

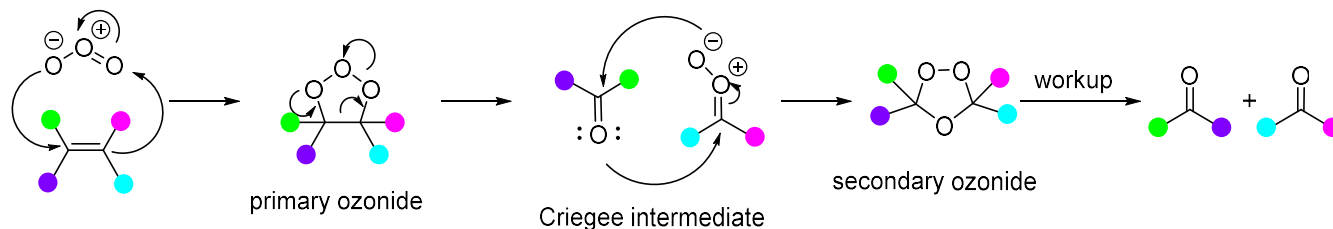
O₃: THREE RECENT ADVANCES IN OZONOLYSIS

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INTRODUCTION

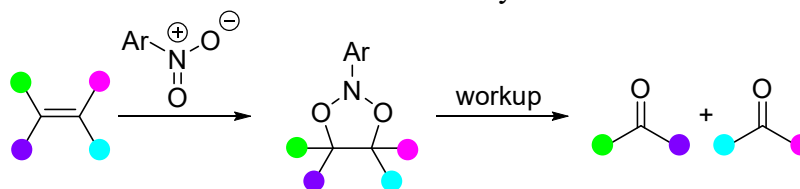
Ozonolysis is one of the most well-known transformations that oxidatively cleaves C–C double bonds into carbonyl compounds. Alkenes are feedstock molecules and their accessibility allows for ozonolysis to be a powerful transformation. Ozone has long been known as a product of electrical storms, but it was not until 1840, that ozone was identified as a molecule. A few years later, in 1845, ozonolysis, was first reported by Schonbein.¹ In over 100 years following its discovery, the mechanism was not fully understood. In 1975, Criegee published the widely accepted mechanism as a series of 1,3-dipolar cycloadditions and reversions to arrive at the secondary ozonide (Scheme 1).² Upon conventional oxidative or reductive workups, either carboxylic acids, ketones, aldehydes or alcohols are produced. Despite the widespread use of ozonolysis, the reaction is rather dangerous as the intermediate ozonides are explosive and ozone is powerful oxidant that is lethal at 5 ppm.³



Scheme 1. Criegee Ozonolysis Mechanism.

NITROARENE-MEDIATED OXIDATIVE CLEAVAGE OF OLEFINS

In 1955 Büchi reported the first use of nitrobenzene (which is isoelectronic with ozone) under irradiation to oxidatively cleave alkenes.⁴ Inspired by this pioneering work, in 2022 the Parasram and Leonori groups independently reported the use of nitroarenes to oxidatively cleave alkenes under anaerobic conditions (Scheme 2). The use of a nitroarene allows for the formation of the more stable 1,3,2-dioxazolidine. The Parasram group

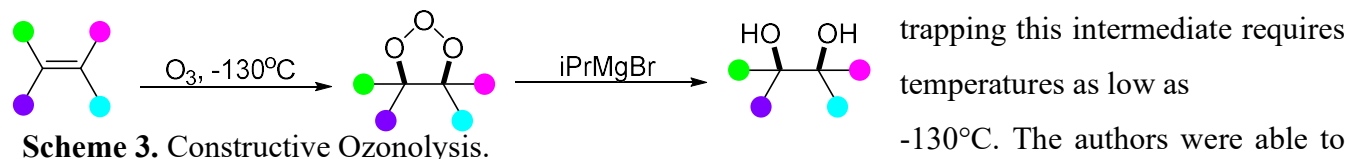


Scheme 2. Nitroarene-mediated oxidation.

used 4-nitrobenzonitrile to oxidatively cleave substituted styrenes and can be used to access products that are incompatible with ozonolysis, such as a synthetically useful pinacol boronic ester substrate.⁵ The Leonori group used different nitroarenes bearing meta and para substituents to the nitro group to oxidize a wide variety of substrates, including natural products and drug molecules.⁶ Tuning the reactivity and stoichiometry of nitroarenes allows for olefin selectivity that ozonolysis cannot achieve.

INTERCEPTING PRIMARY OZONIDES FOR SYN-DIHYDROXYLATION

Trapping intermediates in the ozonolysis pathway has been of interest to furnish a range of products. The Thomas group proposed trapping primary ozonides to furnish vicinal diols (Scheme 3).⁷ Primary ozonides are highly unstable and readily decompose at temperatures as low as -100°C. As a result,

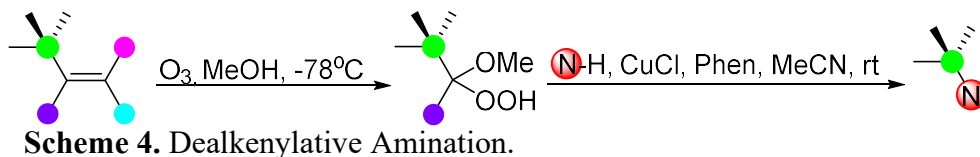


Scheme 3. Constructive Ozonolysis. open the primary ozonide using isopropyl magnesium bromide. This constructive ozonolysis resulted in modest yields of the syn-vicinal diols. Despite the limitations involving substrate scope and the inability to scale up in batch, this is the first use of a primary ozonide as a synthetic intermediate.⁷

DEALKYLATIVE AMINATION VIA OZONOLYSIS AND COPPER CATALYSIS

Capturing secondary ozonides or peroxides is a more commonly used synthetic strategy. The Kwon group proposed using ozonolysis and copper catalysis to form a C-N bond from a C(sp³)-C(sp²) bond. By capturing the peroxide intermediates formed under methanolysis conditions, the Kwon group was able to couple different nitrogen heterocycles and alkenes in good to excellent yields with varying diastereoselectivity

(Scheme 4).⁸ Further, this method allows for the



installation of masked amines that can be deprotected to arrive at important bioactive molecules, while being cost and step-efficient. This new amination method is complementary to the current C=C π bond amination methods as this method focus on aminating the adjacent sp³ carbon as opposed to the sp² carbon.

CONCLUSION AND FUTURE DIRECTIONS

Ozonolysis is an almost 200-year-old reaction and has been used widely by chemists to furnish oxidation products from alkene starting materials. In the years since its discovery, many advances in the diversification of products have been described. Nitroarenes can be used as ozone surrogates, but the full leverage of these surrogates remains to be seen in terms of product diversity. Furthermore, improving the synthetic feasibility of capturing primary ozonides, and improving the diastereoselectivity of dealkenylative amination, and the direct coupling of primary amines are important future contributions.

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