Oxidative Cleavage of Alkenes by Photosensitized Nitroarenes

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Dedicated to Professor Frank Glorius on the occasion of his 50th birthday

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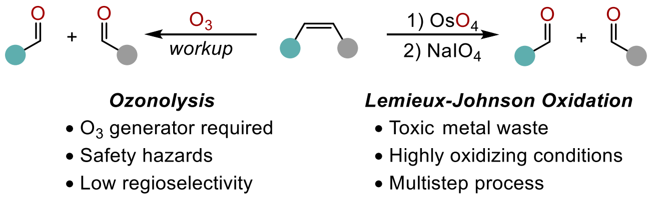
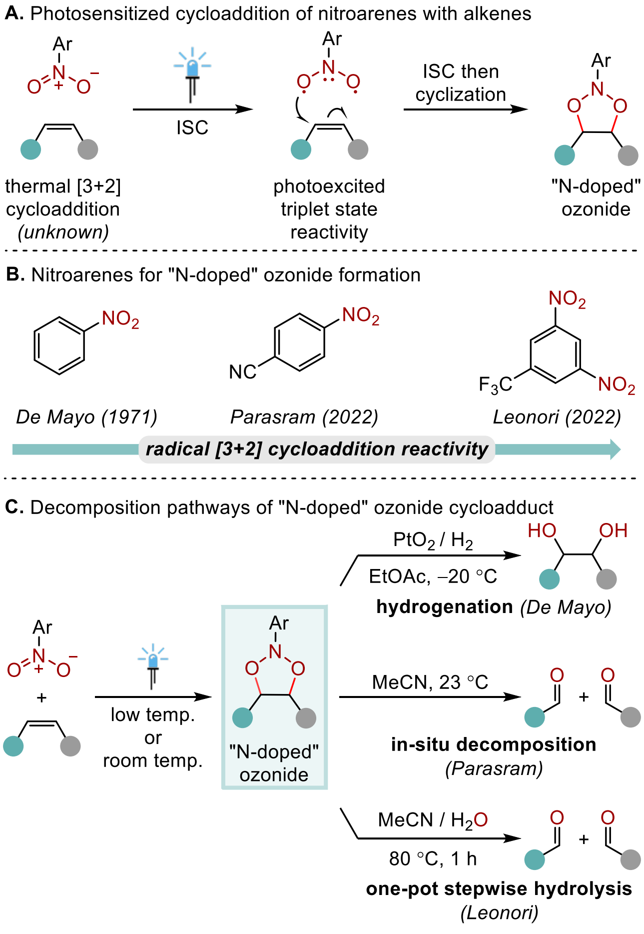
Abstract: Oxidative cleavage of alkenes into carbonyl molecules mainly relies on either ozonolysis or Lemieux-Johnson oxidation involving high valent transition metal oxides. Safety, technical concerns and highly oxidizing conditions of both these procedures limited their adoption in streamlined synthesis. Like ozone, photosensitized nitroarenes can deliver the similar types of [3+2] cycloaddition products with alkenes through biradical formation and the resulting “N-doped” ozonides can safely be converted to the corresponding carbonyl compounds through hydrolysis. The high prevalence of nitroarenes with diverse electronic and steric profiles combined with the mild oxidizing power allow to modulate site-selectivity and tolerate highly sensitive functional groups ideal for application in complex molecular setup.

A selective cleavage of alkene C=C double bonds suitable for late-stage diversification is challenging. Generally, ozonolysis is the well-known textbook procedure for introducing oxygen atoms across C=C double bonds in alkenes. In practice, the explosive nature of ozone combined with its high toxicity (lethal dose: 5 ppm) have limited its widespread use in regular laboratory synthesis.[1] In addition, the requirement for an ozone generator to convert molecular oxygen into ozone along with the difficulty to control the stoichiometry for gaseous reagents further complicates the technical issues (Scheme 1). Alternatively, the Lemieux-Johnson oxidation generally utilizes osmium tetraoxide or potassium permanganate in combination with sodium periodate in a two-step dihydroxylation-oxidation process.[2] Despite better control over reagent dosing and reaction conditions, the strong oxidative conditions of this approach limit functional group tolerance and also generates toxic heavy transition metal waste. In short, the extreme oxidizing power of the terminal oxidants in both of these traditional methods obstruct their use for oxidative cleavages of alkenes in late-stage modifications.[3]



Scheme 1. Existing protocols for oxidative cleavage of alkenes.

In a completely different approach, nitroarenes can be used as a mild oxygen transfer reagent under anaerobic conditions. Classically, the high electron-withdrawing effect of nitro group has been exploited in several valuable ionic transformations at the α-position (Henry reaction, Nef reaction, Michael addition, amide synthesis).[4] In sharp contrast, nitro groups have rarely been used directly in oxygen transfer reactions. Recent findings disclosed that nitroarenes can trap reactive C-centred radicals in monohydroxylation reactions.[5] Still, chemical reactions involving direct participation of nitro groups are less known.

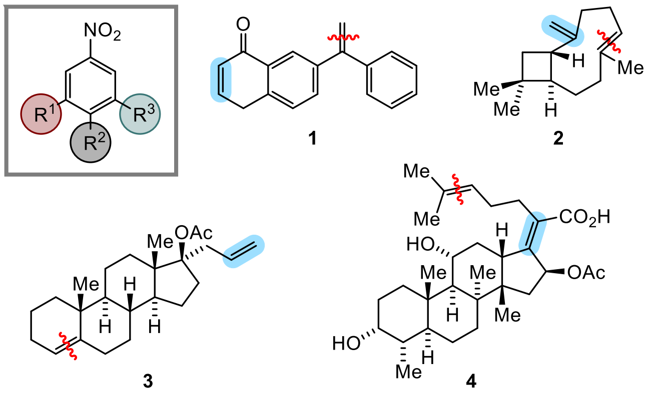


Scheme 2. Nitroarenes as ozone surrogates for alkene cleavage. ISC: intersystem crossing

The nitro group is isoelectronic to ozone. Yet, comparable thermal 1,3-dipolar cycloadditions of nitroarenes with alkenes are not feasible from ground states owing to high kinetic energy barriers.[6] Initial pioneering work by Büchi and Ayer revealed that nitrobenzene can participate in a radical cycloaddition with alkenes through a higher energy photoexcited triplet state and the formation of analogous “N-doped” ozonides was proposed (Scheme 2A).[7] However, the use of high energy UV light as well as unselective decomposition of the [3+2] cycloadduct hindered the effective translation of this reactivity into synthetic methodologies. Later, the De Mayo group was able to isolate the proposed “N-doped” ozonide at low temperature with nitrobenzene (Scheme 2B).[8] They also elegantly converted those cycloadducts to vicinal dihydroxylation products under hydrogenation conditions at low temperature (Scheme 2C). Nevertheless, detailed reactivity studies of nitroarenes in such cycloaddition reactions with an aim to engage unactivated alkenes in a stoichiometric fashion were not performed. Likewise, an effective route to convert those “N-doped” ozonides into carbonyl compounds suitable for synthetic applications was absent.

The recent independent reports by the research groups of Parasram and Leonori have now addressed this longstanding problem by exploring the excited state reactivities of nitroarenes with alkenes under mild purple light photosensitization conditions.[9,10] Unlike powerful mercury lamps, mild photosensitization conditions allowed formation of the “N-doped” ozonide and a controlled cleavage of the alkenyl C–C bond to generate the corresponding carbonyl compounds in high yields (Scheme 2C). Parasram and co-workers identified 4-cyanonitrobenzene as an effective one step oxygen transfer agent for styrenes at room temperature.[9] A nonstereospecific radical cycloaddition pathway was established for the “N-doped” ozonide formation and subsequent fragmentation pathways were studied in detail.

In contrast, Hammett plot analysis of nitroarenes containing multiple substitutions at the arene ring allowed Leonori and co-workers to identify a series of reactive nitroarenes suitable for engaging various unactivated alkenes. While electron deficient nitroarenes generally showed high reactivities, performing the reaction at low temperature (−30 °C) was crucial for selective formation of “N-doped” ozonides in high yields.[10] In an overall one-pot two-step approach, those “N-doped” ozonides were converted to the corresponding carbonyl compounds by hydrolytic work-up at high temperature.



Scheme 3. Regioselective cleavage at one site in complex alkenes. Red wavy bond denotes the preference for alkenyl cleavage over the blue highlighted alkene.

Functionalized nitroarenes are commercially available in wide varieties and are cheap dosable reagents. Unlike ozonolysis, another commendable feature of this method is that the reactivity profile of nitroarenes can be easily fine tuned by choosing a suitable substitution pattern on the pendant aromatic ring depending on the target alkene. A well-known problem in oxidative cleavage is achieving high regiocontrol in molecules with multiple reactive sites. Parasram and co-workers used simple 4-cyanonitrobenzene to achieve high regioselectivities for **1** (Scheme 3). On the other hand, Leonori group modulated the nitroarene electronics to amplify the small reactivity differences among different alkene sites within the same molecule (Scheme 3). In these cases, generally the most electron rich alkene is the preferred site of attack under nitroarene limiting conditions. Such site-selective late-stage oxidative cleavage of only one alkene is generally very difficult to achieve with existing protocols and one of the highly promising features of this method.

The excited state reactivity of nitroarenes with alkenes and subsequent cleavage pathways provides a new tool for synthetic chemists. This anaerobic approach with a high degree of modularity should find application in the construction of complex molecular skeletons due to the mild reaction conditions and operational simplicity. Though, an obligatory two step approach and stoichiometric requirement of nitroarenes could be two major areas of concern for industrial applications and would likely see further improvements. Likewise, the reversible nonstereospecific nature of the radical [3+2] cyclization might inhibit further exploration towards asymmetric modifications.[9] Nevertheless, this novel reactivity mode will pave new ways of using nitroarenes in various anaerobic oxygen transfer reactions.

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Keywords: alkenes • cycloadditions • oxidations • diradicals • nitroarenes

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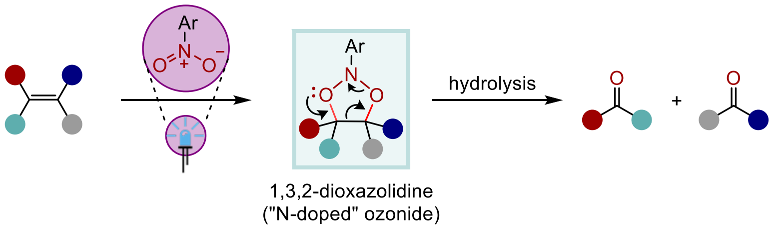

Ozonolysis made easy: This article highlights the recent seminal findings on the possibility to use photoexcited nitroarenes as modular and easily dosable reagents which can mimic the reactivity of ozonolysis for the oxidative conversion of alkenyl bonds into carbonyl groups in a highly selective fashion.