# Reactivity of oximes for diverse methodologies and synthetic applications

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**Abstract** Oximes are valuable synthetic building blocks with reactivity modes enabling their use in diverse methodologies from cycloadditions to bioconjugation. Their reactivity towards photocatalysis and transition metals makes them ideal starting materials for *N*-containing heterocycles, amino alcohols, and amines. Developments in oxime reactivity since 2016 have enabled transformations such as addition of iminyl radicals to alkenes to generate functionalized imines, and [2+2]-cycloadditions to access azetidines. The unique properties imparted by the oxime *N*–*O* bond have also been recognized for their utility in materials applications. In this Review, we demonstrate the innovative use of this powerful functional group, focusing on *N*–*O* bond fragmentation and cycloadditions, along with applications including dynamic materials, energetic materials, and biocatalytic oxime reductions. An outlook is provided, highlighting the contributions of methodologies based on oxime starting materials, along with the challenges of using oximes for diverse applications and insight into future directions in these areas.

**Introduction** Oximes are valuable, versatile scaffolds of interest in medicinal and materials chemistry, as well as for synthetic use.[1] Unique properties of oximes (**1**) include dual nucleophilic sites at the oxygen and nitrogen along with an ambiphilic carbon, making them strong candidates for divergent reactivity (Fig. 1). Oximes share some commonalities with imines, including the ability to access amines through reduction or the ability to isomerize about the double bond. Despite their structural similarities, oximes have advantages over imines in terms of stability, such as a greater resistance to hydrolysis. Simple acyclic oximes (**3**), such as aldoximes (**7**) and ketoximes (**8**), are frequently accessed via a condensation reaction between a carbonyl (**2**) and a hydroxylamine. More complex oximes such as cyclic isoxazoline (**6**) can be synthesized via a [3+2]-cycloaddition reaction of an oxime chloride (**4**) and an alkene. Substitution reactions of the chloride (**4**) with an alcohol are often used for the synthesis of imidates (**5**) (Fig. 1).[2]

The most common oxime scaffolds include aldoximes (**7**) and ketoximes (**8**). Ketoximes (**8**) are well known for their participation in the Beckmann rearrangement, which converts oximes to amides under acidic conditions.[3–5] While acyclic oximes isomerize from their excited state,[6,7] isoxazolines (**6**) are locked in place, giving them longer lived excited states capable of undergoing further reactivity.[8] Imidates (**5**) are distinguished by a *C*–*O* bond, and are highly useful for the synthesis of heterocycles.[9]

Oximes can also be classified by the substitution of the *O*-atom. Oximes with aryl or alkyl substitution on the *O*-atom are classified as oxime ethers (**9**), which are considered highly valuable as privileged scaffolds for pharmaceutical applications and heterocycle synthesis.[1] The reactivity of oxime ethers (**9**) can be modulated by varying the *O*-substituent, a strategy which has been used for both thermal or photochemical activation.[10–14] Oximes with a carbonyl on the *O*-atom are oxime esters (**10**) which are especially interesting in the field of photocatalysis, with new methodologies being developed in single electron transfer (SET)[11,13–17] and triplet energy transfer (EnT)[7,18] manifolds. Oxime carbonates (**11**) are classified as oximes with a carbonate group including the oxime *O*-atom, and α-imino-oxy acids (**12**) are classified by the presence of a carboxylic acid group in the α-position relative to the oxime *O*-atom. The properties of oximes coupled with the variability in reactivity and properties for each oxime class makes this functional group extremely versatile.

A common reactivity mode of oximes is the formation of iminyl radicals (**14**). These radicals have a rich history which includes pioneering work focused on their addition into π-systems, often using strong oxidants and harsh conditions to generate the reactive radical.[19,20] Since these first methodologies using iminyl radicals, new methods have been developed to generate them under more mild conditions. Specifically, photoredox approaches have been extensively studied for the fragmentation of *N*–*O* bonds.[11–13,16,21] Continuing progress has expanded these photochemical methods to include triplet energy transfer[18] or excitation with visible-light without the requirement of a photocatalyst.[22] Oxime esters (**10**) are popular for the generation of iminyl radicals (**14**), which usually occurs via a single electron reduction resulting in *N*–*O* bond fragmentation with concomitant decarboxylation of the ester fragment.[11–17] In contrast, oxime ethers (**9**) can be activated for *N*–*O* bond fragmentation by hydrogen atom transfer (HAT) or SET. Additionally, α-imino-oxy acids (**12**) can be cleaved to yield an iminyl radical through single electron oxidation.[11–15,17] In addition to advances in their generation, iminyl radicals have found applications beyond addition into π-systems, such as ring-opening and HAT processes.[13,23] Analogously, imidate radicals, which were first derived from the photolysis of *N*-bromo imidates[24], were originally used for intramolecular cyclizations with

an alkene, but today have been used for a plethora of amino-alcohol formation reactions.[23,25] Rapid expansion in the area of oxime *N–O* bond fragmentation for the formation of iminyl radicals (**14**) has been observed recently. This review discusses advances in transition metal and photochemical mediated *N–O* bond fragmentation of oximes reported since 2016.

Cycloaddition reactions of oximes is a common reactivity mode that has historically focused on 1,3-dipolar cycloadditions for the formation of isoxazolines (**6**)[26], which have recently been recognized as ideal starting materials for novel [2+2]-cycloadditions to generate strained 4-membered heterocycles, azetidines and azetines.[8,27] Cycloaddition reactions are not the only reactivity mode for the oxime *C=N* double bond, the reduction of oximes has also been explored as a source of alkyl amines. The reduction of oxime ethers (**9**) was originally carried out with diborane, turning a ketone or aldehyde into an amine, via an intermediate oxime.[28] Shortly after this, enantioselective variants of the reduction of oximes began appearing with the addition of norephedrine as a chiral auxiliary.[29] These reports demonstrate the broad field of oxime reactivity and this pioneering work sets the stage for the contents of this review. Herein, examples from 2016-2021 of oxime reactivity including *N–O* bond fragmentation, iminyl radical (**14**) generation and reactivity[30], cycloaddition reactions[13,31], formation of amides and nitrones[3], asymmetric reductions, and applications[32] of oximes will be discussed. The alkoxy radical of the oxime (**13**) has been studied for its synthetic utility. Examples of the formation of *N*-oxyl radicals (**13**) and their reactivity, have been reviewed previously and will not be discussed herein.[33]

**Mechanisms of N–O bond fragmentation** The reactivity of the oxime *N–O* bond has been heavily explored due to its facile fragmentation resulting in versatile iminyl radicals. Transition metal-catalyzed *N–O* bond fragmentation can be divided into two main classes: (1) SET for the formation of iminyl radicals (Fig. 2a) and (2) insertion of a transition metal into the *N–O* bond (Fig. 2b). Interestingly, SET methods of *N–O* bond fragmentation can be reductive or oxidative depending on the class of oximes.[11–17] Transition metal-catalyzed SET uses metals such as iron, nickel, copper, and silver to form a radical anion (**16**) from oxime ester **15** that can then fragment to result in the iminyl radical **17** and the corresponding carboxylate (Fig. 2a).[13] Conversely, the insertion mechanism involves coordination of a metal such as rhodium, cobalt, or palladium to oxime **18**, forming **19** for subsequent fragmentation of the *N–O* bond through oxidative insertion (**20**) (Fig. 2b).

Photochemical *N–O* bond fragmentation has experienced a recent surge in development, providing access to a variety of *N*-, *O*- and *C*-centered radicals, in some cases allowing the oxime to act as a bifunctional reagent.[34,35] Recent advances in the field have led to the development of several methods for photochemical *N–O* bond fragmentation. Specifically, oxime esters (**21**) can undergo *N–O* bond fragmentation through sensitization to their triplet excited state via EnT. From the triplet excited state (**22**), decarboxylative *N–O* bond fragmentation can occur, resulting in an iminyl radical (**23**) and a *C*-centered radical (**24**) (Fig. 2c).[18,34,36,37] While triplet energies of oximes are dependent on their structure, common visible-light-absorbing photocatalysts are suitable to sensitize a variety of activated oxime esters.[34,37] An alternative photocatalytic *N–O* bond fragmentation mechanism proceeds via HAT and proton coupled electron transfer (PCET) from an excited state photocatalyst (Fig. 2d).[38] This method is accessible for benzyloxy oxime ethers (**25**), and results in the formation of an aryl aldehyde byproduct from fragmentation of **26**, selectively generating the iminyl radical **17**, which is ideal when bifunctional reactivity is not desired. Similarly, SET is a common tool for *N–O* bond fragmentation via photocatalysis (Fig. 2e).[39–41] Photochemical SET to an oxime ester moiety (**15**) leads to formation of a radical anion **16**, which can further fragment to an iminyl radical (**17**) (Fig. 2e).[11–17]

Alternatively, *N–O* bond fragmentation can occur via thermolysis rather than photocatalysis (Fig. 2f). The bond dissociation energy (BDE) for *O*-phenyloximes (**27**) is around 35 kcal $mol^{-1}$, which suggests that heat, such as microwave irradiation, can promote homolysis of these bonds resulting in an iminyl radical (**17**) and an oxygen centered radical (**28**).[42] Recent progress in this area includes the development of oximes capable of undergoing fragmentation at lower temperatures[43], and the modification of previous cyclization conditions to allow multicomponent coupling to synthesize functionalized pyrrolines[44] and dihydropyrrole-functionalized phenanthridines.[45]

**Transition metal-mediated *N–O* bond fragmentation**

**A. Transition metal SET** The generation of iminyl radicals via transition metal catalysis and their inherent reactivity has enabled the synthesis of *N*-heterocycles, including pyrrolines, lactams, phenanthridines, fused pyridines and pyrroles.[13] In general, the types of reactions these iminyl radicals participate in are (1) ring opening to form an alkyl radical, (2) 1,5-HAT followed by cyclization, and (3) 5-exo-trig/dig cyclization reactions with an alkene or an alkyne (Fig. 3a). Although these reactivity platforms are well established, innovations in iminyl radical formation and reactivity continue to expand the synthetic utility of oximes.

Cyanoalkylated β-lactams can be synthesized from fluorinated cyclobutanone derived oxime esters (**30**) and unactivated alkenes (**29**) using Cu-catalysis (Fig. 3b). Upon ring opening and radical addition into the alkene, the reactive $Cu^{III}$ intermediate (**32**) undergoes reductive elimination to form cyanoalkylated four-membered lactams (**31**).[46] Nickel is also a common transition metal for the formation of iminyl radicals. After the Ni-catalyzed SET for ring opening of cyclobutanone oxime esters (**33**), the resulting *C*-centered radical was able to participate in a radical cascade cyclization with vinyl azides to access 3,4-diydro-2*H*-pyrroles (**35**) and phenanthridines (**36**) (Fig. 3c). Interestingly, under these conditions, 5- and 6-membered cyclic oximes could be used in the ring-opening reaction, which is a common limitation for methodologies using cycloketone oxime esters. This improvement allows for the use of a variety of readily available substrates, compared to previous examples relying exclusively on 4-membered rings.[47] In subsequent work it was shown that the solvent *N*,*N*-dimethylacetamide (DMAc) can facilitate the SET in the presence of tetrahydroxydiboron and a radical borylation can occur to form **34**.[48] Other notable cross-coupling partners compatible in the Ni-catalyzed ring opening of cyclobutanones (**37**) includes alkyl, alkynyl, aryl, and vinyl organozinc reagents to form cyanoalkylated products (**38**) (Fig. 3d).[49]

Iron has been shown to mediate SET with oximes to form reactive iminyl radicals. Extended alkyl chain containing oximes (**39**) were investigated, and 1,5-HAT occurred upon formation of the iminyl radical (**40**). The resulting radical (**41**) can be carbonylated (**42**), oxidized (**43**), and trapped by the imine to cyclize and form a six-membered lactam (**44**) through a radical cascade (Fig. 3e).[50] A radical cascade reaction using an alkyne tethered oxime (**45**) resulted in fused pyridine products (**49**). Following Fe-mediated SET and iminyl radical (**46**) formation, 1,5-HAT occurs to form the *C*-centered radical **47**. This reactive intermediate can then undergo an intramolecular 5-exo-dig cyclization resulting in vinyl radical **48** that participates in a subsequent cyclization with a variety of alkenes to synthesize fused pyridines (**49**) (Fig. 3f). Competing intramolecular *C–N* bond forming and intermolecular *C–C* bond forming pathways highlighted the challenges associated with harnessing radical **47**.[51] Oximes incorporating tethered γ,δ-alkenes (**50**) tend to spontaneously cyclize upon iminyl radical (**52**) formation through a 5-exo-trig cyclization, resulting in the formation of an exocyclic primary or secondary *C*-centered radical (**53**). The addition of carbon monoxide could be used to carbonylate the resulting radical. Subsequently, addition of an alcohol or amine nucleophile resulted in ester and amide products (**51**), which were previously inaccessible from this method (Fig 3g).[52,53] Similarly, this has been used to access phosphorylated pyrrolines[54] (**54**) and to introduce alkyl groups using alkyl boronic acids (**54**).[55]

**B. Metal coordination and insertion** The fragmentation of the *N–O* bond can be achieved via metal insertion (Fig 2b). This pathway involves the coordination of the metal to the oxime prior to insertion. These non-free-radical reactions of oximes have been divided into cyclizations and rearrangements. The transition metal-mediated cyclizations often involve the formation of a metallacycle. Following this strategy, a Narasaka-Heck *C–H* activation cascade to access spirocyclic compounds (**56**) from oxime esters (**55**) was achieved on both $sp^3$ and $sp^2$ systems (Fig. 3h). Insertion of Pd in the polyfluorinated benzyl ether oxime *N–O* bond (**57**) can subsequently form metallacycle **58**, which can then go through a concerted metalation-deprotonation, completing the *C*($sp^3$ or $sp^2$)-*H* activation, followed by reductive elimination to form cyclic product **56**. The Narasaka-Heck intermediate metallacycle, which has been designed in this case to avoid β-hydride elimination, is exploited in a novel manner for *C*($sp^3$)-*H* activation as opposed to nucleophile trapping, providing an avenue to access challenging spirocyclic scaffolds.[56] Under Lewis acidic conditions, a similar coordination between the metal and oxime (**59**) is observed. Instead of resulting in a metallacyclic transition state, this coordinated species undergoes a Beckmann-like rearrangement where, from the coordinated species **60,** elimination of the acetate and migration of the aryl group results in intermediate **61,** which is then trapped by an amine nucleophile to form **62**. Finally, oxidation of **62** leads to benzimidazole **63** (Fig. 3i).[57]

**Photocatalytic *N–O* bond fragmentation** The use of photochemistry to access iminyl radicals for the formation of pyrrolines and other heterocycles has been extensively studied.[30,39,40,58] Herein, examples of photochemical *N–O* bond cleavage reported since 2018 will be discussed. A focus will be on reactions relying on EnT mechanisms.[18,58]

*N–O* bond fragmentation can occur in oxime esters (**21**) following sensitization to the triplet state (**65**), via EnT, to provide the iminyl radical **67** and the *C*-centered radical **66** from intermediate **65** (Fig. 4a). Both radicals are capable of further reactivity, as demonstrated in the formation of imine **68** upon recombination of **66** and **67**.[37] Alternatively, the *C*-centered radical **66** can undergo a variety of functionalization reactions (deuteration, halogenation, arylation, borylation) to provide aryl products (**69**).[36] Additionally, this approach can access the bifunctional reactivity of oximes, as demonstrated by the addition of the *C*-centered radical **66** and iminyl radical **67** across a double bond to form **70**.[34] This reaction is facilitated by the persistence of the iminyl radical, which prevents premature reaction of this component and allows selective functionalization of the alkene (Fig. 4a). Analogously, oxyimination of unactivated alkenes using oxime carbonates as bifunctional reagents rather than oxime esters can similarly be used to generate α-imino carbonates. Oxime carbonates (**11**) undergo *N–O* fragmentation to maintain the carbonate group as an *O*-centered radical, in contrast to the decarboxylative mechanism for oxime esters, which allows for the addition of both an *O*-centered and iminyl radical.[35]

The synthesis of amino alcohols (**75**, **79**) from oxime starting materials has been developed employing imidate radical chaperones (**71**) (Fig. 4b).[25,59] This strategy uses imidate radicals (**72, 76**) generated through initial coordination of the copper catalyst to the oxime, followed by sensitization to the triplet state via a photocatalyst, promoting insertion of the Cu catalyst into the *N–O* bond (**72**). Stereoselective 1,5-HAT from the imidate radical (**72**), followed by capture of the resulting radical **73** in a stereoselective fashion by the catalyst, and subsequent imination, results in the enantioselective formation of oxazoline **74**.[25] Notably, the combination of photocatalysis and copper catalysis enables the above mechanism, overcoming the well-known challenge of achieving enantioselectivity in reactions with radical intermediates. The versatile imidate radical **76** can also add into a double bond to generate oxazoline **77** with a pendant radical, enabling further functionalization. In contrast to the previous 1,5-HAT pathway, this addition of the imidate radical across an alkene allows incorporation of a second nucleophile (e.g. CN, SCN, vinyl, allyl, $N_3$) through copper-catalyzed cross coupling, providing products (**78**) that can easily be converted to amino alcohols with additional desirable functional groups (**79**).[59]

Unlike oxime esters or carbonates which generate two distinct radical intermediates, oxime ethers (**9**) only generate iminyl radicals upon fragmentation, along with an aldehyde byproduct. This method allows selective formation of the iminyl radical, avoiding potential side reactivity of an additional *C*-centered radical when it is not desired. Following this approach, the synthesis of pyrrolines **81** was assisted by PCET between **80** and a photocatalyst to form intermediate **82**, which subsequently fragments to iminyl radical **83** (Fig. 4c). During the course of the reaction, the 2-butanone additive functions as a *H*-atom source to enable HAT, forming a radical which ultimately closes the catalytic cycle.[38] This method has more recently been used to generate cyclobutanone-derived iminyl radicals, which fragment and add to α,β-unsaturated ketones.[60]

*N–O* bond fragmentation can also be mediated by electron transfer, as seen for α-imino-oxy acids. The carboxylate derivative of **84** is activated by SET to generate the iminyl radical via a decarboxylative mechanism. Subsequent radical cyclization to a pyrroline radical is followed by trapping with a Co-(II) catalyst (**87**) which then performs β-hydride elimination to furnish **85** (Fig. 2d). Cobalt complex **87** can also undergo addition to an alkene to generate **86**.[61] A similar mechanism of activation can be achieved for oximes **88** and **90** with a simple cerium catalyst (Fig. 2e). This method is unique as it proceeds by light-induced ligand to metal charge transfer (LMCT) from intermediate **89**. This LMCT step results in fragmentation of the oxime, and the resulting iminyl radical can undergo subsequent reactivity depending on its structure to access **91** or **92**.[62] The use of a simple cerium salt as a photocatalyst for this transformation is notable as other photocatalysts, such as those relying on iridium, can be expensive for scaleup applications, meaning further development in this area could be impactful to the application of these methods.

Similarly, iminyl radicals can react intramolecularly to form other desirable *C*-centered radicals through rearrangement or fragmentation. The SET mediated fragmentation of cyclobutanone derived oximes (**93**) followed by facile rearrangement of **94** to *C*-centered distal nitrile radicals (**95**) is a popular example of this approach to generate carbon radicals to undergo *C*–*C* bond forming reactions (Fig. 4f).[63] This approach can access a variety of products (**96**-**98**) following addition of **95** into either styrenes (**96**, **98**)[64,65] or carbon monoxide (**97**)[66] (Fig. 4f). The generation of acyl radicals following *N*–*O* bond fragmentation of $\alpha$-acyl oxime esters (**99**) has also been established (Fig. 4g). These acyl radicals (**100**) can add to radical acceptors **101** or **103** to generate a variety of products **102**, **104**, or **105** depending on conditions.[67,68] While this method does not incorporate the oxime nitrogen or oxygen atoms in the final products, methodologies developed using acyl radicals generated with this approach exhibit the range of reactivity provided by oxime starting materials.

**Photochemical oxime cycloadditions** Cycloaddition reactions are desirable for their efficiency and high atom economy, using imine *C*=*N* double bonds as a powerful tool for the synthesis of *N*-containing heterocycles. Oximes, which are more stable than alkyl or aryl imines, can offer advantages as imine equivalents for these reactions, and have propelled advances of light-mediated [2+2]-cycloadditions to form azetidines, known as the *aza* Paternò-Büchi reaction (Fig. 5a). Initial approaches to this reaction were plagued by a limited substrate scope arising from the requirement of the imine substrate to undergo direct excitation with UV light.[6] Additionally, isomerization of excited state imine or oxime substrates causes preferential relaxation to the ground state superseding [2+2]-cycloaddition (Fig. 5a).[6,7]

Cyclic oximes, more specifically 2-isoxazolines (**6**), were initially recognized for their potential to undergo this reaction as stable imine equivalents. Singlet state oximes (**108**) arising from direct excitation were shown to undergo the *aza* Paternò-Büchi reaction with aromatic alkenes (**109**) upon exposure to UV light (Fig. 5a).[69–72] However, the requirement of direct oxime excitation to the singlet state limits the scope of this transformation. Additionally, the alkene scope is limited to a selection of aromatic and conjugated compounds including furans[71] and indenes.[72] In efforts to develop a more general *aza* Paternò-Büchi reaction, studies have focused on visible light-mediated EnT catalysis, wherein one reaction component (the oxime or alkene) is sensitized by the photocatalyst to form a triplet biradical that then adds into the ground state of the other reaction component in a stepwise [2+2]-cycloaddition proceeding via a 1,4-biradical intermediate. These reports address the challenge of oxime isomerization via two approaches: First, intramolecular cycloaddition of a triplet alkene (**106**) with a ground state oxime (**107**) and second, cycloaddition of triplet 2-isoxazoline carboxylates (**110**), which are unable to undergo isomerization, with unactivated alkenes (**111**) (Fig. 5a).

The first EnT *aza* Paternò-Büchi reaction of oximes is characterized by sensitization of an ene-amide (**112**) by xanthone. This method employs unactivated oximes and hydrazones (**112**) to access the polycyclic azetidine products (**113**). This transformation is atroposelective owing to an axial-to-point chirality transfer, allowing the azetidine products to be accessed enantioselectively (Fig. 5b). While mechanistic studies revealed catalyst quenching by both the ene-amide and the oxime or hydrazone moiety, it was concluded that the [2+2]-cycloaddition proceeds via initial triplet energy transfer sensitization of the ene-amide.[73] This transformation was notable as the first EnT photocatalysis method to access azetidines by the *aza* Paternò-Büchi reaction.

An alternative methodology for the intramolecular triplet alkene approach is the *aza* Paternò-Büchi reaction of acyclic styrenes and dienes with unactivated oximes (**114**) enabling the synthesis of more general bicyclic azetidine scaffolds (**115**) (Fig. 5b). The use of oximes as imine equivalents in this methodology allowed for the easy deprotection of the resulting azetidine products, to form the free azetidines. Additionally, the use of a substrate with an ester tether resulted in fused azetidines which could be converted to the monocyclic azetidine via reduction of the lactone.[74] In contrast to the previous method developed by Sivaguru, this methodology utilized an iridium photocatalyst (**64**•$PF_6$) which allowed for the transformation to be conducted with visible light rather than UV light to form azetidines under exceptionally mild conditions. However, a remaining limitation of this transformation, similar to the previously published example from Sivaguru, is the requirement for an activated alkene, limiting the scope of this transformation to styrenes and dienes.

Indoles with tethered oximes (**116**) can be employed to form highly strained polycyclic azetidines (**117**) or distal polycyclic ene-amines (**118**) via divergent radical reactivity (Fig. 5b). Starting material **116** is sensitized to a triplet biradical on the indole alkene, which then adds into the tethered oxime to generate a 1,4-biradical intermediate **119**. From this point, the intermediate undergoes *C*–*N* bond formation to access the azetidine product **117**, or for substrates with aliphatic substituents in the indole 3-position, can undergo 1,5-HAT to from benzindolizines **118**. These divergent pathways are representative of the different reactivity available to biradicals (**119**), which can undergo both radical recombination and 1,5-HAT in a similar fashion to the iminyl radical.[75]

The triplet state of isooxazoline (**121**) can be utilized for intermolecular *aza* Paternò-Büchi reactions with unactivated alkenes (**120**) (Fig. 5c). The switch to an ester or nitrile substituted isoxazoline (**121**) from aryl isoxazolines, used in previous singlet state *aza* Paternò-Büchi reactions (**108**), allowed for the synthesis of the azetidine products (**122**) via EnT, revealing the tunability of isoxazolines for either triplet or singlet state reactivity. Sensitization of the isoxazoline substrate to the triplet state makes this transformation amenable to a large range of alkene substrates including feedstock chemicals, a notable advance over previous methods which require activated alkenes. Additionally, the intermolecular nature of this reaction allows for further generality of the azetidine products. While this method is limited to the cyclic isoxazoline substrate to prevent oxime isomerization, the resulting products can easily be converted to free azetidines **123** and **124** via *N*–*O* bond cleavage.[8]

Photochemical [3+2]-cycloadditions are also suitable for oxime substrates. For example, hydroxylamine pyrrolidine product **127** is generated from cyclopropane **125** and oxime **126** (Fig. 5d). In this transformation, cyclopropane **125** is opened to **128** via photochemical reduction, and subsequently undergoes a [3+2]-cycloaddition with the *C*=*N* double bond of the oxime to generate **127**. Interestingly, this reaction did not require any terminal reductant, as oxidation of the radical anion resulting from the cycloaddition closed the catalytic cycle. While a hydrazone was found to be a more efficient substrate for this transformation, the use of an oxime allowed the initial reaction discovery and demonstrated an alternative [3+2]-cycloaddition to access heterocycles from oximes.[76]

**Addition and rearrangement of oximes** The nucleophilicity of the nitrogen and oxygen atoms in oximes offers divergent reactivity opportunities. This dual reactivity was highlighted in the iridium catalyzed-allylation of oximes **129** in a chemo- and enantioselective manner for the synthesis of 5-, 6-, or 7-membered cyclic oximes (**130**) or allylic nitrones (**131**).[77,78] The difference between reaction conditions, specifically $Sc(OTf)_3/Cs_2CO_3$ or $Cl_2CHCO_2H$, controls the selectivity of the allylation products. It was postulated from experimental and computational studies that the acidic *N*-allylation proceeds through a thermodynamic equilibrium, whereas the *O*-allylation is under kinetic control.[77] The cyclic nitrone product (**133**) from **132** could further react with an alkene through an intramolecular 1,3-dipolar cycloaddition to form **134** (Fig. 6a). A Cu-catalyzed variant of this allylation reaction was also disclosed, where difunctionalization of the pendant alkene was observed producing similar cyclic nitrones and isoxazolines.[79] Formation of cyclic hydroxylamines through oxime derived nitrones was also reported in the chemo-, regio-, and enantioselective addition of oximes (**135**) to allenes (**136**). A π-allyl rhodium complex with the aryl oxime (**139**) is proposed to give rise to branched allylic nitrone product **137**. Subsequent 1,3-dipolar cycloaddition of the resulting nitrone (**137**) was demonstrated for the synthesis of *N*-allylated chiral isoxazole **138** (Fig. 6b).[80]

A unique application of oximes was highlighted in the synthesis of TKX-50 (**141**), a potential candidate for the generation of energetic materials. Generally, *C*–*C* bond activation is challenging owing to the unfavorable thermodynamics of insertion into a *C*–*C* bond. Although detailed mechanistic information for this transformation has not been disclosed, this work demonstrates a challenging oxime fragmentation pathway to facilitate a self-coupling *C*–*C* bond formation (Fig. 6c).[81]

One of the most traditional reactions of oximes is the Beckmann rearrangement, where under acidic conditions oximes rearrange to the corresponding amide.[3,5] Recent innovations in the Beckmann rearrangement include a visible light-induced photoredox approach. An organic photocatalyst was used to oxidize aryl oxime **142** to iminoxyl radical **143** which undergoes nucleophilic attack by water to form *N*-centered radical **144**. Subsequent 1,2-rearrangement (**145**) and radical chain propagation provide anion

**146**, followed by dehydration and tautomerization to form amide product **147** (Fig. 6d).[82] The overall redox neutral process and use of an inexpensive organic dye as the photocatalyst makes this approach appealing. A Beckmann-type rearrangement was also employed for the synthesis of carbamoyl fluorides (**149**, **150**) from both linear and cyclic amides (**148**) (Fig. 6e). The corresponding nitrile containing carbamoyl fluoride (**150**) could be further cyclized under basic conditions via the nitrile enolate as a nucleophile and the highly electrophilic carbamoyl fluoride.[83]

**Bioconjugation and dynamic materials** Beyond *N*–*O* bond fragmentation and the synthesis of novel ring systems through cycloaddition and allylation reactions, oximes and their reactivity have permeated a broad area of disciplines. Specifically, the formation of oximes via condensation has found numerable applications in the synthesis of polymers. Oxime ligation between a hydroxylamine and a carbonyl is a widely used strategy for bioorthogonal click chemistry and hydrogelation.[32] More recently, red light was used to oxidize furan **151** to conjugated aldehyde **152** which could then participate in a condensation with a polyethylene glycol (PEG)-supported hydroxylamine. This condensation resulted in a 3D network of cross-linked hydrophilic polymers (**153**) (Fig. 7a). An important advancement was the use of red light to initiate the furan oxidation and cross-linking, which falls into the therapeutic optical window of tissue (600-900 nm) negating the need for a photosensitizer or high energy light. The stability and efficient synthesis of oximes in bioconjugation leads to new methods for polymer end group modification and network formation.[84]

The close relation between oximes and nitrones, specifically the oxime/nitrone equilibrium, enabled the formation of linear/cross-linked poly(oxime-urethanes). Under ambient conditions, polyaddition of the nitrone form (**155**) of oxime **154** and an isocyanate (**156**) was found to occur (Fig. 7b). At elevated temperatures of 100 °C, a thermally dissociative mechanism was found to take over giving rise to a self-healing/recyclable material. The forward and reverse reactions were facilitated by the dual functionality of oximes and the corresponding nitrone; a nucleophilic oxygen and proton acceptor nitrogen (Fig. 7b).[85] In order to fine-tune a material's responses, dynamic linkages can be introduced to incorporate a dual-responsive nature. The inclusion of aryl boronic esters (**159**) to the oxime (**158**) ligation creates a complex network. Boronic acids help promote oxime condensation reactions, an additional benefit of the material design. Combining multiple dynamic chemistries generates gels with tunable properties to be exploited for complex, stimuli-responsive materials (Fig. 7c).[86]

Other 3D networks, like nanoparticles, have benefited from oxime ligation. Oxime-containing macromolecular structures are able to dissociate and reconstruct upon introduction of a stimulus, which holds promise for the synthesis of self-healing gels.[32] Polyester fragments containing ketones (**160**) were reacted with amino-oxy linkers (**161**) in aqueous or organic mediums. The resulting oxime-containing nanoparticles were analyzed for their pH-responsive behavior, showing a fast degradation mechanism. The oxime cross-linked material **162** includes a *C*=*N* double bond which can be reduced to form stable alkoxyamine linkages (**163**)**,** resulting in a much slower hydrolysis. Together, this tunable degradation allows for opportunities in controlled drug release (Fig. 7d).[87]

**Oxime reduction** New conditions for oxime *C*=*N* double bond reduction have recently emerged. Enzymes offer many advantages in such reactions including enhanced reactivity and greater selectivity. It was found that a variety of structurally different ene-reductases are capable of reducing activated oximes. When applied to activated oximes such as **164**, the analogous amines (**165**) are formed which immediately dimerize and oxidize to form tetrasubstituted pyrazines (**166**). Alternatively, treatment of **165** with alcohol dehydrogenase furnishes amino alcohols **167**.[88] The use of laccase and TEMPO with oxime **168** provided intermediate ketone **169**. Addition of a trans-aminase was used to form chiral amines (**171**), whereas substitution of the trans-aminase with a keto-reductase resulted in chiral alcohols (**170**) (Fig. 7e).[89]

Chiral spiroborates have been used previously in the reduction of *O*-benzyl oximes to primary amines, but dendrimer-supported chiral spiroborates (**174**) were only recently applied to reduce oximes (Fig. 7f). The dendrimer-supported catalyst improved the enantioselectivity and catalytic reactivity for the reduction of oxime **172** to amine **173** due to the uniform orientation of the active sites. Importantly, the dendrimer enables the catalyst to be recycled (Fig. 7f). The synthetic utility was showcased via the synthesis of (*S*)-Dapoxetine, a selective serotonin reuptake inhibitor.[90]

More traditional reduction approaches involving metal catalysis and borohydrides have been tuned to reduce oximes. A unique deuteration/reduction protocol for the reduction of oxime **175** to amine **176** was completed using samarium diiodide and $D_2O$ (Fig. 7g). The method was amenable to late stage targets by reductively deuterating oxime derivatives of nabumetone, a nonsteroidal anti-inflammatory derivative and pregnenolone, a steroid derivative.[91] While many of these methods fragment the labile *N–O* bond, asymmetric hydrogenation of oximes (**177**) was applied to the synthesis of chiral hydroxylamines (**178**). Application of the described conditions resulted in overcoming the previous challenges related to keeping the labile *N–O* bond intact. By using a robust cyclometalated Ir(III)-catalyst (**179**) at room temperature, the *N–O* bond was kept intact and high enantioselectivity of the resulting hydroxylamines was observed (Fig. 7h).[92]

**Outlook** Although recent years have seen advances in innovative uses of oxime starting materials, important challenges remain (Fig. 8a). There is opportunity for increased development of transformations using well understood oxime reactivity and oxime-derived intermediates. Especially in the area of *N–O* bond fragmentation, new ways to utilize the oxime derived radicals could provide desirable transformations under very mild conditions. An innovative example of the combination of catalysis methods to perform a desirable transformation is seen in the photocatalytic/palladium-mediated cross coupling reaction to form **182**. The use of a photocatalyst to trigger *N–O* bond cleavage of **180** results in subsequent fragmentation to generate the acyl radical, which then combines with the palladium catalyst to undergo *C–H* activation of **181** and subsequent cross coupling to form **182** under very mild conditions (Fig. 8b).[93]

Another challenge of methods using iminyl radicals generated from the *N–O* bond fragmentation is the loss of a large portion of the oxime (Fig. 8a). Additionally, the requirement of activating groups inhibits the cost and time associated with using oximes as radical precursors. Approaches for *N–O* bond fragmentation with simpler starting materials would be an important advances in this field. A significant step towards improving the efficiency of these methods is the use of oximes as bifunctional reagents to add across alkenes, for both oxime esters and oxime carbonates (Fig. 4a).[34,35] To avoid the use of high-molecular weight leaving groups on the oxygen in *N–O* bond fragmentation methods, the use of unprotected oximes provides an ideal solution. In a recent example, a phosphine acted as an *O*-atom abstractor with unprotected oximes (**183**). This reaction proceeds via the formation of a phosphoranyl intermediate under mild photocatalytic conditions, which then fragments into an iminyl radical and subsequently adds intramolecularly to the alkene in **183** to generate **184** (Fig. 8b).[94] While the use of phosphoranyl radicals as *O*-atom abstractors is well known, the merging of these methods with photocatalysis offers the potential for further development.[95]

In the area of oxime cycloaddition reactions, a remaining challenge is overcoming oxime isomerization to achieve the *aza* Paternò-Büchi reaction with acyclic oximes (Fig. 8a). While this has not yet been addressed, the use of 2-isoxazolines in these reactions is an advance for this reaction because it allows for reactivity with unactivated alkenes, and easy formation of the monocyclic azetidine products (Fig. 5c).[8] Finally, the enantioselective reactions of iminyl radicals and cycloadditions remain a challenge owing to the radical intermediates present in these mechanisms. One example of an enantioselective *aza* Paternò-Büchi reaction is the atroposelective [2+2]-cycloaddition relying on the substrate structure.[73] An exciting chiral-catalyst-mediated approach was recently used for cyclization of iminyl radicals to generate oxazolines enantioselectively (Fig. 4b).[25] This method, which employs both a photocatalyst and a chiral copper catalyst, is a noteworthy step forward in the field of *N–O* bond fragmentation and iminyl radical additions, and further development of these strategies could enable highly desirable enantioselective transformations.

Along with developments in the field of oxime chemistry being focused on addressing challenges in oxime reactivity, oximes are similarly important for the development of new catalysts and materials. The exploitation of oxime-polymers, for either reduction to alkoxyamine linkages or isomerization, yields useful insight for the synthesis of dynamic materials. In the field of catalyst development, a solid-state triplet energy transfer photocatalyst, K-PHI facilitated the [3+2]-cycloaddition between oxime **185** and alkene **186** to form **187**.[96] This catalyst had previously been explored for other applications in energy storage, but it is capable of activating oxygen by EnT to generate singlet oxygen which reacts with the oxime starting material (**185**). Development of an alternative photocatalyst can be seen in the use of a simple cerium catalyst for *N–O*

bond fragmentation, replacing the need for an expensive iridium photocatalyst (Fig. 4e).[62] Further developments in oxime fragmentation include moving away from transition metal catalysts, as seen in the *N–O* cleavage and coupling sequence of **188** and **189**, in which the reaction was conducted in DMAc/$H_2O$ without an additional catalyst to form **190** (Fig. 8c). This method is an important step towards a more green-chemistry approach to *N–O* bond fragmentation.[97]

The recent developments in reactions of oxime starting materials have demonstrated the versatility of this functional group for applications such as *N–O* bond fragmentation to generate highly useful radicals, [2+2]-cycloadditions to synthesize *N*-heterocycle products, enantioselective reductions to access chiral amines and hydroxylamines, and the synthesis of crosslinked polymers. The unique properties of oximes make them a high value starting material for the development of new transformations.

**Web Summary:**

Oximes are valuable motifs with diverse reactivity. Important developments in oxime reactivity are described, including *N–O* bond fragmentation through transition metal and photocatalysis, [2+2]-cycloaddition reactions, asymmetric reduction and applications in materials science. Developments in transition metal catalysis and photocatalysis highlights the utility of oximes as powerful synthetic building blocks.

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**Competing Interests:**

The authors declare no competing interests.

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Figure Captions:

**Figure 1.** Overview of oxime scaffolds. Oximes (**1**) possess unique characteristics imparted by their nucleophilic nitrogen and oxygen, and ambiphilic carbon. The synthesis of oximes can be accomplished in simple and scalable steps, such as condensation of a hydroxylamine with a carbonyl (**2**). Imidates (**5**) and isoxazolines (**6**) are easily accessible from oxime chlorides (**4**). Common oxime scaffolds discussed herein are pictured, and oxime classifications by the *O*-atom substituent are shown. These scaffolds can provide access to common radicals, such as iminyl radical **14** and *N*-oxyl radical **13** (reviewed elsewhere).

**Figure 2.** General mechanisms for *N*–*O* bond fragmentation. Oxime *N*–*O* bond fragmentation can occur through a variety of transition metal (M) and photocatalysis methods. **a** Single Electron Transfer (SET) from transition metal catalysts leads to the iminyl radical (**17**) through fragmentation of a radical anion intermediate (**16**). **b** Transition metal insertion into the *N*–*O* bond leads to the breaking of the *N*–*O* bond. **c** Triplet energy transfer (EnT) from a photocatalyst leads to iminyl radical (**23**) formation from oxime esters (**21**) by decarboxylative fragmentation from the triplet state (**22**). **d** Oxime ethers (**25**) undergo fragmentation to the iminyl radical (**17**) following hydrogen atom transfer (HAT) from a photocatalyst. **e** Photocatalyst mediated SET to oxime esters (**15**) results in fragmentation of the intermediate radical anion (**16**) to form an iminyl radical (**17**). **f.** Heat mediates fragmentation of oxime ethers (**27**) via thermal homolysis.

**Figure 3.** Generation of iminyl radicals via transition metal catalysis. **a** Overview of common reactions. **b** Cu-Catalyzed single electron transfer (SET) cyclobutanone ring opening and radical addition into alkene (**29**) to form β-lactam **31**. **c**. Hydrogen atom transfer (HAT) and intramolecular cyclization of cyclobutanone oxime **33** with vinyl azides to result in 3,4-dihydro-2H-pyrroles (**35**) and phenanthridines (**36**). Divergent reactivity includes a radical borylation to form boronic esters (**34**). **d** Cyclobutanone oxime (**37**) ring opening and functionalization with organozinc reagents. **e** Iminyl radical **40** generated via Fe-catalyzed SET, subsequent 1,5-HAT and carbonylation to form lactam product **44**. **f** Oxime bearing a pendant alkyne undergoes 5-exo-dig cyclization following 1,5-HAT from the iminyl radical **46**. Vinyl radical **48** reacts with an extraneous alkene to form fused pyridine **49**. **g** Alkene containing oxime cyclizes upon formation of the iminyl radical (**52**). The resulting *C*-centered radical can be further functionalized (**54**). **h** Oxime **55** with Pd undergoes an intramolecular Narasaka-Heck reaction to form spirocyclic cyclobutane **56**. **i** Coordination of $Zn(OTf)_2$ to oxime acetate **59** promotes a rearrangement to nitrilium ion **61** and subsequent attack by a nucleophile and oxidative cyclization to form *N*-arylbenzimidazole **63**. *Abbreviations*: DMAc, *N*,*N*-dimethylacetamide; dtbpy, 4,4′-di-tert-butyl-2,2′-dipyridyl; THF, tetrahydrofuran; acac, acetylacetonate; Phen, phenanthroline; DMF, *N*,*N*-dimethylformamide; DCE, 1,2-dichloroethane.

**Figure 4.** Photo-mediated *N*–*O* bond fragmentation transformations. **a** Fragmentation by triplet energy transfer (EnT) to oxime esters (**21**) results in the formation of iminyl (**67**) and *C*-centered (**66**) radicals, used to form functionalized imines (**68**, **70**) or functionalized aryl products (**69**). **b** A combination of EnT and Cu-catalysis leads to the formation of oxazine (**74**, **78**) products from imidates (**71**), via *N*–*O* bond fragmentation followed by asymmetric hydrogen atom transfer (HAT) or addition to an alkene.**c** HAT from an oxime benzyl ether (**80**) results in fragmentation of the *N*–*O* bond, generating an iminyl radical (**83**) that undergoes intramolecular alkene addition. **d** *N*–*O* bond fragmentation of α-imino-oxy acids (**84**) occurs by single electron transfer (SET) and fragmentation generating an iminyl radical, which can perform Co-mediated addition to an alkene. **e** Photocatalysts promote *N*–*O* bond fragmentation through a ligand to metal charge transfer (LMCT) mechanism, generating iminyl radicals for hydrizination. **f** Cyclobutanone derived iminyl radicals (**94**) rearrange to *C*-centered radicals (**95**), used in a variety of transformations. **g** Further fragmentation of iminyl radicals leads to the formation of acyl radicals (**100**), which can add intermolecularly to alkenes. *Abbreviations*: Nu, nucleophile; $L_n$, ligand; DMAc, *N*,*N*-dimethylacetamide; Mes-$Acr^+$, 9-mesityl-10-methylacridinium; dmgH, dimethylglyoximate; $dmgH_2$, dimethylglyoxime; HFIP, hexafluoro-2-propanol; 4-CN-py, 4-cyanopyridine; TMB, tetramethylbenzidine; ppy, phenylpyridine; DCE, dichloroethane; DMF, *N*,*N*-dimethylformamide; rt, room temperature.

**Figure 5.** Photo-mediated cycloaddition reactions of oximes. **a** The *aza* Paternò-Büchi reaction is the photomediated [2+2]-cycloaddition between imines and oximes, however, this transformation is limited, because for many oximes, isomerization from the excited state precludes cycloaddition. Current methods

enabling this transformation rely on three strategies: an activated triplet state alkene (**106**) reacting with a ground state unactivated oxime (**107**), an activated singlet state oxime (**108**) reacting with the ground state of an activated alkene (**109**), or an activated triplet state oxime (**110**) reacting with a ground state unactivated alkene (**111**). **b** Methods utilizing an activated triplet state alkene in intramolecular *aza* Paternò-Büchi reactions to generate polycyclic azetidines. For indole derived substrates **116**, hydrogen atom transfer (HAT) can occur for specific substrates resulting in hydroxylamines **118**. **c** Intermolecular *aza* Paternò-Büchi reaction relying on triplet excited state isoxazolines (**121**) and unactivated alkenes (**120**) generates bicyclic azetidines (**122**) that are converted to free oximes by *N*–*O* bond cleavage. **d** [3+2]-Cycloaddition reaction between cyclopropane **125** and oxime **126** mediated by single electron transfer (SET) for the formation of **127**. *Abbreviations*: THF, tetrahydrofuran; dFppy, difluorophenylpyridine; ppy, phenylpyridine; M, metal; Ln, ligand; rt, room temperature.

**Figure 6.** Nitrone and amide synthesis via oximes. **a** Enantioselective *N*– and *O*– allylic alkylation of oxime **129**. Nitrone **133** can undergo a 1,3-dipolar cycloaddition to form **134**. **b** Rh-Catalyzed enantioselective addition of oxime **135** to allene **136** for the synthesis of nitrone **137** which can be further elaborated to isoxazoline **138**. **c** *C*–*C* cleavage and oxime release for the synthesis of energetic material TKX-50 (**141**). **d** Photoredox Beckmann rearrangement. **e** Fluorinative Beckmann rearrangement of linear and cyclic amides. *Abbreviations*: rt, room temperature; DMSO, dimethylsulfoxide; DCE, 1,2-dichloroethane; HFIP, 1,1,1,3,3,3-Hexafluoro-2-propanol; cod, 1,5-cyclooctadiene.

**Figure 7.** Oxime containing polymers and chiral reductions of oximes. **a** Red-light enabled oxime ligation with a polyethylene glycol (PEG) hydroxylamine for polymer cross-linking. **b** Equilibration of oxime **154** and nitrone **155**. At room temperature (rt) oxime polyurethane **157** is formed, whereas elevated temperature induces the reverse reaction giving rise to a healable material. **c** Complex, stimuli-responsive materials can be synthesized via oxime ligation (**158**) and boronic ester formation (**159**). **d** Nanonetworks can be formed via oxime ligation between polyester **160** and hydroxylamine **161**. The oxime linkage can be reduced to the more stable alkoxyamine linkage. **e** Oxime reduction via ene-reductase to chiral amine **165** which can be further reduced to amino alcohol **167** or undergo spontaneous cyclization to tetrasubstituted pyrazine **166**. Oxime **168** is converted to ketone **169** which can be reduced to alcohol **170** or converted to primary amine **171**. **f** Dendrimer catalyst enables reduction of oxime **172** to chiral amine **173**. **g** Oxime **175** is reduced with $SmI_2$ in $D_2O$ to incorporate deuterium. **h**. Reduction of oxime **177**, while keeping *N*,*O*-bond intact to form hydroxylamine **178** via Ir(III)-complex **179**. *Abbreviations*: PBS, phosphate buffered saline; TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxyl; $NADP^+$, nicotinamide adenine dinucleotide phosphate; DMSO, dimethylsulfoxide; THF, tetrahydrofuran.

**Figure 8.** New and future directions for development of oxime reactivity. **a** Challenges and areas for future development in oxime reactivity and applications include: expanding the uses for iminyl radicals to more diverse reactions, improving the atom economy of reactions relying on *N*–*O* bond fragmentation, increasing the generality of cycloaddition reactions, and developing enantioselective methods, especially for reactions proceeding through radical intermediates. **b** Advancements in new directions of catalysis with oximes include transition metal and photochemical tandem catalysis methods, and the use of photochemical methods to access phosphine *O*-atom abstractors, enabling *N*–*O* bond fragmentation of unprotected oximes. **c** Reactions of oximes enable the development of new types of catalysts and reaction conditions. The development of a solid state photocatalyst for an oxime cycloaddition demonstrates the diversity of this functional group in enabling new transformations. Solvent-promoted methods are also in development, allowing *N*–*O* bond fragmentation without metal catalysts. *Abbreviations*: TFA, trifluoroacetate; ppy, phenylpyridine; phen, phenanthroline; *p*-tol, para-toluene; DMF, *N*,*N*-dimethylformamide; K-PHI, potassium poly(heptazine imide); DMAc, *N*,*N*-dimethylacetamide; rt, room temperature.