxides led chemists toward research into functionalization methods (Figure 3). Minisci, Kumamato–De La Mare–Rust, De La Mare–Kochi–Rust, and Kochi–Mains published several reports of the reduction of peroxides to alkoxy radicals and attempts to functionalize alkyl radicals. Until this

point, most researchers had focused on identifying the degradation products from the thermolysis and iron(II)-mediated reduction of peroxides. Minisci, on the other hand, had an eye for the synthetic opportunities available for alkyl


Figure 3 Early reports of reducing tertiary hydroperoxides with iron(II) and copper(I) with intentional radical functionalization

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radicals. From 1958 to 1970, Minisci reported several instances of alternative radical functionalizations, achieving nitrosation,[38] azidation,[39] cyanation,[39] isothiocyanation,[40] halogenation,[41–43] and arylation.[44] From various tertiary hydroperoxides and alkoxy hydroperoxides, Minisci used ferrous or cuprous salts to initiate the radical cascades. He coupled the alkyl radicals with nitric oxide, sodium azide, potassium cyanide, ammonium thiocyanate, hydrohalic acids or potassium iodide, and pyridine to realize these novel transformations. The last transformation, using pyridine as the radical trap, constitutes the venerable 'Minisci reaction.' In 1960, Kumamoto, Rust, and De La Mare demonstrated a chlorination through the reduction of 2-tetrahydropyranyl hydroperoxide with iron(II) chloride or a combination of iron(II)sulfate and copper(II) chloride.[45] In 1961, just one year later, De La Mare, Kochi, and Rust found that, after ring opening of the reduction product from methylcyclohexyl hydroperoxide, the primary alkyl radical was oxidized by cupric sulfate to yield an olefin after copper(II)-promoted β-hydride elimination.[46] In 1963, this same trio proved that the same ferrous/cupric conditions were suitable for the reduction of hydroxycyclohexyl hydroperoxide to yield 5-hexenoic acid.[47] In 1965, Kochi and Mains moved from iron(II) to a copper(I) catalyst to initiate tertiary hydroperoxide fragmentation, detecting acetone and ethylene gas as products.[48] In the period from 1955 to 1970, the synthetic potential of peroxide degradation gained the momentum that led to today's applications of alkyl peroxide reduction.[49]

Dealkenylative functionalization is powerful because it both installs the peroxide and reduces it within a streamlined process. Early studies of peroxide degradation were limited by the few synthetic options available for preparing alkyl peroxides, requiring isolation of the peroxide prior to decomposition. Acylation, autoxidation, condensation, and substitution dominated the early techniques for peroxide synthesis (Figure 4). In 1858, Brodie generated the first synthetic perester from benzoyl chloride and sodium peroxide.[50] In the 1940s, Milas expanded the scope of acylation by using *tert*-butyl hydroperoxide and a variety of acid chlorides.[51] Another simple method for peroxide formation is condensation, with the first instance reported in 1895 by Wolffenstein, who stirred three equivalents of acetone with hydrogen peroxide and formed the explosive triacetone-triperoxide.[52] Autoxidation was also common in this era. Two separate groups conducted the first intentional autoxidations in 1897. Both Bach and Engler–Wild combined carbon monoxide and oxygen over water to form percarbonic acid.[53,54] Alternatively, peroxides may be formed through substitution. In 1938, Milas demonstrated S_N1 chemistry with tertiary alcohols and hydrogen peroxide; in 1940, he described S_N2 chemistry with a primary alkyl halide and sodium peroxide.[55,56] Variations of these four methods have been expanded upon over time, but none of them is capable of introducing a peroxide from an alkene.

Following the discovery of the Diels–Alder cycloaddition, alkenes became a target for peroxide synthesis using pericyclic chemistry or metal-mediated methods (Figure 5). Oxygen and ozone were quickly identified as renewable and compatible pericyclic partners for alkene peroxidation. In 1928, Windaus and Brunken formed a six-membered endoperoxide through (4+2) photochemical cycloaddition of singlet oxygen with ergosterol.[57] Almost 40 years later, Bartlett and Schapp conducted the first (2+2) photochemical cycloaddition to form a four-membered endoperoxide. They irradiated a solution of diethoxyethylene and oxygen with a porphyrin photosensitizer to form the cycloadduct.[58] Singlet oxygen was also used in the 1953 Schenck-ene reaction to install an allylic hydroperoxide.[59] Criegee explored the interaction between ozone, discovered by Schönbein in 1838,[60] and alkenes. In the late 1940s, Criegee identified peroxide intermediates formed through a (3+2) dipolar cycloaddition and retro-(3+2) cycloaddition.[61–63] He discovered that the ozonation of 1,2,3,4,5,6,7,8-octahydronaphthalene in methanol led to a stable α-methoxyhydroperoxide, a reactive intermediate that would later be exploited for dealkenylative functionalization.[64] These three species—singlet oxygen, ozone, and triplet oxygen—are ideal reagents for subsequent reduction of the peroxide intermediate be-

**Figure 4** Early methods of peroxide synthesis
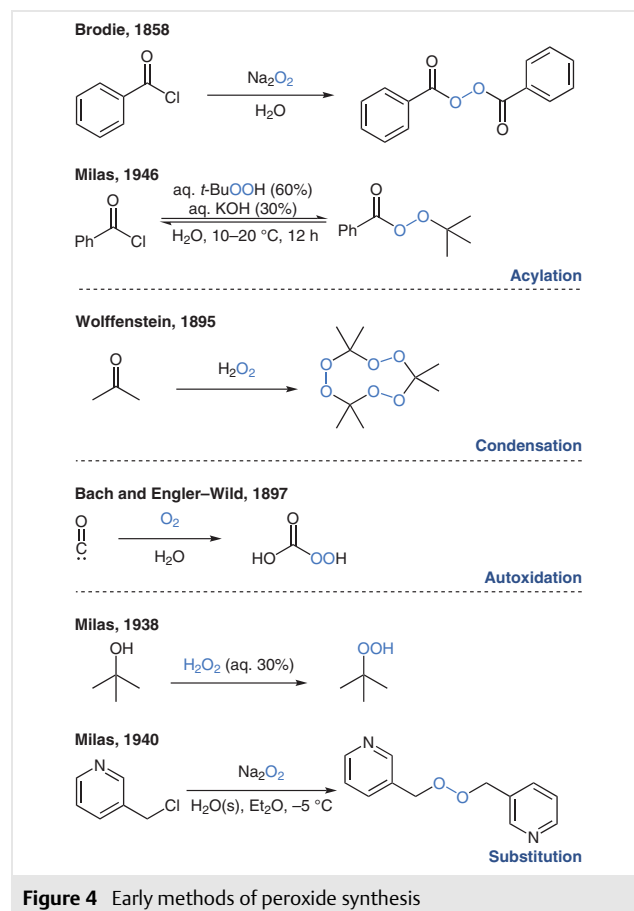
cause they may not require isolation of the alkyl peroxide product, with excess ozone and oxygen being removable without a trace. In 1989, Isayama and Mukaiyama developed a method using triplet oxygen to install an alkyl peroxide.[65] With catalytic cobalt(II) and an alkylsilane, they added triplet oxygen regioselectively to an alkene via radical intermediates, marking the first example of a metal-catalyzed peroxidation. In more recent metal-mediated peroxidations, Li spearheaded the subfield of metal-mediated difunctionalization of alkenes. In a 2011 example, Li's group used iron(II) chloride, *tert*-butyl hydroperoxide, and aldehyde derivatives to difunctionalize styrenes with peroxide and β-peroxy ketones.[66] While Li pioneered the field, other groups difunctionalized alkenes with peroxides and a plethora of other functionalities by applying metal salts of manganese, iron, copper, silver, cobalt, and rhodium.[67] Finally, a very recent method for peroxidation, from 2020, in-

volved molybdenum(VI)-catalyzed epoxidation of allylic alcohols in a Henbest manner and in situ attack of peroxide to open the epoxide.[68] This stereoselective method of peroxidation used known stereoselective epoxidation methods. Whether it involves oxygen/ozone or a metal-mediated process, the peroxidation of alkenes is a relevant topic for peroxide chemists because it is critical for dealkenylative functionalization.

Toward the end of the 1950s, all of the pieces necessary for dealkenylative functionalization were available, and chemists began using them in tandem (Figure 6). In 1957, Bailey and Bath published an early example of ozone-mediated peroxide degradation. By treating dibenzoylpropene
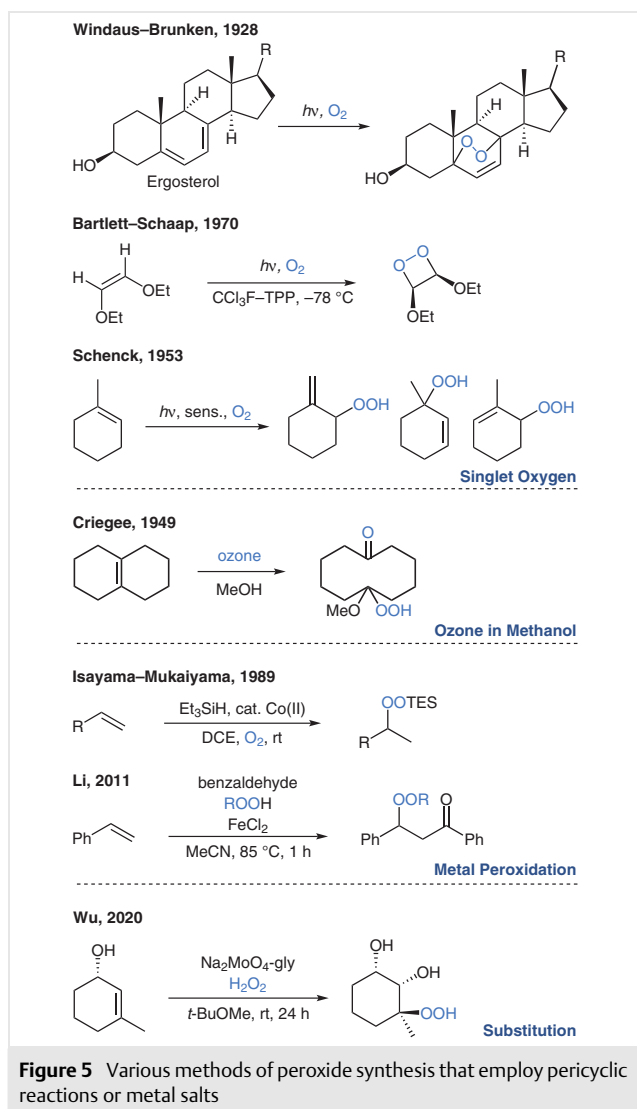
Figure 5 Various methods of peroxide synthesis that employ pericyclic reactions or metal salts
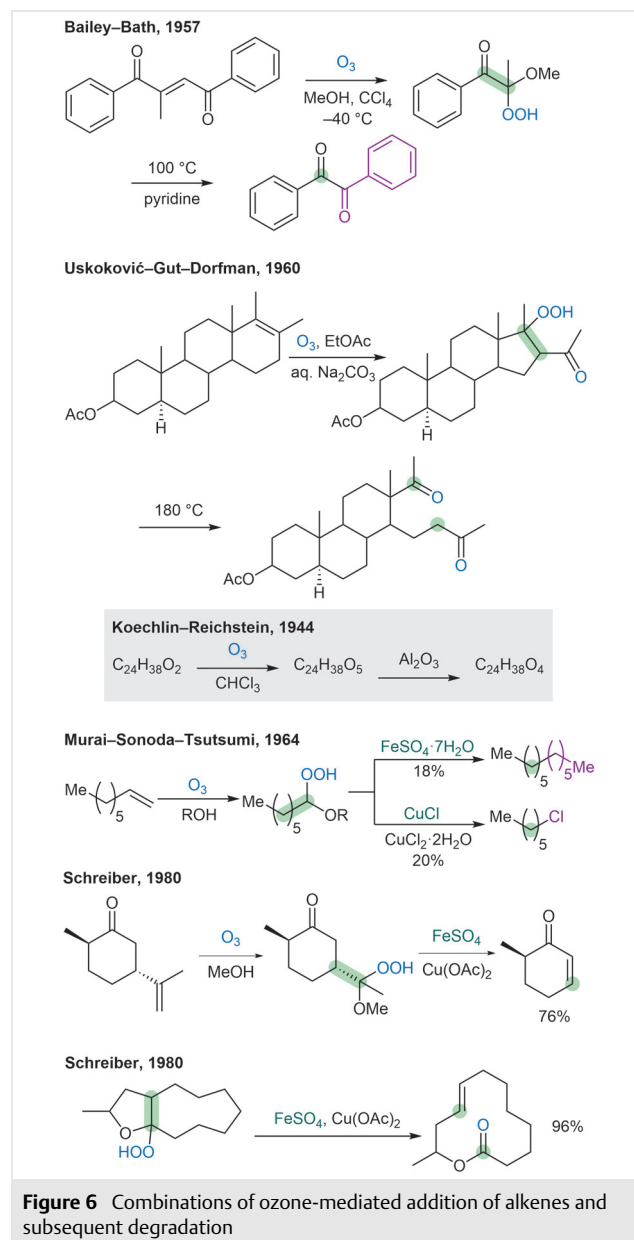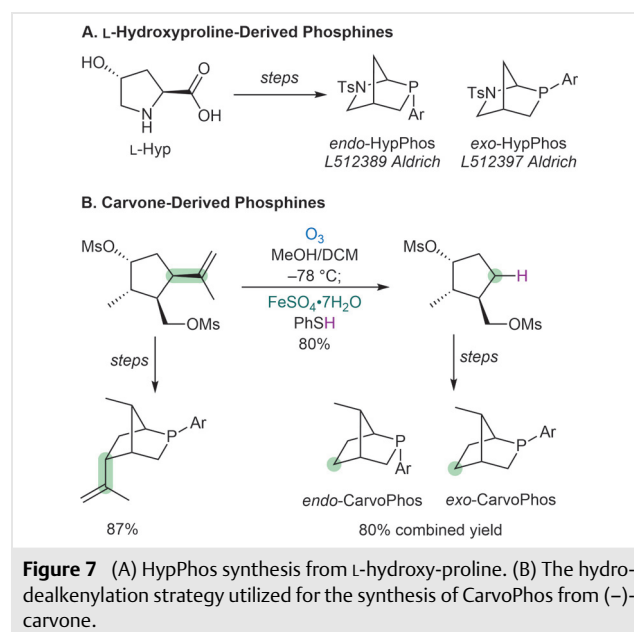

Figure 6 Combinations of ozone-mediated addition of alkenes and subsequent degradation

with ozone, they induced a hydroperoxide, which degraded under thermolytic conditions.[69] Despite the lack of an initiator, a radical process was postulated, due to the formation of benzil, an unexpected side product. The next example of peroxide installation by ozone and subsequent radical peroxide degradation appeared in 1960, reported by Uskokov-ić–Gut–Dorfman.[70] They thermolyzed a hydroperoxide at 180 °C to initiate the radical cascade and noted that the elemental analysis and melting point of their decomposition product were similar to those reported by Koechlin and Reichstein in 1944.[71] Although they had not mentioned the word 'hydroperoxide,' Koechlin and Reichstein reported the aluminum oxide assisted degradation of $C_{24}H_{38}O_5$ to $C_{24}H_{38}O_4$, without reporting any structures for this reaction. This paper provides possibly the first instance of radical peroxide degradation from an ozone-generated peroxide. In 1964, Murai, Sonada, and Tsutsumi finally combined ozonolysis and transition-metal-mediated peroxide reduction for chemical synthesis.[2] The Criegee intermediate from the ozonolysis of 1-octene was trapped with ethanol, forming an α-ethoxyhydroperoxide. Using either iron(II) sulfate or CuCl–CuCl$_2$, the dimerized or chlorinated products from the reduction of this hydroperoxide were identified as n-dodecane and n-hexyl chloride. Schreiber employed a similar method in 1980. He used ozone to install a hydroperoxide and then iron(II) sulfate and copper(II) acetate to form a dealkenylated enone product from (–)-dihydrocarvone, a terpenoid. The same article contained the first example of metal-mediated reduction of a hydroperoxide in the total synthesis of a natural product, (±)-recifeiolide.[3] Since then, the conditions popularized by Schreiber were applied in several total syntheses, but only oxidative termination had ever been achieved.[72] Dealkenylative functionalization, initiated in 2018, revamped this historic method, improving upon precedent to make it a more relevant tool for the synthetic organic chemist.

4   Motivation to Pursue Dealkenylation

In 2014, the Kwon group designed trans-4-hydroxy-l-proline-derived [2.2.1] bicyclic phosphines (HypPhos) for catalysis of enantioselective allene–imine [3+2] annulations to obtain chiral pyrroline products (Figure 7).[73] While both the endo- and exo-HypPhos catalysts performed excellently, achieving up to 99% yield and greater than 99% enantiomeric excess (ee), only one antipode of HypPhos was readily available. To address this limitation, they selected carvone to build the [2.2.1] phosphine because it is a chiral terpenoid available commercially in both enantiomeric forms. In 2018, the group set out to make (–)-carvone-derived [2.2.1] bicyclic phosphines (CarvoPhos).[8] From a common dimesylate intermediate, they synthesized several [2.2.1] bridged bicyclic phosphines, but isolated only exo-Carvo-Phos derivatives. The performance of these catalysts was

mediocre, achieving ee values in the range of 35–98%. Working under the assumption that steric crowding of the endo-face of the catalyst by the isopropenyl group precluded the formation of endo-CarvoPhos, they considered the hydrodealkenylative removal of the isopropenyl group. Employing iron(II) sulfate heptahydrate and benzenethiol, a hydrogen atom donor (HAD), provided access to the hydrodealkenylated product from the α-methoxyhydroperoxide intermediate. Lacking the isopropenyl group, both exo- and endo-CarvoPhos performed similarly to the previously reported HypPhos catalyst, achieving yields ranging from 88 to 99% and ee values from 84 to 99%. With successful hydrodealkenylation of the isopropenyl group from the dimesylate, the Kwon group launched an investigation into the extent and applications of this methodology.

Figure 7 (A) HypPhos synthesis from L-hydroxy-proline. (B) The hydrodealkenylation strategy utilized for the synthesis of CarvoPhos from (–)-carvone.

5   Dealkenylation in the Present

Building on their success in using hydrodealkenylation in the synthesis of CarvoPhos, the Kwon group pursued peroxide reduction with a HAD as a powerful synthetic tool for cleaving the C(sp³)–C(sp²) bonds of alkenes and installing C(sp³)–H bonds in terpene derivatives (Figure 8). The group coined the term 'hydrodealkenylation' to describe this transformation.[9] Using iron(II) sulfate heptahydrate and benzenethiol as the HAD, bicyclic and monocyclic terpenes bearing an isopropenyl group underwent clean removal of this substituent with installation of a hydrogen atom. Isopropenyl-containing substrates that fared well in this transformation, with yields from 62 to 94%, included nootkatone, (–)-isopulegol, (–)-cis-limonene oxide, Wieland–Meischer ketone precursors, betulin, and betulinic acid. Even when reacting (–)-isopulegol on a scale of 100 mmol, a high iso-

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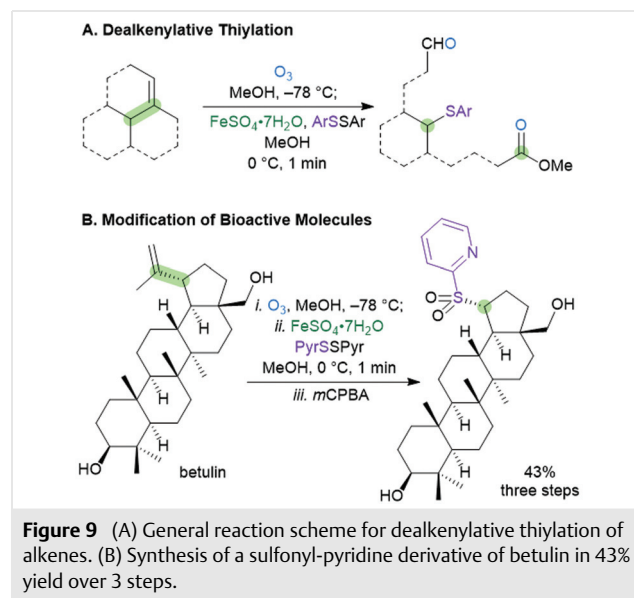lated yield of 89% was achieved. Cyclic substrates bearing exomethylene units underwent radical ring-opening processes to form esters tethered to the alkyl chain in yields of 26–89%. Methylenecyclohexanes [e.g., (±)-camphene and (−)-β-pinene] smoothly underwent the ring-opening transformation. Cycloalkenes [e.g., methylcyclohexene, (+)-α-pinene, (−)-nopol and (−)-α-cedrene] efficiently produced aldehyde products in yields of 60–88%. Because some of the substrates were fairly low in weight, instant acetal protection of the aldehydes was performed. Hydrodealkenylation was exemplified as a powerful synthetic strategy for organic chemistry by application in the formal syntheses of five natural products: (−)-pupukeanone,[74] (−)-seychellene,[75] (−)-7-epibakkenolide,[76] periconianone A,[72i] and a chiral steroid,[77] with their known synthetic routes shortened by five, four, three, two, and two steps, respectively. On *ChemRxiv* in late 2022, the Newhouse group demonstrated the first use of hydrodealkenylation in a total synthesis in their construction of (carvone-derived) (+)-shearilicine.[15] The group used the method to cleave an isopropenyl group from a tricycle. In 2023, the natural product vilmoraconitine was also synthesized using hydrodealkenylation to open a bicycloalkene moiety and access an aldehyde.[16] The benefits of this reaction are self-evident in terms of both strategic and sustainability standpoints.

After the success of hydrodealkenylation, it became apparent that conditions for the addition of other radical coupling partners needed to be explored. A few months after their publication of hydrodealkenylation, the Kwon group released dealkenylative thiylation (Figure 9).[10] In this method, after cleavage of the $C(sp^3)$–$C(sp^2)$ bond, a $C(sp^3)$–S bond is formed through radical trapping using a diaryl disulfide. From an optimization study with a bicyclic hydroxyketone bearing an isopropenyl group, diphenyl disulfide and other diaryl disulfides proved to be the best thiylating reagents. Moving away from hydrogen atom donors caused the rate of radical addition to decrease; therefore, the number of equivalents of disulfide was doubled (3.0 equivalents instead of 1.5) to compensate.

Figure 9 (A) General reaction scheme for dealkenylative thiylation of alkenes. (B) Synthesis of a sulfonyl-pyridine derivative of betulin in 43% yield over 3 steps.

With optimized conditions in hand, many of the terpene substrates that had not been employed in hydrodealkenylation—including (±)-sabinene, (+)-2-carene, α-terpineol, and norbornylene—were used to demonstrate the pertinence of the thiylation process. The yields of isopropenyl cleavage products ranged from 58 to 80%, *exo*-methylenecycloalkane cleavage products from 35 to 80%, and cycloalkene cleavage products from 5 to 75%. Several synthetic transformations applicable to thiylated products were explored, including oxidation, alkylation, elimination, 'cross-coupling,' and lactonization. In the provided example, betulin was subjected to dealkenylative thiylation, with the resulting thioether then oxidized to the sulfone derivative for use in cross-coupling reactions (Figure 9).[78]
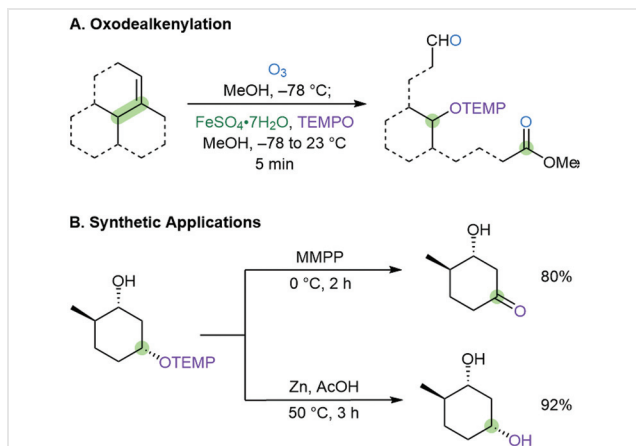

Figure 8 (A) General reaction scheme for hydrodealkenylation of alkenes. (B) Examples of hydrodealkenylation of alkenes. (C) Formal synthesis of (−)-seychellene from (−)-carvone.

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After dealkenylative thiylation, the next logical step was to use (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), a well-known persistent radical reagent, to achieve aminoxylation (Figure 10).[11] The reaction conditions for dealkenylative aminoxylation were similar to those for hydrodealkenylation. First, ozonolysis of the alkene in methanol yielded a hydroperoxide, which was subjected to reduction mediated by iron(II) sulfate, leading to an alkyl radical that was terminated by TEMPO to form a $C(sp^3)$–O bond. The rate constant for alkyl radical coupling with TEMPO ($>7.6 \times 10^8$ M^{-1} s^{-1})[79] was larger, by a few orders of magnitude, than that for thiylation with diaryl disulfides (ca. 6×10^5 M^{-1} s^{-1})[80] and similar to that for hydrogen atom transfer with benzenethiol (1.3×10^8 M^{-1} s^{-1}).[81] Therefore, only 1.5 equivalents of TEMPO were required. The TEMPO adduct was further oxidized to achieve Cope elimination, furnishing the oxodealkenylation product. Optimization revealed that 2.5 equivalents of magnesium monoperoxyphthalate hexahydrate (MMPP) was the best oxidant, providing access to the desired ketone in one pot. Isopropenyl cleavage resulted in yields of 50–95%. For non-isopropenyl-containing substrates, there were two reported instances of keto-ester formation (58% and 87%), one instance of aldehyde-methyl ester formation (82%), and keto-aldehyde formation (67%) with two regioisomers. The Kwon group focused mainly on oxidation of the TEMPO adduct, but reduction is also possible. For example, zinc-mediated reduction of the TEMPO adduct from (−)-dihydrocarveol, in the presence of acetic acid, produced the alcohol rather than the ketone.

Figure 10 (A) General reaction scheme for oxodealkenylation of alkenes. (B) Oxidative and reductive conditions for transforming the TEMPO adduct obtained from aminoxylated (−)-dihydrocarveol.

The next approach that the Kwon group took was cleaving the $C(sp^3)$–$C(sp^2)$ bonds to form new $C(sp^3)$–$C(sp^2)$ bonds. The first example of this type of C–C bond formation was dealkenylative alkenylation (Figure 11).[12] Alkene formation is important in organic synthesis because olefins are among the most versatile synthetic intermediates.[1] Early olefinations from alkyl radicals relied on β-hydride elimi-

nation using a copper(II) species, as demonstrated by De La Mare–Kochi–Rust.[46,47] The Kwon group considered β-nitroolefins such that the resulting radicals could undergo radical elimination of the nitro group to form alkenes instead. Monoterpenoids [e.g., (−)-isopulegol, cis-(−)-limonene oxide, trans-(+)-dihydrocarvone], a diterpenoid [(+)-nootkatone], and a triterpenoid (betulin) all underwent dealkenylative styrylation. After successes with other monoterpenoid derivatives with yields of 30–76%, the Kwon group explored altering the nitroolefin by adding substituents to various positions of styrene and keeping the alkene consistent. This approach fared well, with product yields ranging from 42 to 78%. The product yield decreased dramatically when the nitroolefin did not contain a β-aryl group and/or if there was a substituent on the α-carbon atom of the nitroolefin, due to steric repulsion. Furthering the scope of the reaction, esters and aldehydes were obtained from exo-methylenecycloalkanes (21–67%) and cycloalkenes (41–60%). In terms of geometric isomers, exclusive formation of the more stable E-alkenylated product was typical; in the absence of exclusive formation, the E-isomer outcompeted the formation of the Z-isomer by an order of magnitude.
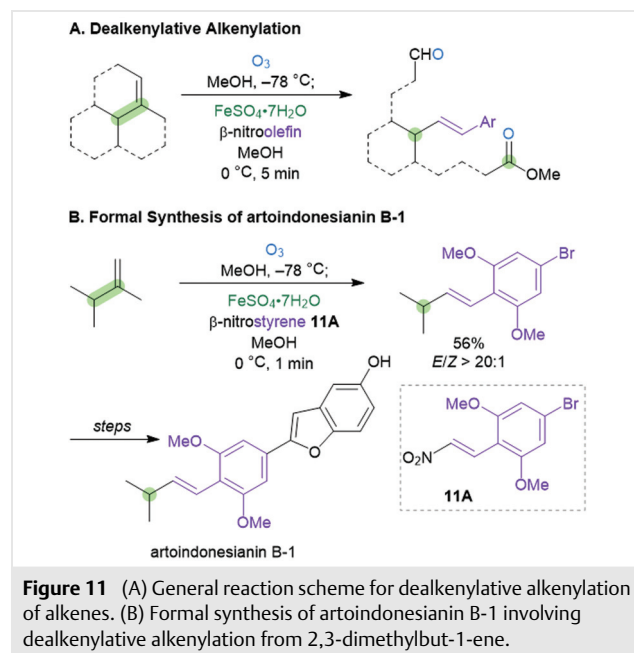
Figure 11 (A) General reaction scheme for dealkenylative alkenylation of alkenes. (B) Formal synthesis of artoindonesianin B-1 involving dealkenylative alkenylation from 2,3-dimethylbut-1-ene.

Because alkenes were obtained as products, subsequent hydrogenation, ozonolysis, and ring-forming reactions confirmed that the alkenylated products had utility for further transformations. Finally, the Kwon group completed formal syntheses of artoindonesianin B-1 (Figure 11)[82] and the synthesis of the drug (E)-metanicotine.[83] One final takeaway from that report was that the rate of radical addition for alkenylation ($<7.6 \times 10^5$ M^{-1} s^{-1})[84] was, like that for thiylation, lower by orders of magnitude relative to the rates of

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hydrogen atom abstraction and aminoxylation. Optimization of the alkenylation process revealed that switching the alkene (peroxide after exposure to ozone) from the limiting reagent to an excess and increasing the number of equivalents of iron(II) sulfate heptahydrate to 3.2 led to the highest product yields. For hydrogenation and aminoxylation, the radical addition rates were sufficiently speedy to outcompete undesired side reactions. With thiylation and alkenylation, however, increasing the number of equivalents of a reagent was necessary to thwart side reactions.

The most recent pertinent report from the Kwon group describes dealkenylative alkynylation mediated by catalytic iron(II), with vitamin C added to regenerate the iron(II) catalyst (Figure 12).[13] Again, Criegee ozonolysis and iron(II)-mediated reduction of peroxides allowed the addition of alkynes to terpenes, transformations that had not been accomplished previously through dealkenylative routes. Similar to alkenylation, addition into the alkyne produced a vinyl radical that underwent β-elimination of an arylsulfonyl unit, rather than a nitro group. In that report, the Kwon group found that the lower rate of radical addition affected the yield of the dealkenylated product, leading them to use catalytic, rather than stoichiometric, iron(II). A greater concentration of the alkyl radical in the reaction pot led to greater formation of undesired side products. As stated earlier, adding a greater number of equivalents of diphenyl disulfide sufficed for thiylation, and increasing the number of equivalents of iron(II) and using the alkene in excess sufficed for alkenylation. The consequence of increasing the number of equivalents of a reagent or using the alkene in excess is an increase in the general cost of a reaction—not ideal from the standpoint of atom economy. Because of the relatively low rate of radical addition into the ethynylsulfone ($<1.8 \times 10^5$ M^{-1} s^{-1}),[84] the solution for alkynylation was to decrease the concentration of the alkyl radical by decreasing the amount of iron(II) catalyst in the reaction pot at any single point in time. Optimization revealed that l-ascorbic acid (vitamin C) was a cheap and robust reductant for regenerating iron(II).

Using various terpenes, terpenoids, and their derivatives, isopropenyl cleavage was successful in installing substituted alkynes. Employing substrates similar to those in the previous reports, yields of 41–86% were achieved. With exomethylene-substituted cycloalkanes, the yields of ring-opened products were 45–67%. With yields from 32 to 45%, cycloalkenes were successfully opened to form alkynylated aldehydes. Widening the substrate scope, modifying the arylethynyl sulfones with electron-withdrawing and electron-donating substituents proved to be successful, with the alkynylated products obtained in yields from 42 to 83%. In contrast to alkenylation, the alkynylations were successful when the aryl group was replaced by an alkyl or silyl substituent, with yields ranging from 41 to 55%. Because alkynes are synthetically amenable to various transforma-
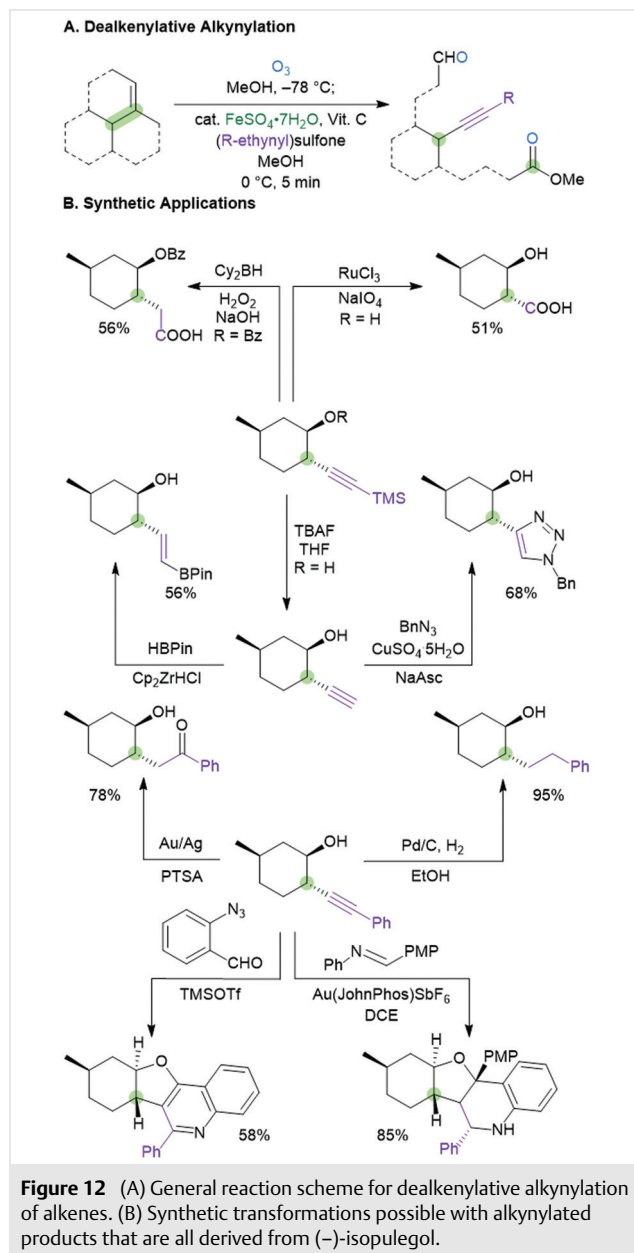
Figure 12 (A) General reaction scheme for dealkenylative alkynylation of alkenes. (B) Synthetic transformations possible with alkynylated products that are all derived from (−)-isopulegol.

tions, the Kwon group performed many relevant reactions with the alkynylated products. Using a trimethylsilyl (TMS)-substituted alkyne, some of these synthetic transformations included hydroboration/oxidation to form a carboxylic acid and Ru/periodate-mediated formation of a chiral carboxylic acid. Upon deprotection of the TMS-substituted alkyne using tetra-*n*-butylammonium fluoride (TBAF), the terminal alkyne was hydroborated to produce a vinylboronate ester, while a copper-catalyzed Huisgen (3+2) cycloaddition allowed the synthesis of 1,2,3-triazoles. For phenyl-substituted alkynes, hydrogenation formed an aliphatic chain in quantitative yield. A silver/gold-mediated hydration to give a phenone proved to be possible. Forma-

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tion of a hexahydrobenzofuran-fused quinoline, using *o*-az-idobenzaldehyde and trimethylsilyl triflate, succeeded with moderate yield. Furthermore, through a gold-catalyzed hy-droalkoxylation/Povarov cascade, a tetrahydroquinoline was successfully synthesized from an alkynol.

Figure 13A Substrates from reported dealkenylative functionalizations that contain isopropenyl substituents that will result in secondary radicals. [a] 100-mmol scale. [b] 10-mmol scale. [c] Gram-scale. [d] 5-mmol scale. [e] 20-mmol scale. * From (–)-*cis*-limonene oxide. † From *R*-(–)-carvone. ‡ From (+)-dihydrocarvone.
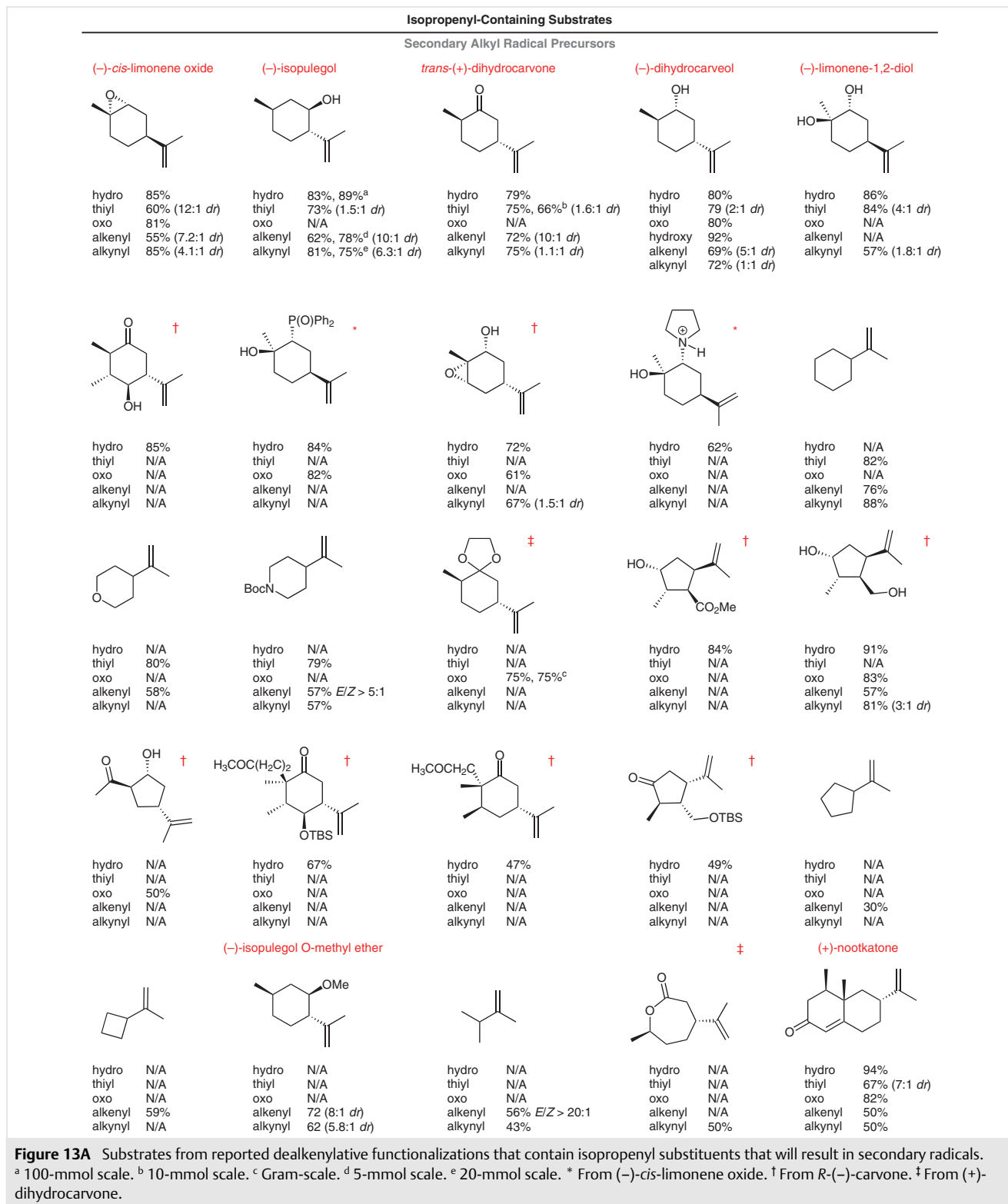
6   Conclusion

Dealkenylative functionalization elegantly addresses a historically underutilized chemical operation: fission of alkenyl C(sp³)–C(sp²) σ-bonds. This one-pot, dump-and-stir, open-to-the-air reaction is powerful because it pairs a two-electron pericyclic process with the one-electron chemistry of iron(II) to yield a method that is simultaneously quick and robust, operationally efficient, and step-economical. The abundance of alkene archetypes (Figures 13A–D) of terpenes and terpenoids elevates the technique because these molecules serve as multipurpose model sub-

Secondary Alkyl Radical Precursors cont.

hydro 85%	hydro 90%	hydro N/A	hydro 80%	hydro N/A
thiyl N/A	thiyl 77% (5.9:1 dr)	thiyl N/A	thiyl 74% (7.5:1 dr)	thiyl 75% (7.5:1 dr)
oxo 75%	oxo 87%	oxo 95%	oxo N/A	oxo N/A
alkenyl N/A	alkenyl 70% (13:1 dr)	alkenyl N/A	alkenyl N/A	alkenyl 62% (1.2:1 dr)
alkynyl N/A	alkynyl 86% (13:1 dr)	alkynyl N/A	alkynyl N/A	alkynyl N/A

		betulin	betulinic acid	
hydro 91%	hydro 90%	hydro 90%	hydro 82%	hydro 78%
thiyl N/A	thiyl N/A	thiyl N/A	thiyl N/A	thiyl N/A
oxo N/A	oxo N/A	oxo N/A	oxo 60%	oxo N/A
alkenyl N/A	alkenyl N/A	alkenyl N/A	alkenyl N/A	alkenyl N/A
alkynyl N/A	alkynyl N/A	alkynyl N/A	alkynyl N/A	alkynyl N/A

hydro 81%	hydro N/A	hydro 88%	hydro 83%	hydro N/A
thiyl N/A	thiyl N/A	thiyl 78% (1.2:1 dr)	thiyl N/A	thiyl N/A
oxo N/A	oxo N/A	oxo N/A	oxo N/A	oxo N/A
alkenyl N/A	alkenyl 62% E/Z > 18:1	alkenyl 32%	alkenyl N/A	alkenyl 76%
alkynyl 41%	alkynyl N/A	alkynyl 45%	alkynyl N/A	alkynyl N/A

Primary Alkyl Radical Precursors

				from (±)-α-ionone
hydro N/A	hydro N/A	hydro N/A	hydro N/A	hydro N/A
thiyl N/A	thiyl N/A	thiyl N/A	thiyl N/A	thiyl N/A
oxo N/A	oxo N/A	oxo N/A	oxo N/A	oxo N/A
alkenyl 44%	alkenyl 64%	alkenyl 43% E/Z > 10:1	alkenyl 45%	alkenyl 37%
alkynyl 63%	alkynyl N/A	alkynyl 60%	alkynyl N/A	alkynyl N/A

hydro 71%	hydro N/A	hydro N/A	hydro N/A	hydro N/A
thiyl 71%	thiyl 58%	thiyl 80%	thiyl N/A	thiyl N/A
oxo N/A	oxo N/A	oxo N/A	oxo N/A	oxo N/A
alkenyl N/A	alkenyl 38% E/Z > 18:1	alkenyl 56%	alkenyl 50%	alkenyl N/A
alkynyl N/A	alkynyl N/A	alkynyl 58%	alkynyl 54%	alkynyl 66%

Figure 13B Substrates from reported dealkenylative functionalizations that contain isopropenyl substituents that will result in secondary radicals, then primary radicals. * From (–)-*cis*-limonene oxide. † From *R*-(–)-carvone. ‡ From (+)-dihydrocarvone. # From *S*-(+)-carvone.

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strates while also providing platforms for method development and opportunities for rapid derivatization into new feedstock chiral building blocks. Manifested into six modes—hydro, thiyl, oxo, hydroxy, alkenyl, and alkynyl—dealkenylative functionalization captures nearly all desir-

able outcomes, although there are examples of radical trapping still to be tested. As modern single-electron chemistry becomes more popular, dealkenylative strategies will likely serve as promising tools for applications in organic synthesis.

Figure 13C Substrates from reported dealkenylative functionalizations that contain alkenes that will result in primary and tertiary radicals. Next, exo-cyclic alkenes are featured that undergo radical ring opening. Finally, one example of an internal alkene is displayed.
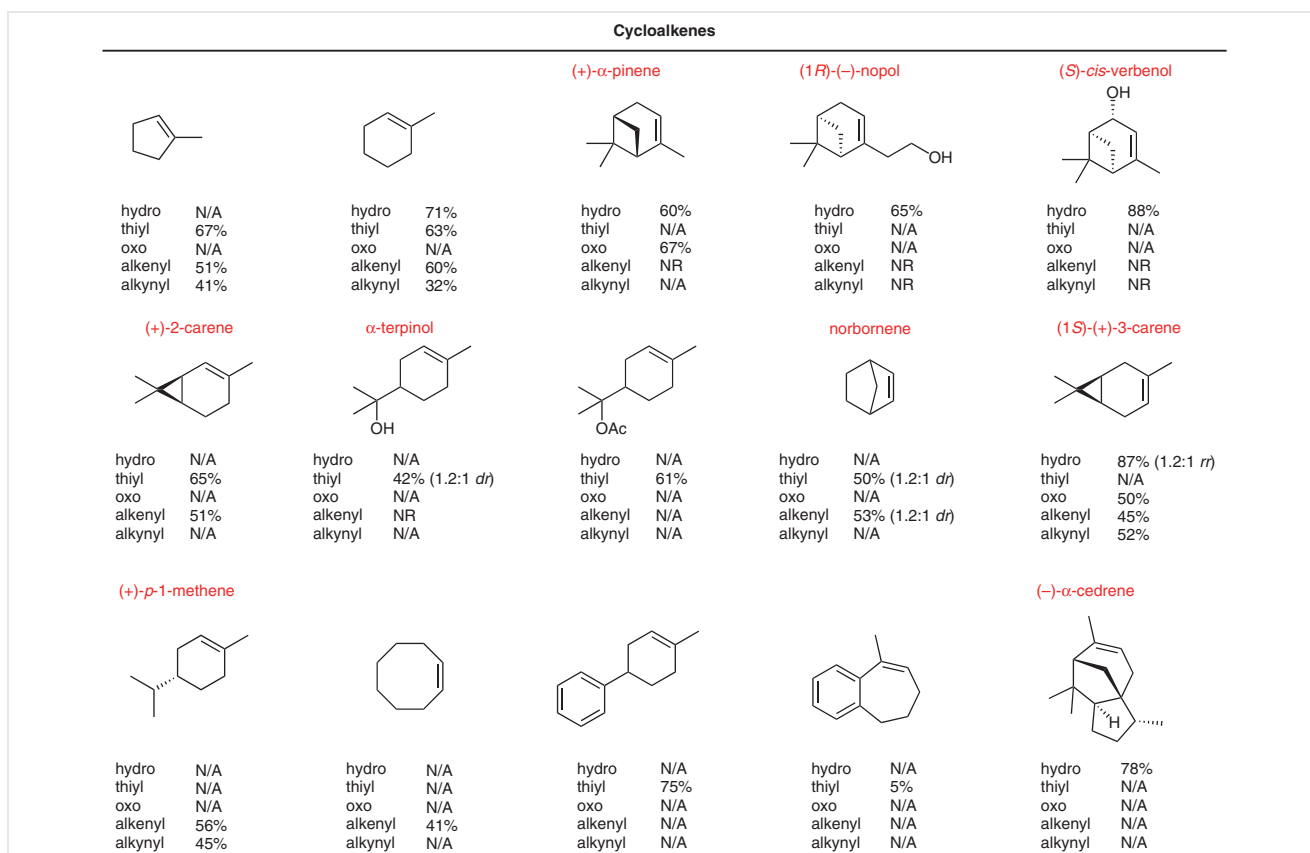
Figure 13D Substrates from reported dealkenylative functionalization reports that contain endocyclic alkenes that will undergo radical ring opening.

Conflict of Interest

The authors declare no conflict of interest.

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