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Author manuscript

Nat Chem. Author manuscript; available in PMC 2013 February 01.

Published in final edited form as:

Nat Chem. ; 4(8): 629–635. doi:10.1038/nchem.1385.

Guided Desaturation of Unactivated Aliphatics

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Abstract

The excision of hydrogen from an aliphatic carbon chain to produce an isolated olefin (desaturation) without over-oxidation is one of the most impressive and powerful biosynthetic transformations for which there are no simple and mild laboratory substitutes. The versatility of olefins and the range of reactions they undergo is unsurpassed in functional group space. Thus, the conversion of a relatively inert aliphatic system to its unsaturated counterpart can open new possibilities in retrosynthesis. In this article, the invention of a directing group to achieve such a transformation under mild, operationally simple, metal-free conditions is outlined. This "portable desaturase" (Tz^{o}Cl) is a bench-stable, commercial entity (Aldrich, cat # L510092) that is facile to install on alcohol and amine functionalities to ultimately effect remote desaturation, while leaving behind a synthetically useful tosyl group.

Introduction

Of all the functional groups in organic chemical space, the olefin must be regarded as one of the most privileged from the vantage point of utility in synthesis. As a result, methods for olefin synthesis and functionalization have been extensively developed and applied in both academic and industrial sectors. Most olefin-forming reactions rely on preoxidized starting materials and fall into four main categories: functionalization of ketones or aldehydes (aldol condensation, Wittig olefination, etc.); modification of other alkenes (olefin metathesis, metal-catalyzed coupling reactions, etc.); reductive transformations of alkynes (stereoselective reduction, reductive coupling, etc.); or synthesis by elimination reactions (from alcohols, halides, etc.).[1] A less explored strategy for olefin synthesis is the *direct*

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Author contributions

A. -F. V. and P. S. B. conceived the original concept for the desaturation reaction; A. -F. V., A. M., W. R. G. and J. O. F. conducted the experimental work and analyzed the results; A. -F. V., W. R. G., A. M. and P. S. B. wrote the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at http://www.nature.com/naturechemistry. X-ray crystallographic coordinates for structures **21, 33, 39, 41, 43** and **44** reported in this paper and in the supplementary information have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 863213, CCDC 863214, CCDC 863215, CCDC 863216, CCDC 863217 and CCDC 863218, and can be obtained free of charge online at http://www.ccdc.cam.ac.uk/data_request/cif.

desaturation of the parent alkane. Within this category, the dehydrogenation of *activated* aliphatics (leading to enones, dienes, styrenes, etc.), generally a more facile process, has been broadly utilized and continues to be investigated.[2] In contrast, the efficient oxidation of *unactivated* alkanes directly to alkenes remains an unmet challenge and approaches to this problem have only rarely surfaced in methodological studies.[3] Select examples of reported strategies for alkane dehydrogenation are shown in Figure 1. Among these, Breslow's groundbreaking work awakened the community to the strategic value of a remote desaturation reaction and provided extensive studies on steroid frameworks.[4–6] In general, these approaches employ high-energy radicals (Figure 1A, B)[4,7] or transition metals (Figure 1C, D)[8–13] to overcome the high kinetic stability of the C–H bond. While these pioneering studies have clarified the difficulties in achieving such a transformation (regiocontrol, product isolation, functional group tolerance), most of these methods lack the generality and practicality required for wide use in complex systems. Important limitations include the use of inconvenient starting materials (e.g., peroxides), poor substrate scope, overoxidation of the resulting olefin, large substrate excesses or harsh reaction conditions. Therefore, the invention of a broadly applicable, mild protocol to achieve regio- and chemoselective desaturation of unactivated aliphatics remains highly desirable.

Our interest in a direct desaturation reaction was sparked during the synthesis of the eudesmane terpenes using a cyclase/oxidase synthetic strategy (Figure 2A).[14] In order to achieve the formal dehydrogenation of substrate **13** to **16**, three individual steps were required, involving (1) *N*-bromination with acetyl hypobromite (**13**→**14**); (2) homolysis/recombination under photochemical conditions to provide a tertiary alkyl bromide (**14**→**15**); and (3) base-mediated elimination (tetramethylpiperidine, 80 °C) (**15**→**16**) to give the desired olefin. In stunning contrast, Nature is able to use desaturase enzymes to achieve direct, selective and controlled oxidations of aliphatic carbon chains with remarkable precision. One striking example is shown in Figure 2B for the biosynthesis of fatty acids.[15,16] This overall process is believed to occur through a number of discrete steps including (1) C-9 specific alkane hydrogen abstraction; (2) single-electron oxidation of the resulting alkyl radical to a carbocation; and (3) stereoselective loss of a proton to provide olefin **20**. Inspired by this approach to olefin synthesis, an analogous laboratory process was pursued. Given the inherent difficulty of controlling an *intermolecular* desaturation,[17,18] as in the case of enzymes, a directing group[19] (portable desaturase) that could be appended onto commonly encountered alcohol and amine functional groups to guide[20] dehydrogenation of unactivated alkanes was designed. In this article, the development of a "portable desaturase" is presented together with a protocol for desaturation that requires no added metal salts, proceeds under mild reaction conditions and most importantly avoids overoxidation of the olefin product.

Three basic criteria were taken into account when designing the portable desaturase: (1) reactivity – the employment of a highly reactive species capable of controlled H-abstraction; (2) practicality – short, scalable synthesis and stability; (3) ease of installation and versatility of the resulting functionality. When considering the reactivity criterion, aryl radicals were identified as highly reactive, very short-lived intermediates (rate of H-abstraction by aryl radicals is of the order of 10^6 M^{-1} s^{-1}),[21] which have rarely been employed in C–H

functionalization reactions[22,23] due to difficulties associated with their efficient generation and promiscuous reactivity.[24–26] An underutilized tactic for generating aryl radicals is the reductive dissociation of aryl triazenes[27] in the presence of acid and catalytic metal salts.[28–30] Traditionally used as protecting groups for anilines[31] and linkers in solid-phase synthesis,[32] aryl triazenes can be prepared in high yields from the corresponding anilines and are stable to basic, reductive and alkylating conditions, even in complex settings.[33,34] In order to append an aryl triazene to alcohols and amines, a functionalized aryl sulfonyl chloride was deemed appropriate, thus leading to a triazene sulfonyl chloride (***o*-T**osyl Tria**z**ene Chloride, Tz^{o}Cl, **21**) as our portable desaturase of interest. The proposed set of events for the guided desaturation is outlined in Figure 2C. After installing the directing group onto the desired substrate to give **B**, treatment with acid in the presence of a single-electron reductant would provide an aryl radical **C** *via* an aryl diazonium intermediate. This inherently high-energy radical could abstract a proximal hydrogen atom to generate a lower energy alkyl radical **D** that could be oxidized to a carbocation **E** and finally terminated to the desired alkene **F**. Additionally, if a suitable metal salt could participate in both the reduction and oxidation steps, a redox cycle could be envisioned to allow for catalysis. The final design element involves the directing group transforming into a simple tosylate or tosylamine at the end of the reaction, a functional group commonly employed in modern organic synthesis.

Results and Discussion

The triazene sulfonyl chloride (Tz^{o}Cl, **21**) was prepared in two steps from commercial 2-bromo-5-methylaniline (see Supplementary Information). Gram-quantities of this directing group can be obtained and stored indefinitely at ambient temperature without notable decomposition. After attaching the directing group to the pilot substrate 2-cyclopentylethanol under straightforward reaction conditions (DMAP, DCM, rt, 90% yield) to give **22**, studies toward alkane desaturation began (Table 1).

When considering metal catalysts for the desired desaturation reaction, copper salts were the obvious starting point due to their ability to promote the reductive dissociation of triazenes (Sandmeyer chemistry)[31,35] and to rapidly oxidize alkyl radicals to carbocations.[36] Indeed, preliminary screening demonstrated the ability of catalytic copper(II) bromide in the presence of TFA to provide the desired olefin **23** in 20% yield when acetonitrile was used as solvent (Table 1, Entry 1); however, this product was accompanied by the inseparable reduction (**24**) and Sandmeyer (**25**) byproducts. Importantly though, under these reaction conditions byproducts resulting from olefin overoxidation were not observed. Switching from acetonitrile to nitromethane was key to suppressing **24** (Entry 2), a byproduct which seemingly arises by H-abstraction from the solvent.[24] During further investigations of the reaction, TEMPO (1 equiv) was added in an attempt to trap a radical intermediate or to inhibit the reaction altogether, but it surprisingly resulted in a *higher* yielding transformation (Entry 3). Intrigued by this result, a control experiment was performed in the absence of copper salts (Entry 4) to reveal that TEMPO alone could facilitate the desaturation in slightly better yield and without the Sandmeyer byproduct **25**. When no additives were employed and the reaction was run only with acid (Entry 5), trace amounts of the desired

product were observed, accompanied by mostly nonspecific decomposition. In the absence of acid, no reaction took place and the starting material was recovered intact (Entry 6).

These exciting *metal-free* desaturation conditions prompted further optimization of the reaction with respect to acid, temperature, concentration and nitroxide radical. Using three equivalents of TFA as the acid, the temperature can be lowered to 60 °C and the reaction time shortened to 1.5 hours to fully consume the starting material and to give the desired olefin **23** and along with minor amounts of **24** in 68% isolated yield (Entry 7). When the stronger triflic acid (2 equiv) was employed, the reaction proceeded efficiently at *room temperature* over 3 hours to give **23** in 54% yield (Entry 8). Increasing the reaction concentration to 0.05 M reduced the yield to 45%. Finally, other nitroxide radical species were tested with the hope to increase the reaction efficiency, but both the less hindered AZADO[37] and the more hindered adamantyl nitroxide[38] were inferior to the cheaper, commercially available TEMPO (Entries 9 and 10). Thus, with two sets of conditions in hand (Entries 7 and 8), the substrate scope of the newly developed desaturation reaction system was explored.

As shown in Table 2, a variety of primary and secondary *alcohols* are viable substrates for the guided dehydrogenation reaction, giving moderate to good yields of olefinic products. In these systems, the desaturation reaction takes place most efficiently when a tertiary carbon center is in a 1,3 relationship to the functionality carrying the portable desaturase and this selectivity implies a 1,7 H-abstraction by the intermediate aryl radical. Such a process has been only briefly described in the literature,[23,39] with aryl radicals usually preferring the 1,5 or 1,6 H-abstraction mode of reactivity.[22,25,40]

When simple *aliphatic secondary alcohols* were employed in the guided desaturation (**26**–**29**), good selectivity for tertiary alkyl positions was detected and desired alkenes were obtained as the only isolable, oxidized products in moderate yields. For these substrates, the reaction proceeded best when TFA was used as acid, whereas TfOH generally led to decomposition. On a substrate designed to test for oxidation at a tertiary alkyl site *versus* a benzylic site, the desaturation reaction provided the olefin product **27** (36% yield) and no styrene derivatives were observed. This data does not rule out the possibility of H-abstraction at the benzylic position, but such potential products may be unstable under the reaction conditions (*vide infra*). Furthermore, because the portable desaturase favors H-abstraction at proximal tertiary alkyl positions, site-selective oxidation can be performed (e.g. **28**) and functional groups such as olefins are also tolerated in the reaction (e.g. **29**). An ideal substrate for the guided desaturation is menthol, which cleanly gives isopulegol tosylate **33** in 92% yield in an efficient desaturation process that is accommodated by the more rigid molecular organization of the substrate.

Aliphatic primary alcohols are also suitable substrates for the guided desaturation reaction. Alkenol tosylates **30** and **31** were obtained in good yield as mixtures of olefin isomers due to uncontrolled elimination from the corresponding tertiary alkyl cations. Cyclic substrates behave well under the desaturation conditions, giving products such as **23** and **32** in good yields (68% and 51% respectively). These substrates reiterate a limitation of the method, the

formation of small amounts of reduction product (e.g., **24**) that are difficult to separate from the desired alkene.

Notably, when applied to alcohol-derived substrates, the desaturation reaction provided only homoallylic tosylates and no allylic tosylates were isolated. However, given the modest yields obtained in certain cases (e.g. **26**–**29**), it is likely that allylic tosylates are being generated (by elimination of the alkyl cation towards the tosylate group), but simply decompose during the reaction. In support of this possibility, tosic acid is always observed as a byproduct in the crude reaction mixture of the alcohol derived substrates. Additionally, this mode of elimination is operative in the case of the allylic tosylamine **35b**, the nitrogen analog of **26**. Therefore, substrates leading to allylic tosylates (e.g. alcohols in a 1,2 relationship to a tertiary center) are not well suited for this method.

In addition to primary and secondary alcohols, *aliphatic amines* are also competent substrates for the guided desaturation reaction, leading to either homoallylic (**34**–**37**) or allylic tosylamines (**38** and **39**). It was found that for amine-derived substrates, TfOH performs slightly better in the desaturation reaction compared to TFA. Indeed, menthylamine behaves well to give **34** in 59% yield, while **35** is obtained in 60% yield as a 10:1 mixture of homoallylic (major) and allylic (minor) tosylamines. Furthermore, allylic tosylamines such as **39** can be prepared selectively in good yield (50%) and amino esters are selectively desaturated to provide valuable dehydroaminoesters (**36**–**38**) in useful yields.

With the goal of exploring this methodology in more complex settings, a series of natural product derived substrates were synthesized and tested under the reaction conditions. As such, dihydrojunenol derivative **40** was identified as a desirable substrate for the desaturation reaction. Although similar in substructure with the simpler menthol, **40** contains two equidistant, but sterically different tertiary sites available for oxidation. Using Procedure A, the desaturation reaction generated a 2:1 mixture of inseparable regioisomers in 46% yield (Figure 3A). This result suggests that H-abstraction with an aryl radical is indifferent to the steric environment around the C–H bond as long as a favorable geometry for abstraction is possible.[41,42]

Dehydroabietyl amine derivative **42** poses an interesting challenge for selective C–H functionalization, given two reactive benzylic sites, a hindered tertiary ring junction and an otherwise unfunctionalized decalin system. Treatment of **42** with TEMPO (1 equiv) in the presence of TfOH (2 equiv) at a temperature as low as 4 °C gave two oxidation products (Figure 3B). The major product was the rearranged and cyclized sulfonamide **43** (30% yield), which arises by an interrupted desaturation process. It appears that upon formation of the tertiary carbocation, a Wagner–Meerwein rearrangement occurs to provide the more stabilized benzylic cation, which is then trapped intramolecularly by the tosylamine moiety. The minor product **44** (16% yield) can be accounted for by initial abstraction from an *unactivated methylene* C–H bond and subsequent termination to the disubstituted olefin. Thus, the guided desaturation affords oxidation products at sites other than the more reactive benzylic positions that would be targeted in intermolecular oxidation processes.

To demonstrate the ability to generate dienes in complex settings, triterpene derivative **45** containing a trisubstituted olefin and a free secondary alcohol was subjected to the reaction conditions (Figure 3C). As a result, **46** was obtained in 47% yield as the major product of the reaction after allylic 1,8 H-abstraction, oxidation and elimination to the most stable diene system. It is of note that the secondary alcohol remains untouched under these conditions and the sensitive diene functionality is safely contained in the final product.[43]

Following the successful desaturation of aminoesters (**36**-**38**, Table 2), this protocol was further tested on a more complex tetrapeptide. When **47** was subjected to the reaction conditions, the desaturated product **48** was isolated in 35% yield without racemization of any of the four chiral centers (Figure 3D). Additionally, the portable desaturase allows for site-selective oxidation on substrates such as **47** that are distinguished by strong chelating ability, multiple sites available for oxidation and reactive functional groups.

Preliminary experiments to clarify both the mechanism of the reaction and the role of TEMPO are shown in Figure 4. The first goal was to confirm the H-abstraction event that productively leads to the olefin product through deuterium labeling (Figure 4A). Thus, when deuterium was incorporated at the tertiary alkyl site in **49**, deuterium transfer was indeed observed in the desaturated product **50**, but the reaction is less efficient (34% yield for **50a**, *vs.* 68% for **23**, see Table 1) and a new minor product was observed that is tentatively assigned to the olefin isomer **50b**. Presumably the stronger deuterium–carbon bond diverts the aryl radical towards the normally less reactive methylene C–H bond.

The second goal was to provide evidence for the formation of the aryl radical intermediate from the triazene precursor (Figure 4B). Thus, when **51** was subjected to the reaction conditions, both cyclization and desaturation took place to give **54** in 47% yield. This result is consistent with the intermediate aryl radical adding across the alkyne to produce a reactive vinyl radical **52**, which performs a favorable 1,5 H-abstraction to generate tertiary alkyl radical **53** that is further oxidized and terminated to an olefin.

Thirdly, in order to clarify the role of TEMPO in the reaction, aniline substrate **55** was prepared and converted into the corresponding diazonium salt, a presumed intermediate in the reaction (Figure 4C). When TEMPO (1 equiv) was added at room temperature, the dehydrogenation event took place and olefin **56** was isolated in 44% yield (Entry 1). When the TEMPO loading was lowered to 0.1 equiv (Entry 2), the reaction provided the product in only a slightly lower yield (31%, TON = 3); meanwhile, the absence of TEMPO led to nonspecific decomposition of the starting material (Entry 3). This data indicates that TEMPO can support a catalytic cycle, but is inefficient under the current reaction conditions. Importantly, these transformations proceed under *acid-free* conditions, implying that TFA is not required in the oxidation events, but merely to liberate the diazonium salt from the starting triazene.

Based on our experimental results and literature precedent, the proposed reaction mechanism for the TEMPO-mediated desaturation reaction is presented in Figure 4E. First, TFA converts triazene **22** into the diazonium TFA salt **58**. TEMPO then promotes its reductive decomposition to aryl radical **59**, an event concomitant with the generation of N_2

and the oxidation of TEMPO to $TEMPO^+$.[44] Once formed, **59** undergoes H-abstraction to generate an alkyl radical intermediate **60** which is oxidized to the corresponding carbocation **61** by $TEMPO^+$ previously formed in the reaction. Spontaneous elimination from **61** leads to the olefin product **23**, with TEMPO acting as a single-electron shuttle in the overall process.[45] Remarkably, no aryl or alkyl-TEMPO recombination adducts are observed. Finally, based on the proposed mechanism, the reaction should be catalytic in TEMPO and preliminary results show that this is true (Figure 4C, TON = 3; Figure 4D, TON = 2), but suffers from low efficiency. Further experiments are currently underway to fully explore this possibility.

In conclusion, a new chemical moiety, Tz^oCl (**21**), has been designed to mimic processes observed in Nature, leading to desaturated aliphatics. The chemistry performed by this directing group is centered on the high reactivity of an aryl radical masked as an aryl triazene. This application expands the chemistry of the aryl radical, as it exploits this reactive intermediate as a useful tool for C–H functionalization. The desaturation reaction described herein is applicable on simple substrates derived from saturated alcohols and amines, giving olefin products in a predictable fashion without any overoxidation. Some of the drawbacks of this method are the modest product yields, the formation of minor amounts of inseparable reduction products and the occasional difficulties in purification. Nonetheless, the guided desaturation reaction can be successfully applied in complex settings, as it shows very good functional group tolerance while leading to useful oxidized products. Additionally, the intriguing reaction mechanism suggests that TEMPO can act as a single-electron shuttle, providing impetus to further investigate a truly catalytic version of this transformation. Studies to expand the scope of this transformation and apply it in two-phase terpene total synthesis will be forthcoming.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank D. -H. Huang and L. Pasternack for NMR spectroscopic assistance, A. Rheingold and C. Moore for X-ray crystallographic analysis, M. Wasa for chiral HPLC assistance and L. Leman for assistance with the peptide synthesis. Financial support for this work was provided by the NIH/NIGMS (GM-097444), MEC-Fulbright program (postdoctoral fellowship for A. M.), NSF (predoctoral fellowship for W. R. G.), the Spanish MECD (predoctoral grant for J. O. F.) and Bristol-Myers Squibb (unrestricted research support).

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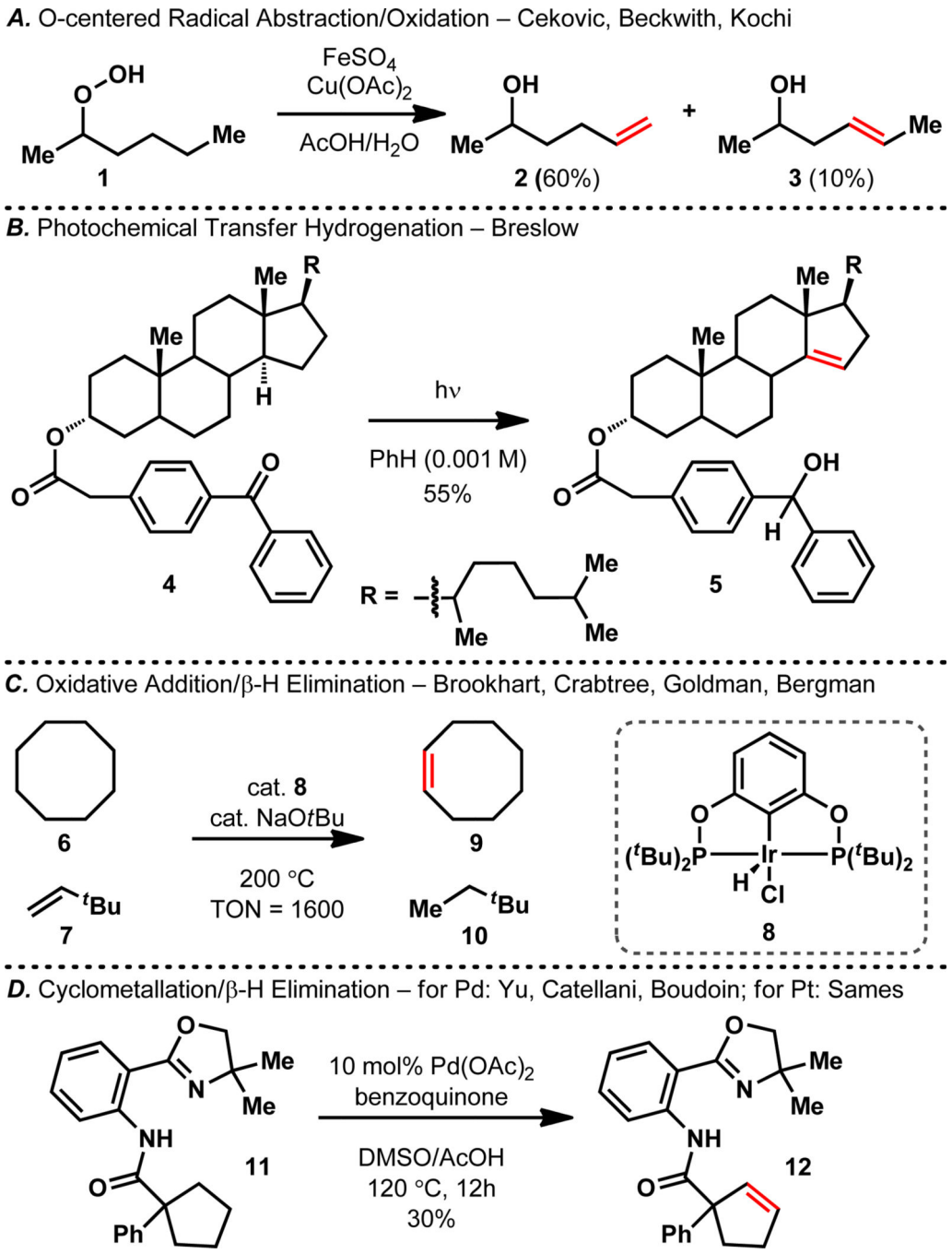


Figure 1. Pioneering studies for alkane desaturation

A. Protocol for dehydrogenation employing peroxide-derived O-radicals. **B.** Breslow's pioneering study of a remote dehydrogenation. **C.** Application of Ir-based catalysts toward the desaturation of cyclic alkanes. **D.** Example of a Pd-catalyzed guided desaturation reaction.

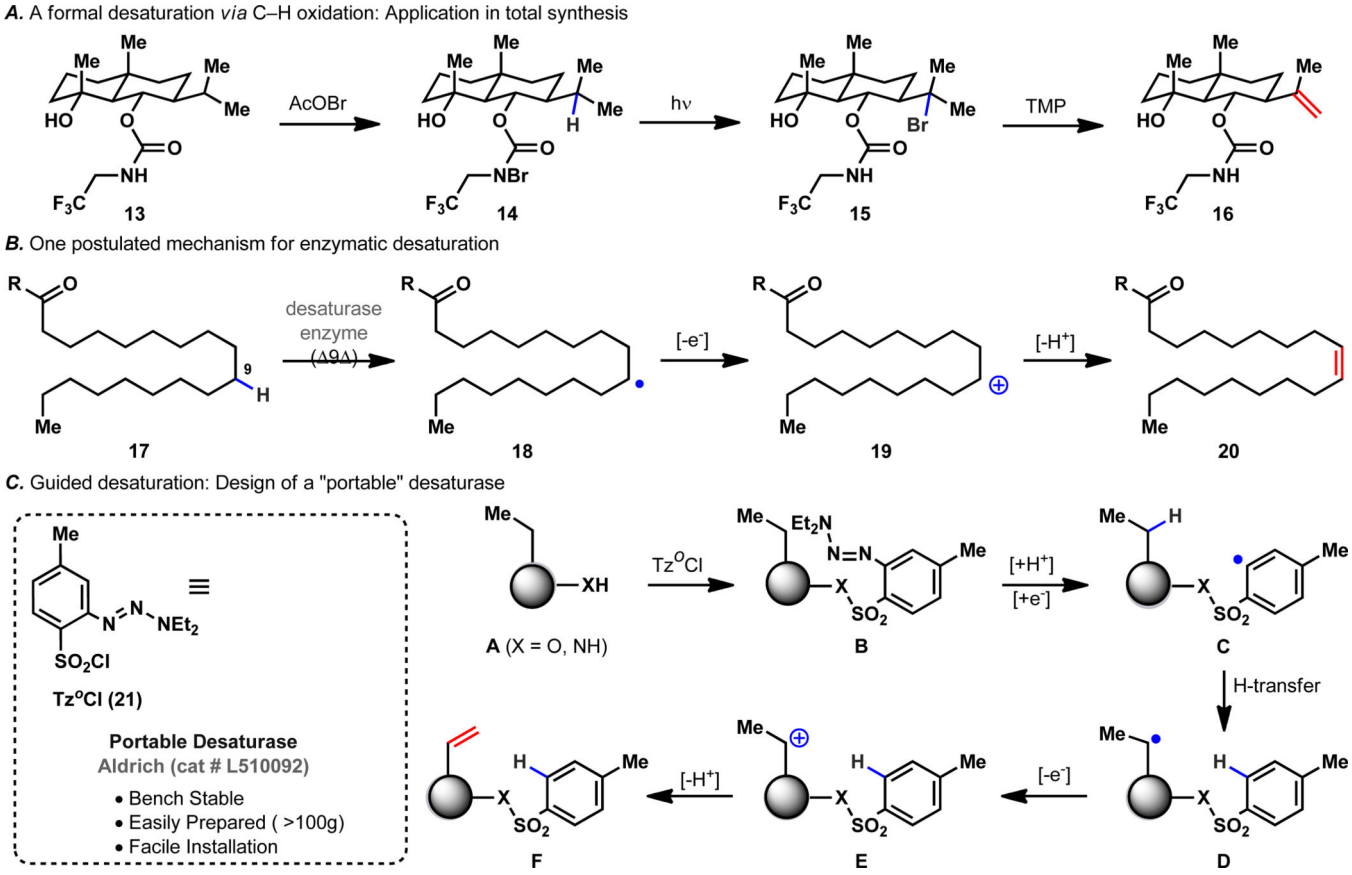


Figure 2. Design of a directing group for desaturation

A. Example of a strategic formal desaturation in the total synthesis of eudesmane terpenes. **B.** Proposed mechanism for the enzymatic desaturation in Nature. **C.** Description of the concept behind the guided desaturation reaction with a portable desaturase.

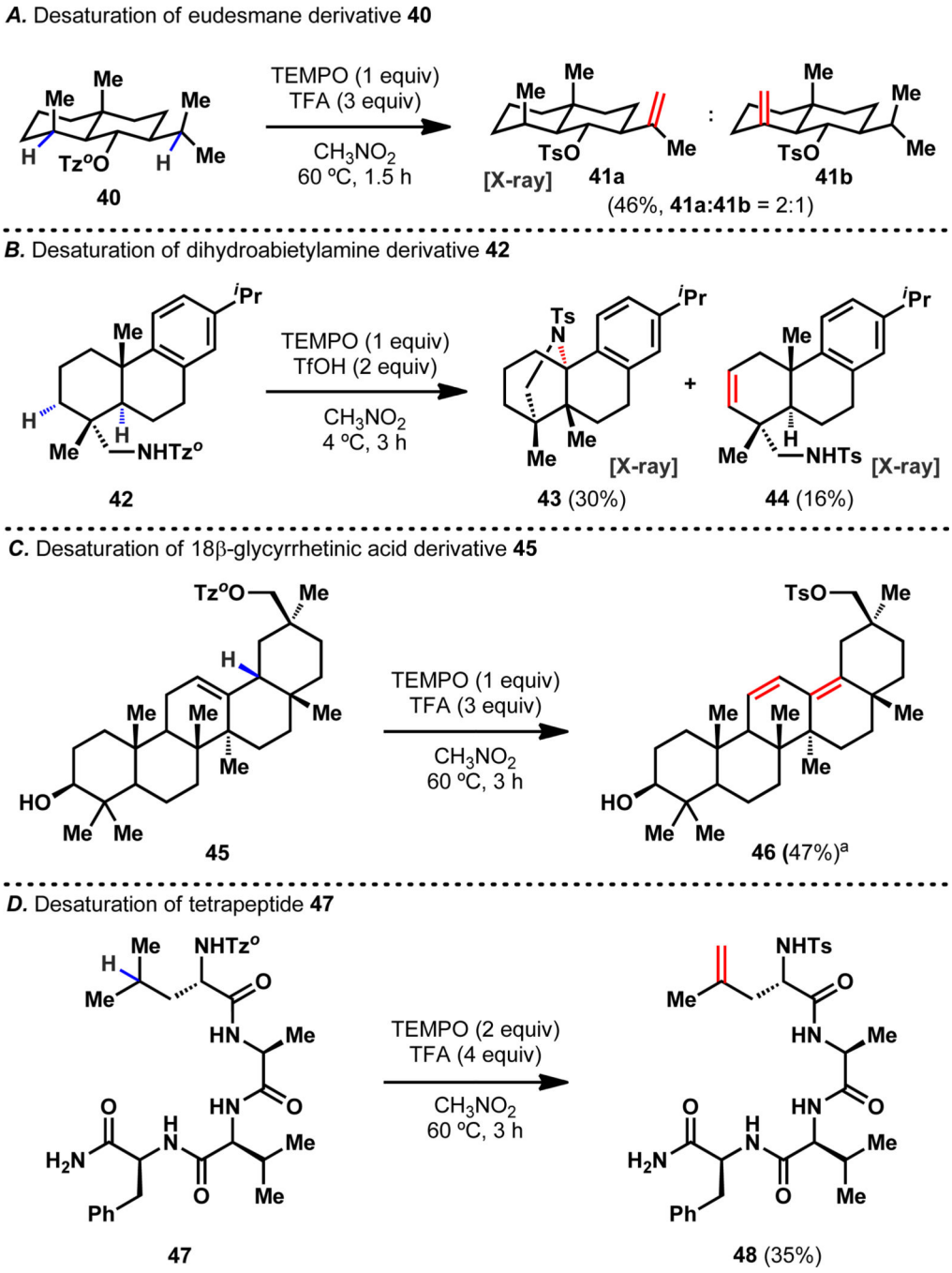


Figure 3. Applications of the guided desaturation reaction on complex substrates

A. Desaturation of a sesquiterpene derivative to a mixture of alkene regioisomers. **B.** Example of an interrupted desaturation reaction and methylene dehydrogenation. **C.** Application of the desaturation reaction towards diene synthesis in a complex setting. **D.** Synthesis of a tetrapeptide incorporating a dehydroleucine amino-acid residue. [a]Yield based on a mixture of product and reduction byproduct (10:1), see Supplementary Information.

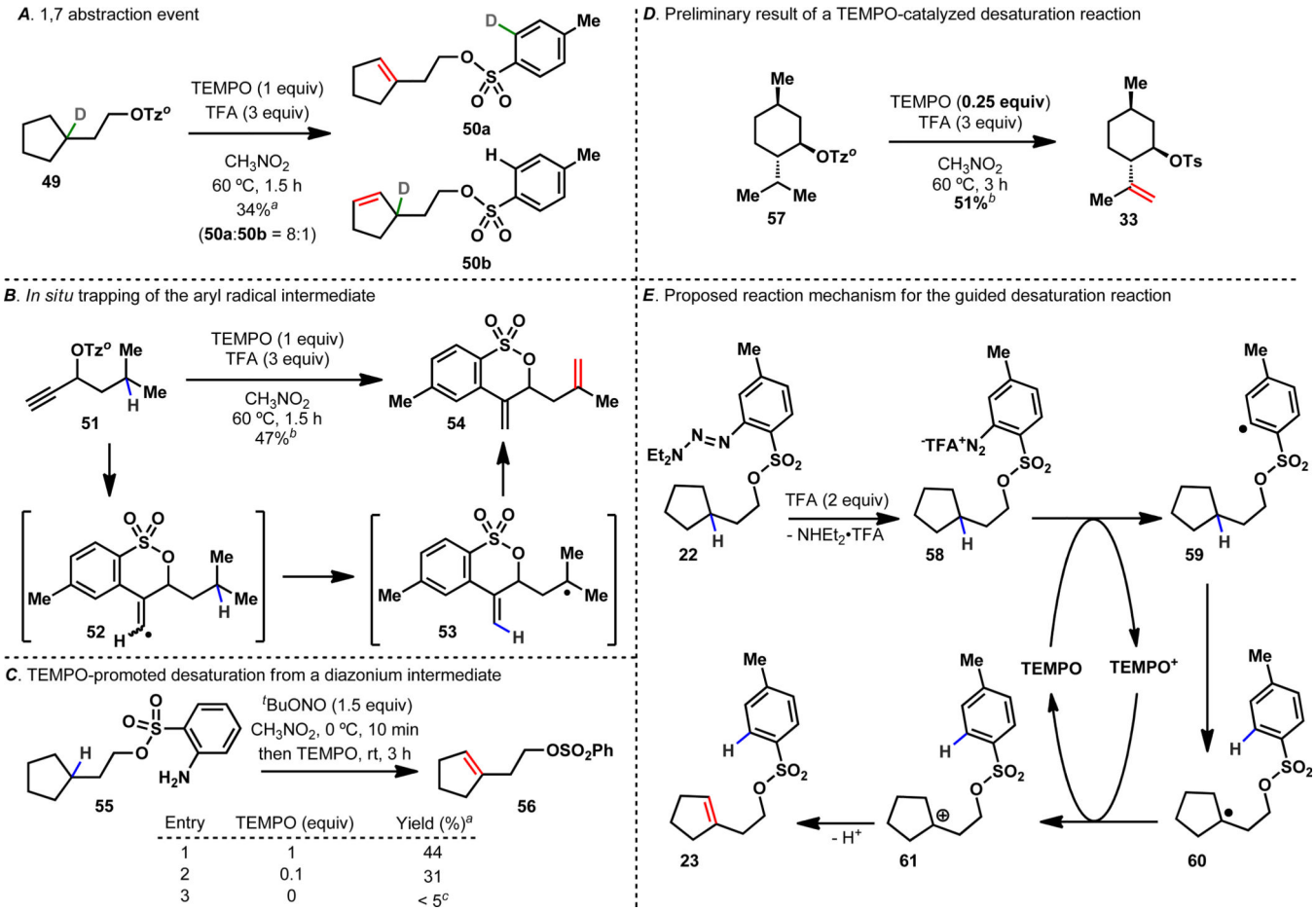
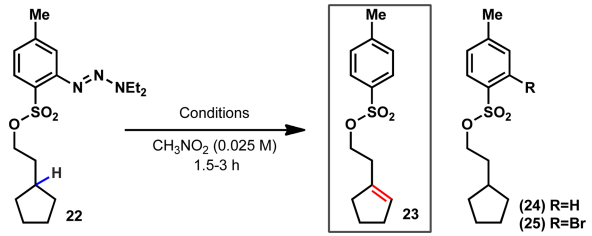


Figure 4. Mechanistic investigations and proposed reaction mechanism

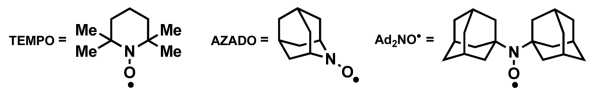
A. Deuterium-labeling study to support a 1,7 abstraction event during desaturation. **B.** Indirect evidence for the *in situ* formation of an intermediate aryl radical. **C.** Example of a desaturation reaction starting from an aniline derivative. **D.** Initial result supporting a catalytic cycle in TEMPO. **E.** Proposed sequence of events for the guided desaturation reaction. [a]Yields are based on ^{1}H-NMR integration relative to an internal standard (1,3,5-trimethoxybenzene); [b]Isolated yield; [c]The reaction resulted in mostly nonspecific decomposition.

Table 1

Development of a portable desaturase.



Entry	Copper Source	Additive	Acid	Temp. (°C)	Yield% (ratio 23:24:25)[a]
1	$CuBr_2$ (5 mol%)	---	TFA (2 eq)	80	34 (20:13:1)[b]
2	$CuBr_2$ (5 mol%)	---	TFA (2 eq)	80	31 (5:1:2)
3	$CuBr_2$ (5 mol%)	TEMPO (1 eq)	TFA (2 eq)	80	40 (6:1:1)
4	---	TEMPO (1 eq)	TFA (2 eq)	80	50 (4.5:1:0)
5	---	---	TFA (3 eq)	80	12 (20:1:0)
6	---	TEMPO (1 eq)	---	80	NR
7	---	TEMPO (1 eq)	TFA (3 eq)	60	68 (10:1:0)[c]
8	---	TEMPO (1 eq)	TfOH (2 eq)	RT	54 (20:1:0) (45[d])
9	---	AZADO (1 eq)	TFA (3 eq)	60	15 (20:1:0)
10	---	$Ad_2NO•$ (1 eq)	TFA (3 eq)	60	24 (20:1:0)



Conditions: reactions run on 0.025 mmol of **22** in CH_3NO_2;

[a] yields and ratios are based on ^{1}H-NMR integration relative to an internal standard (1,3,5-trimethoxybenzene);

[b] reaction run in CH_3CN (0.025 M);

[c] cisolated yield;

[d] reaction run at 0.05 M.

Table 2

Substrate scope for the guided desaturation reaction