ORGANIC CHEMISTRY

Hydrodealkenylative C(sp^3)–C(sp^2) bond fragmentation

Andrew J. Smaligo, Manisha Swain, Jason C. Quintana, Mikayla F. Tan, Danielle A. Kim, Ohyun Kwon*

Chemical synthesis typically relies on reactions that generate complexity through elaboration of simple starting materials. Less common are deconstructive strategies toward complexity—particularly those involving carbon-carbon bond scission. Here, we introduce one such transformation: the hydrodealkenylative cleavage of C(sp^3)–C(sp^2) bonds, conducted below room temperature, using ozone, an iron salt, and a hydrogen atom donor. These reactions are performed in nonanhydrous solvents and open to the air; reach completion within 30 minutes; and deliver their products in high yields, even on decagram scales. We have used this broadly functionality tolerant transformation to produce desirable synthetic intermediates, many of which are optically active, from abundantly available terpenes and terpenoid-derived precursors. We have also applied it in the formal total syntheses of complex molecules.

A common ideal in chemical synthesis is the assembly of complex molecules from simple precursors, often accompanied by the need to install carbon centers with precisely defined stereochemical arrangements. Despite the bevy of methods available to accomplish such goals, sometimes it can be more efficient to reorganize starting materials already containing the required complexity and/or stereochemistry into the desired molecular structures. Furthermore, deconstructive strategies can provide access to challenging, or otherwise inaccessible, molecular structures (*1*–*3*). The literature contains many examples of C–C bond fragmentations (Fig. 1A). Some well-established C(sp^2)–C(sp^2) bond scissions are oxidative cleavage (e.g., ozonolysis) and olefin metathesis (*4*–*6*). There are also reports of C(sp^3)–C(sp^3) bond fragmentations (*1*, *7*–*9*), albeit in much smaller numbers, but these transformations typically require activation of the C–C bond through the effects of a neighboring heteroatom, ring strain, or a leaving group in the reactant. Nevertheless, general methods for the functionalization of C(sp^3)–C(sp^2) bonds remain elusive. Given the profuse number of organic molecules containing these linkages, activation of such bonds in a controllable manner would be extremely useful.

The net reaction described here involves cleavage of a C(sp^3)–C(sp^2) bond, followed by formation of a new C(sp^3)–H bond (Fig. 1B). We refer to this process as hydrodealkenylation, coined with a nod to the hydrodealkylation process that is most commonly exemplified in the conversion of toluene to benzene in the presence of H_2 gas at high temperatures and pressures (*10*). Our reaction design was based on previous reports of Fe^{II} transferring an electron to the α-alkoxy hydroperoxides generated upon ozonolysis of alkenes in the presence of an alcohol. The resulting oxyradicals can subsequently engage in various forms of homolytic cleavage to produce alkenes, dimers, or halides (*11*–*15*). Nevertheless, these methods often occur with poor efficiencies and/or have limited utility. We have found that employing a readily available Fe^{II} salt with a hydrogen atom donor (HAD) under Schreiber conditions promotes C(sp^3)–C(sp^2) bond cleavage and subsequent construction of a new C(sp^3)–H bond (*16*). Given the ubiquity of olefins in terpenes and other organic molecules, we envision several applications for this transformation: new retrosynthetic disconnections to aid total syntheses, the late-stage diversification of both small and large biologically active molecules, and the facile generation of useful value-added compounds from abundantly available starting materials (Fig. 1C). The huge difference in price between (–)-isopulegol and (1*S*,3*R*)-3-methylcyclohexanol, used in the synthesis of androgen modulators, highlights the contrast between the current accessibility of these two structurally similar compounds (*17*–*19*).

After refining the reaction parameters promoting the fragmentation of the isopropenyl group in the hydroxy ketone **1a** (table S1), we obtained the desired hydrodealkenylation product **2a** in 90% yield when using 1.2 equivalents of ferrous sulfate heptahydrate (as the Fe^{II} salt) and 1.5 equivalents of benzenethiol (as the HAD). The reaction proceeded rapidly and produced only diphenyl disulfide, a benign by-product. Applying the optimized conditions, we investigated the substrate scope of the hydrodealkenylation. Table 1 reveals that a number of bicyclic ketones and enones (**1b** to **1f**) underwent fragmentation cleanly to give their hydrodealkenylation products (**2b** to **2f**) in high yields (80 to 94%). We prepared

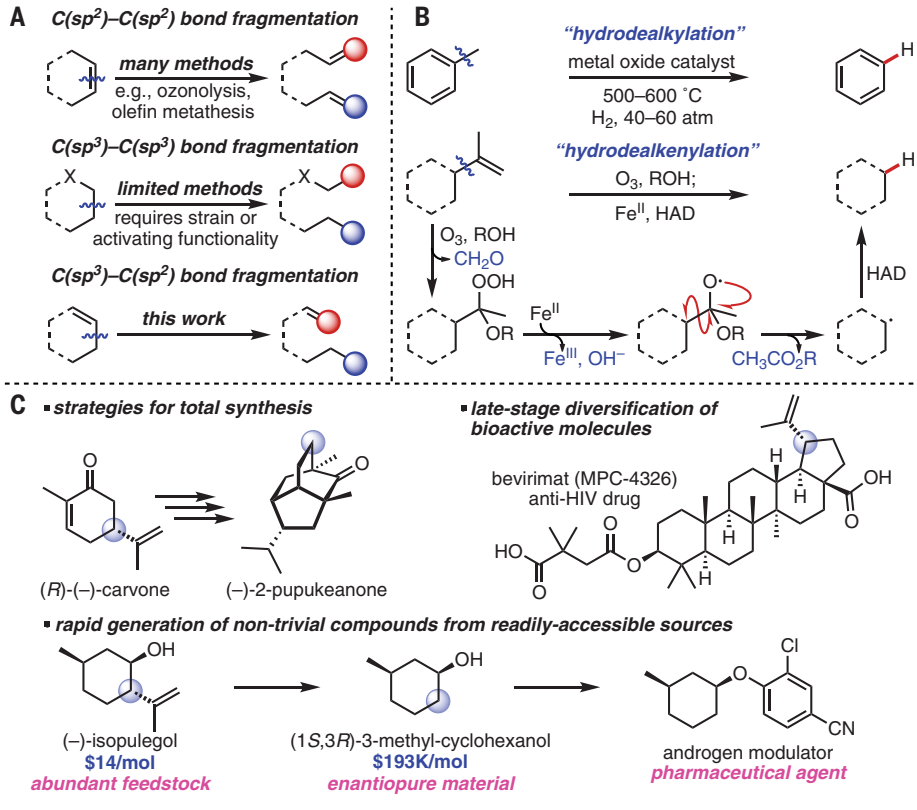

Fig. 1. Concept and applications of hydrodealkenylative fragmentation of C(sp^3)–C(sp^2) bonds. (**A**) Deconstructive fragmentation of C–C bonds. (**B**) Overview and proposed mechanism of hydrodealkenylation. (**C**) Applications of hydrodealkenylation. X, activating functionality; R, alkyl group.

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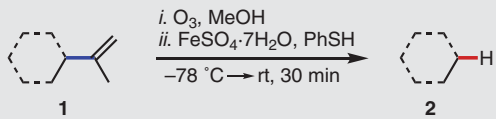
both enantiomers of the Wieland-Miescher ketone (**2e** and **ent-2e**), a prevalent synthetic intermediate used in more than 50 total syntheses (*20*), from the readily accessible dienediones **1e** and **ent-1e**. Naturally occurring terpenoids were also viable substrates, providing the hydrodealkenylation products **2g** to **2j**, valuable building blocks in both total synthesis and the preparation of pharmaceutical agents (*19*, *21*–*23*), in good yields (79 to 89%). The epoxide in (–)-*cis*-limonene oxide (**1g**) was opened diastereoselectively under the reaction conditions to furnish the *trans*-alkoxy alcohol **2g** as the sole product (presumably facilitated by a Lewis-acidic Fe^{III} species). The carvone-derived hydroxy ester **1k** and diol **1l**, both of which have been used in a number of synthetic applications (*24*–*27*), smoothly delivered their products **2k** and **2l**, respectively. As anticipated, the primary hydroxyl group in the diol **1l** underwent intramolecular trapping of the intermediate carbonyl oxide, producing the acetylated product **2l**. Betulin (**1m**) and betulinic acid (**1n**), naturally occurring triterpenoids displaying wide biological activities (*28*), gave the hydrodealkenylation products **2m** and **2n**, respectively. The hydroxy ketone **1o**, containing four stereocenters, provided the fragmentation product **2o**. Facile conversion of the indanol **1p** to **2p** illustrated the excision of the 2-propenyl substituent attached to a primary alkyl carbon. The substrates **1q** to **1t** delivered their fragmentation products **2q** to **2t** in good yields (72 to 86%), further displaying the potential of this transformation for derivatization of chiral pool–based auxiliaries. We also converted the ammonium salt **1u** to the amino alcohol **2u** after performing a basic workup. As

Table 1. Substrate scope of the hydrodealkenylation. Experiments performed on ≥1.0-mmol scale unless otherwise noted. Yields shown refer to isolated yields after SiO_2 chromatography. See the supplementary materials for experimental details. MeOH, methanol; PhSH, benzenethiol; Me, methyl; Ph, phenyl; rt, room temperature.



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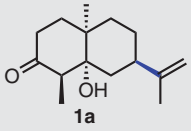
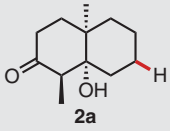
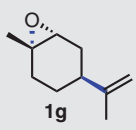
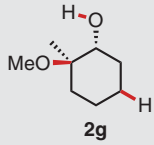
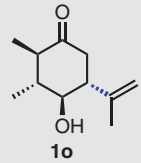
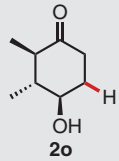
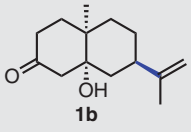
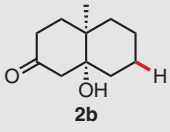
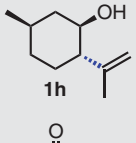
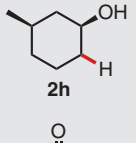
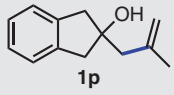
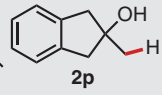
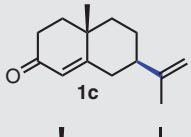
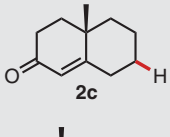
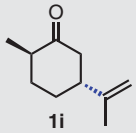
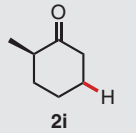
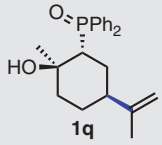
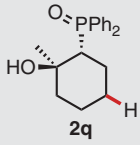
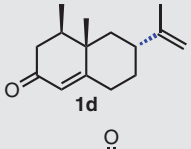
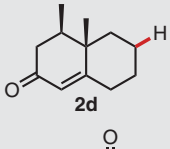
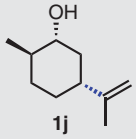
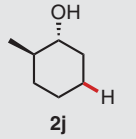
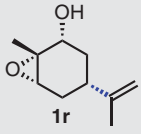
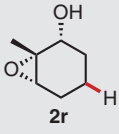
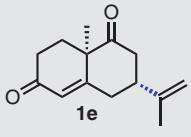
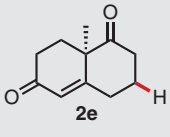
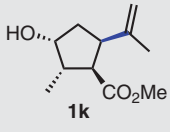
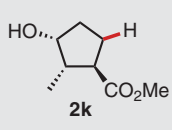
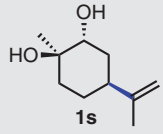
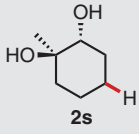
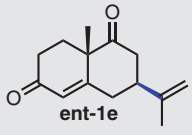
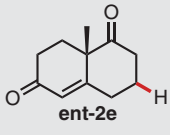
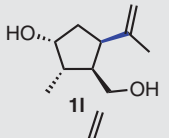
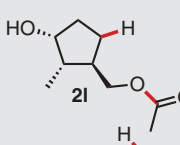
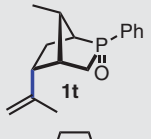
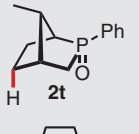
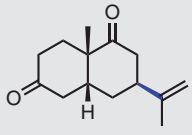
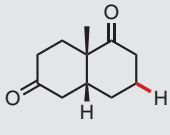
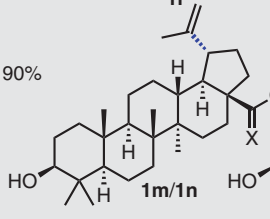
 1a	 2a	90%	 1g	 2g	85%	 1o	 2o	85%
 1b	 2b	85%	 1h	 2h	83% 89%*	 1p	 2p	71%
 1c	 2c	80%	 1i	 2i	79%	 1q	 2q	84%
 1d	 2d	94%	 1j	 2j	80%	 1r	 2r	72%
 1e	 2e	90%	 1k	 2k	84%	 1s	 2s	86%
 ent-1e	 ent-2e	91%	 1l	 2l	91%	 1t	 2t	82%
 1f	 2f	90%	 1m/1n	2m X = H_2 88% 2n X = O 83%†		1u	2u	62%‡

*100.0-mmol scale. †0.2-mmol scale. ‡After basic workup.

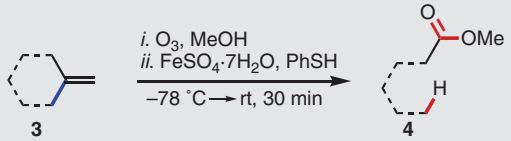
validation of the robustness of this reaction, fragmentation of (–)-isopulegol (**1h**) on 100-mmol scale furnished the enantiomerically pure alcohol **2h** in 89% yield. Both antipodes are attainable for every chiral product in Table 1 (except **2d**, **2m**, and **2n**), owing to the ready accessibility of the enantiopure terpenoid precursors.

To amplify the synthetic utility of this hydrodealkenylation, we extended it to other types of $C(sp^3)$–$C(sp^2)$ linkages. Table 2 reveals that starting materials containing exomethylene units (**3**) provided carboxylic ester products (**4**) after the loss of a one-carbon unit as formaldehyde. Methylenecyclohexane (**3a**) smoothly furnished methyl hexanoate (**4a**). The naturally occurring terpene (±)-camphene (**3b**) generated a single diastereoisomer of the cyclopentanecarboxylic ester **4b**. The α-alkoxy hydroperoxide intermediate fragmented to generate the tertiary carbon radical exclusively, rather than the alternative secondary carbon radical, before hydrogen atom abstraction. By contrast, (–)-β-pinene (**3c**) provided a 1:1 regioisomeric mixture of the products **4c** and **4c′**, a result of indiscriminative radical scission. Subjecting methyleneadamantane (**3d**) to this process furnished a single diastereoisomer of the bicyclo[3.3.1]nonane ester **4d**. The reaction of (–)-caryophyllene oxide (**3e**) produced the lactone **4e**—the result of epoxide opening (compare with **2g**) and subsequent intramolecular lactonization.

We further elaborated the substrate scope by converting various cycloalkenes (**5**) to ethylene glycol acetals of the aldehydes (**6**), involving the loss of a two-carbon (or more) unit as a methyl ester during Fe^{II}-mediated reductive fragmentation (Table 3). Because of the volatility of the aldehyde products, we protected them immediately and isolated them as 1,3-dioxolanes. Methylcyclohexene (**5a**) cleanly delivered the acetal of pentanal **6a**. More compelling is the ability to generate optically active products from readily available and enantiomerically pure terpene and terpenoid starting materials. Although cyclobutane moieties are particularly valuable synthetic intermediates and are also present in many natural products, enantioselective preparations of these ring systems can be challenging, especially when compared with those of smaller and larger carbocycles (*29*–*31*). Cyclobutane-containing bridged terpenes are, however, prevalent; combined with hydrodealkenylation, they provide ready access to variants of this scaffold. (+)-α-Pinene (**5b**) and (–)-nopol (**5c**) produced opposite enantiomers of the cyclobutylacetaldehyde acetals **6b** and **ent-6b**. (*S*)-*cis*-Verbenol (**5d**) smoothly dispensed the corresponding aldol acetal **6d**, containing two stereocenters, and (–)-α-cedrene (**5e**) provided the *cis*-fused octahydropentalene **6e**, with three stereocenters.

The ease of operation, efficiency, and functional-group compatibility of the hydrodealkenylation were further confirmed through its application in the formal syntheses of several biologically active natural products (Fig. 2). In a notable example—en route to the isotwistane sesquiterpenoid (–)-2-pupukeanone—we generated the bicyclic ketoester **2v** directly from **1v** in 78% yield. Previously, this conversion required six steps and gave the product in only 28% overall yield (*32*). In another example, we obtained the ketoester **2w**, an intermediate leading to (–)-seychellene, directly from its precursor **1w** in 81% yield. Although our net yield was slightly lower than that reported for the five-step route (91%), the simplicity of our

Table 2. Generation of esters via $C(sp^3)$–$C(sp^2)$ bond fragmentation. Experiments performed on 2.0-mmol scale. Yields shown refer to isolated yields after SiO_2 chromatography. See the supplementary materials for experimental details. r.r., regioisomeric ratio.



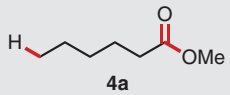
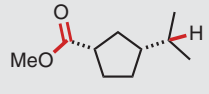
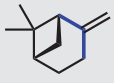
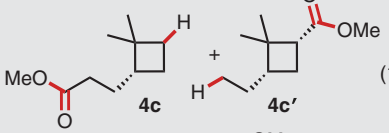
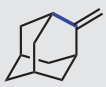
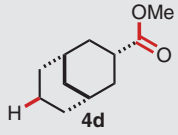
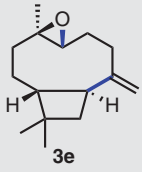
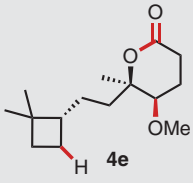
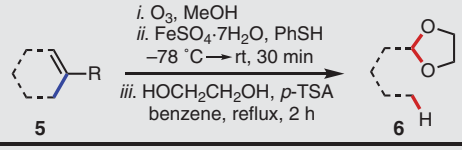
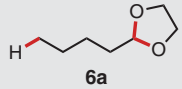
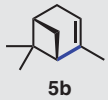
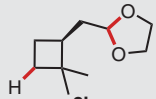
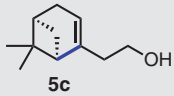
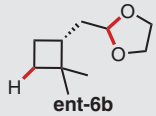
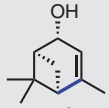
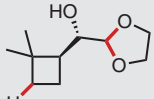
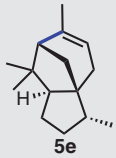
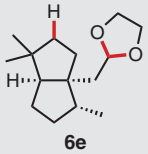
Starting Material	Product	Yield
 3a	 4a	80%
 3b	 4b	89%
 3c	 4c + 4c′	83% (1:1 *r.r.*)
 3d	 4d	81%
 3e	 4e	26%

Table 3. Generation of masked aldehydes via $C(sp^3)$–$C(sp^2)$ bond fragmentation. Experiments performed on 2.0-mmol scale. Yields shown refer to isolated yields after SiO_2 chromatography. See the supplementary materials for experimental details. *p*-TSA, *para*-toluenesulfonic acid.



Starting Material	Product	Yield
 5a	 6a	71%
 5b	 6b	60%
 5c	 ent-6b	65%
 5d	 6d	88%
 5e	 6e	78%

method obviates the five purifications required by the former (*33*). Other examples included one-pot conversions of the silyloxy dione **1x**, an intermediate leading to the sesquiterpenoid periconianone A (*34*); the dione **1y**, an intermediate in the preparation of the spirocyclic sesquiterpenoid (–)-7-epibakkenolide-A (*35*); and the silyloxy ketone **1z**, a chiral steroid precursor (*36*).

We then performed several experiments to support the mechanistic involvement of a free carbon radical in these hydrodealkenylations and establish the possibility of engaging the radical intermediate in other useful transformations (Fig. 3). Subjecting (1*S*)-(+)-3-carene to the reaction conditions generated the corresponding cyclopropylcarbinyl radical, with subsequent rearrangement, hydrogen atom abstraction, and dioxolane protection supplying a 1:0.85 mixture of the products **6f** and **6f′** in 87% yield. When we substituted TEMPO (2,2,6,6-tetramethylpiperidin-1-yl) for the HAD, we obtained the TEMPO adducts **7a** and **7a′** in a combined isolated yield of 91%. Single-crystal x-ray diffraction of the major product **7a** confirmed the equatorial stereochemistry of the aminoxyl group. Similarly, employing diphenyl disulfide as a radical trap produced the thioethers **8a** and **8a′** in a combined isolated yield of 40%. For this transformation, the diastereoselectivity was higher (8:1 diastereomeric ratio), and the major product again displayed an equatorial—in this case, phenylthio—group.

We envision that the straightforward nature of the hydrodealkenylation, performed with inexpensive and commercially available reagents and instruments, will engender innovations in synthesis and the use of chiral pool–based starting materials. Fundamentally, this unusual disconnection should prove useful in both retrosynthetic analyses and late-stage synthetic modifications.

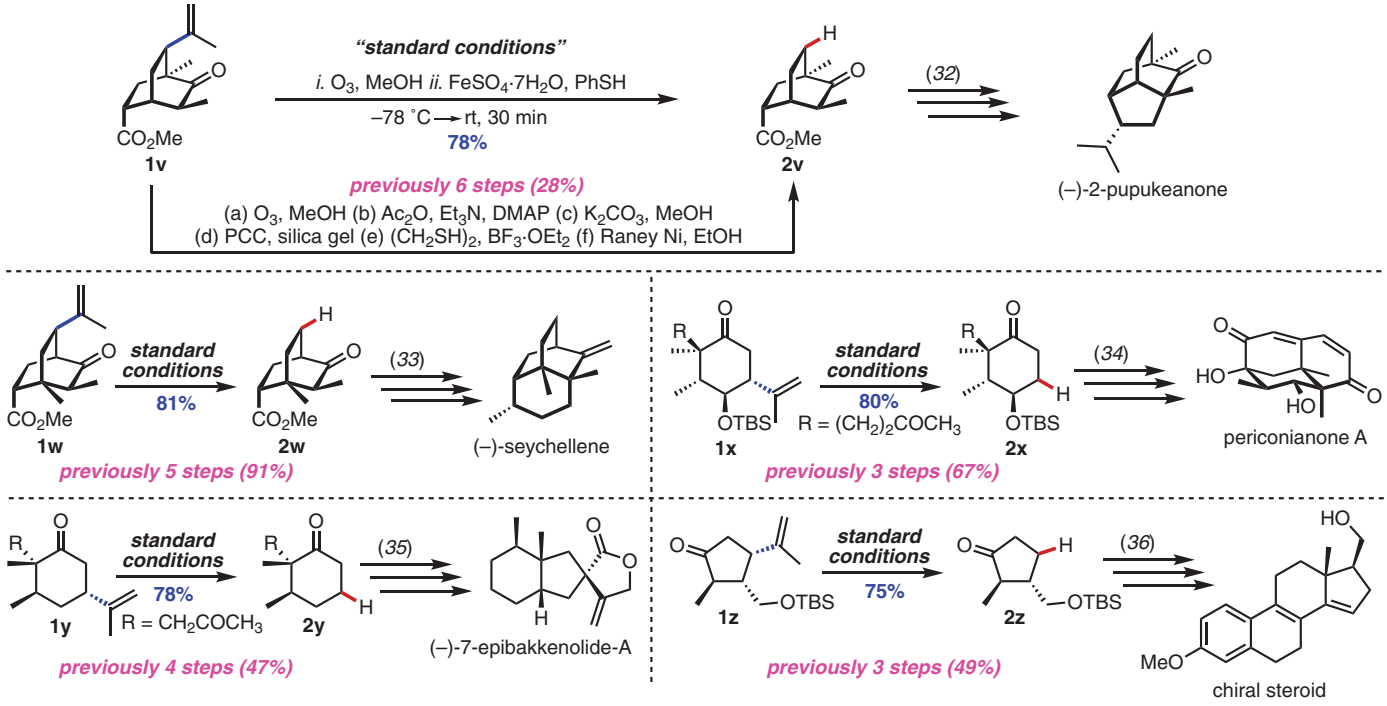


Fig. 2. Applications of hydrodealkenylation in total synthesis. Experiments performed on 1.0-mmol scale. Yields shown refer to isolated yields after SiO_2 chromatography. See the supplementary materials for experimental details. Ac_2O, acetic anhydride; Et_3N, triethylamine; DMAP, 4-dimethylaminopyridine; PCC, pyridinium chlorochromate; $BF_3{\cdot}OEt_2$, boron trifluoride diethyl etherate; EtOH, ethanol; TBS, *tert*-butyldimethylsilyl.

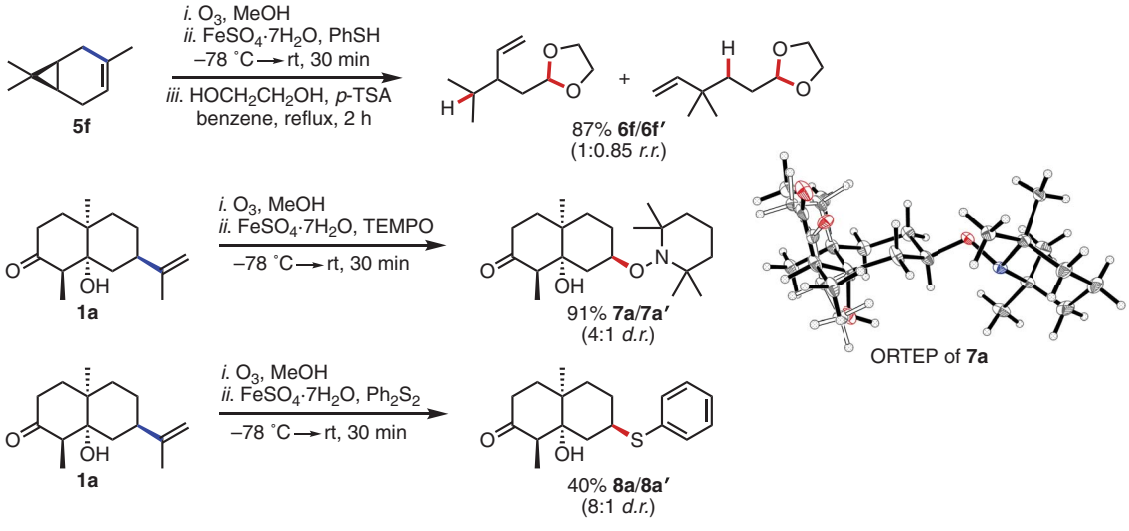


Fig. 3. Observations consistent with the intermediacy of a carbon radical. Experiments performed on ≥0.5-mmol scale. Yields shown refer to isolated yields after SiO_2 chromatography. See the supplementary materials for experimental details. d.r., diastereomeric ratio; Ph_2S_2, diphenyl disulfide; ORTEP, Oak Ridge thermal ellipsoid plot.

Furthermore, the ease with which these carbon-centered radicals can be trapped opens a gateway for employing common alkenes, seldom used as radical precursors, in a plethora of known radical transformations.

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SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/364/6441/681/suppl/DC1
Materials and Methods
Figs. S1 to S3
Table S1
Characterization Data
References (*37*–*100*)

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Hydrodealkenylative C(sp^3)–C(sp^2) bond fragmentation

Andrew J. Smaligo, Manisha Swain, Jason C. Quintana, Mikayla F. Tan, Danielle A. Kim and Ohyun Kwon

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Excising an olefin

Plants produce an abundance of structurally complex terpene compounds that are useful precursors to pharmaceuticals and other fine chemicals. However, the carbon frameworks of these compounds constrain the available pathways for diversification. Smaligo *et al.* now show that successive treatment with ozone, an iron oxidant, and a hydrogen-atom donor can cleanly cleave pendant olefins from terpenes and related compounds (see the Perspective by Caille). Breaking the bond between saturated and double-bonded carbon centers offers a direct route to desirable chiral intermediates from readily available, inexpensive precursors.

Science, this issue p. 681; see also p. 635