Recent Applications of Oxetanes in the Synthesis of Heterocyclic Compounds

Christian A. Malapit and Amy R. Howell*

Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060, United States

ABSTRACT: Oxetanes are valuable intermediates in organic synthesis, and strategic manipulations of this strained heterocycle continue to emerge. In this Synopsis, recent, distinct approaches to construct heterocyclic systems using oxetanes are described. These include ring expansion, ring opening, and C-2 functionalization.

Oxetanes are important motifs in some synthetic and natural products and have received considerable attention as versatile elements in drug discovery. The strained nature of oxetanes and the availability of diverse methods for their preparation have provided opportunities for the discovery of novel transformations. Although numerous advances have been made in the ring opening and functionalization of oxetanes in the past few decades, new strategies to exploit their potential as synthetic intermediates to construct biologically important heterocycles continue to emerge. This Synopsis will focus on recent transformations of oxetanes for the synthesis of heterocyclic compounds. These are categorized based on reaction types and will include the following: (1) oxetane expansions, (2) ring openings accompanied by formation of new heterocycles, and (3) the generation and reactions of oxetane oxocarbenium ions. In each section, both intra- and intermolecular transformations will be discussed. In this paper, the term oxetane expansion pertains to the formation of larger heterocycles that conserve the atoms originally present in the oxetane, while ring opening is used when at least one (but not all) of the atoms in the oxetane is retained in the newly formed heterocycle.

Oxetane Ring Expansions. Many of the oxetane ring expansions reported in the literature rely on an activating group at C2 (Scheme 1a). One of the earliest reports of a ring-expansion reaction of oxetanes dates back to 1966 when Noyori and co-workers demonstrated the asymmetric insertion of methyl diazoacetate into 2-phenyloxetane to form methyl 3-(phenyltetrahydrofuranyl)-2-carboxylate under chiral Cu(II) catalysis (Scheme 2). This transformation was revisited by Katsuki and Fu, using a range of 2-aryloxetanes and chiral pyridine or bisazaferrocene Cu complexes, respectively, to furnish 2,3-disubstituted tetrahydrofurans with moderate to good diastereoselectivities and with excellent enantioselectivities. Katsuki suggested that these carbenoid insertions proceed through oxygen ylides (and perhaps zwitterionic intermediates) that undergo ring expansion, with the regioselectivity controlled by the presence of the stabilizing aromatic moiety at C2.

Katsuki showcased the utility of the overall insertion in the total syntheses of trans-(+)-whisky lactone and (-)-avenaciolide, where the C2 stabilization came from acetylenic moieties. Njardarson extended this approach to 2-vinyloxetanes reacting with carbenoids to form 3-vinyltetrahydrofurans. Alper and co-workers utilized vinyl group activation at C2 of oxetanes to access zwitterionic \( \pi \)-allyl-Pd species, which then reacted with heterocumulenes via a net cycloaddition to form 6-membered heterocycles (Scheme 3). This method was extended to fused-bicyclic vinyl oxetanes, resulting in the stereoselective synthesis of cis-fused bicyclic heterocycles.

More recently, Njardarson and co-workers have further demonstrated the utility of vinyl oxetanes, showing they can also be opened to allylic intermediates using either transition metals or protic acids. In an extension of their very nice work on the rearrangement of vinyloxiranes to functionalized...
tetrahydrofurans, the Njardarson group has described a Cu(II)-
catalyzed expansion of vinyl oxetanes to the corresponding
dihydropyrans (Scheme 4).\(^{11}\) The transformations proceeded
with high efficiency under Cu(OTf)\(_2\) catalysis. Brønsted acids,
such as TfOH and \(\text{p-TsOH}\), were also found to catalyze this
process. The outcome led to the proposal that the reaction
proceeds through an allylic intermediate, which undergoes
cyclization with the oxygen atom in a 6-endo fashion.

Furthermore, an enantioselective version was achieved by the
desymmetrization of a dialkenyl oxetane using chiral catalysts.
Although yields were lower compared to copper catalysis, chiral
phosphoric acids/amides provided the dihydropyrans in up to
90% ee.

Gagosz and co-workers have cleverly used C\(_2\) activation to
promote oxidative Cu(I)-catalyzed ring expansion of alkynyl
oxetanes (Scheme 4b).\(^{12}\) An interesting divergence in product
selectivity was delivered by varying the nature of the pyridine
oxide oxidant. Mechanistically, it was proposed that the
formation of lactone \(2\) or dihydrofuranaldehyde \(3\) could
originate from the same allenloxypropyridinium intermediate. It
was found that the electron-deficient oxidant, 3-bromopyridine
oxide, gave exclusive formation of \(3\), since 3-bromopyridine is a
good leaving group during the 5-exo cyclization. In contrast, use
of the more electron-rich oxidant, 4-methoxypyridine oxide,
favored cyclization in a 6-endo fashion, providing lactone \(2\) as
the only observed product.

We and others have shown that C\(_2\)-spirocyclic cyclopropanes
can function as useful activators in expansions and rearrange-
ments of oxetanes. During our exploration of the reactions of
oxaspirohexanes \(4\), we discovered their unprecedented Pt(II)-
catalyzed rearrangement to 3-methylenetetrahydrofurans
(Scheme 5a).\(^{13}\) This outcome requires an alternative Pt(II)-
insertion pathway to that usually observed for reactions of
Zeise’s dimer with cyclopropanes having oxygen substitution.\(^{14}\)
Mechanistic studies by \(^{13}\)C-labeling, coupled with DEPT NMR,
confirmed a regioselective insertion of Pt(II) into the distal
methylene carbons of the cyclopropane to form a platincya-
clobutane as the key intermediate. This platincyclobutane
opened, together with the oxetane ring, to form Pt-allyl
intermediates. Cyclization led to the formation of synthetically useful 3-methylenetetrahydrofurans. To our knowledge, this is the first alkoxy-substituted platincyclobutane that has been observed spectroscopically.

In another example of the utility of oxaspirohexane systems, Zhang reported acid-mediated ring expansions of spirocyclopropyl oxetanes (Scheme 5b). When a series of these oxaspirohexanes was treated with HCl or HBr, spirocyclopropyl-fused butenolides were formed. When HI/I2 was used, spirocyclopropyl fused γ-butyrolactones were obtained in high yields.

Several groups have demonstrated that the alkoxide of ring-opened oxetanes can be utilized in situ as a nucleophile in subsequent intra- or intermolecular reactions to provide new heterocycles (Scheme 6). Schreiner and Fokin disclosed the ring expansion of oxetanes using dimethylsulfoxonium methylide. This overall methylenation of oxetanes was found to be regioselective via SN2-type ring opening, followed by ring closure with displacement of DMSO, providing C-2 substituted tetrahydrofurans. Kleij and co-workers developed aluminum and iron catalysts for the incorporation of carbon dioxide into oxetanes yielding 6-membered organic carbonates. Although this catalytic method was found to be effective only for oxetanes bearing C-3 substitution, other catalytic systems have been reported to generate aliphatic carbonates or their corresponding polymers. Minehan showed that the reactive intermediates obtained from n-BuLi-induced rearrangement of allyl 1,1-dichlorovinyl ethers can be successfully intercepted by oxetanes to cleanly provide δ-lactones.

Overall, the ring-expansion reactions described above provide access to new, usefully functionalized heterocycles. In the cases where the oxetanes are readily accessible, the approaches represent efficient access to these systems. While the requirement for C-2 activation limits the scope of some of the transformations, it has been demonstrated that a variety of groups can provide this activation, thus broadening the utility.

**Oxetane Openings.** The regio- and stereoselective ring opening of oxetanes with nucleophiles has been well established in organic synthesis as a route to functionalized alcohols. If the nucleophile is a heteroatom within the oxetane-containing molecule, a different heterocyclic system can be constructed in the process of opening the oxetane (Scheme 7). The most common approach involves intramolecular nucleophilic attack at the C-2 position of the oxetane. Corey first observed this during a BF3·OEt2 mediated cyclization/ring-opening cascade of an acetyl ester obtained from readily available 3-methyl-3-hydroxymethyl oxetane to form a bridged carboxylic ortho ester (Scheme 8a). Subsequently, several other groups demonstrated the use of ethers or peroxides as nucleophiles in intramolecular opening of oxetanes, providing other oxygen-containing heterocycles. Masaki reported a Lewis-acid mediated process with an oxygen nucleophile, accompanied by transfer of ethereal benzylic and allylic groups, to access several cyclic ethers. A general protocol for stereoselective synthesis of 1,2-dioxolanes and 1,2-dioxanes was developed by
Dussault through cyclization of oxetane hydroperoxides. Likewise, the Dussault group also found that ozonolysis in methanol of olefin-substituted oxetanes could generate hydroperoxylketal intermediates that spontaneously undergo 5-exo cyclization to form alkoxy-1,2-dioxolanes. In recent work, Grainger pursued an acid-mediated ring opening of fused oxetanes with pendant methoxyarenes to obtain spirocyclic dihydrobenzofurans. Danishefsky showcased an intramolecular oxetane opening strategy using a nitrogen nucleophile in the total synthesis of gelsemine (Scheme 8b). Bach developed a base-mediated intramolecular oxetane opening with sulfur, nitrogen, or oxygen, including a phenoxide nucleophile.

More recent reports have illustrated how acid (Lewis or protic) activation of oxetanes makes them susceptible to intramolecular opening by OH moieties. Jacobsen and co-workers achieved an asymmetric intramolecular opening of oxetanes using (salen)Co(III) complexes to access enantioenriched tetrahydrofurans and dihydrobenzofurans (Scheme 9a). To further exemplify the efficiency of this catalytic reaction, the use of trimeric (salen)Co(III) allowed catalyst loadings as low as 0.01 mol %, often providing tetrahydrofurans with improved enantioselectivity. An unusual activation of an oxetane to reaction with an intramolecular OH was seen in our attempt to prepare the natural product, laureatin (Scheme 9a). An NBS-mediated ring opening/cyclization cascade of an oxetane alcohol gave an epoxytetrahydrofuran rather than the expected laureatin core. The outcome was rationalized as arising from nucleophilic reaction of the oxetane, rather than the alcohol, with the initially formed bromonium ion, generating a bicyclic oxetane oxonium ion intermediate. Subsequent reaction of the alcohol with C-2 of the oxetane provided an epoxytetrahydrofuran in a stereospecific fashion.

Novel spirooxazoline derivatives were prepared by Zhang et al. through acid-mediated sequential reactions of spirooxetanes obtained from initial photocycloaddition of isoquinolinetrione with oxazoles (Scheme 9a). Carreira developed a novel access to isoxazoles from a base mediated rearrangement of nitromethyleneoxetanes, generated in situ from nitroalkanes and oxetan-3-one. Mechanistic studies provided evidence for the formation of highly strained oxetene intermediates that undergo ring opening with nitronate anions, and subsequent dehydration provides isoxazole aldehydes.

With their ongoing efforts in examining reactivity profiles of oxetanes derived from 3-oxetanones, Carreira and co-workers also developed a facile synthesis of highly functionalized morpholines, piperazines, and thiomorpholines by utilizing an indium-catalyzed ring opening of spirooxazolidine oxetanes with subsequent ring expansion of the oxazolidine (Scheme 9b). The cascade reaction is believed to involve indium-catalyzed Strecker reaction of the spirocyclic oxetanes with trimethylsilyl cyanide to afford oxetane nitriles. Lewis acid activation of the oxetanes promotes an intramolecular 6-exo cyclization, leading to the formation of densely functionalized...
morpholines and related heterocycles with excellent diastereoselectivities.

An efficient synthesis, involving enantioselective desymmetrization of oxetanes with amine nucleophiles, of tetrahydroisoquinolines bearing a C-4 stereocenter was developed by Sun et al. (Scheme 9b). This protocol was successfully applied to a formal synthesis of (+)-cyclocelabenzine. Moreover, this attractive transformation was extended to a multicomponent aza-Diels—Alder reaction that led to the stereoselective synthesis of complex bioactive polycyclic alkaloid-type compounds containing indoline, tetrahydroquinoline, and tetrahydroisoquinoline moieties.

Oxetane Oxocarbenium Ions: Generation and Transformations. In the last two decades, we have developed protocols for the preparation and exploitation of unusual oxetanes. In particular, we reported the first general approaches to 2-methyleneoxetanes and 1,5-dioxaspiro[3.2]hexanes. These two oxetane-containing systems demonstrated analogous reactivity in the generation of oxetane oxocarbenium ions when treated with suitable Lewis acids or electrophiles (Scheme 10). These oxocarbenium ions could be intercepted with nucleophiles, and the reaction outcome can be diverted to two distinct pathways, ring opening or 1,2-addition. While there have been several functionalization strategies for oxetanes, specifically at the C-3 position, in this section we report our work on the generation of oxetane oxocarbenium ions and their reactivity with nucleophiles via 1,2-addition. This constitutes an attractive method for C-2 functionalization of oxetanes.

We first exploited the generation of an oxetane oxocarbenium in an intramolecular iodoetherification of a 2-methyleneoxetane to provide the first synthesis of a [2.2.0]-fused ketal system (Scheme 11). In the same year, the generation of oxetane oxocarbenium ions from dioxaspirohexanes was first discovered in their reaction with DIBAL-H or Me₃Al. In these reactions, aluminum served as a Lewis acid, generating the oxetane oxocarbenium ions.
oxocarbenium ion; subsequent reaction with hydride or a methyl group provided 2-hydroxymethyloxetanes. Recognizing that this protocol offered a way to functionalize oxetanes at the C-2 position, the methodology was expanded to heteroatom nucleophiles, specifically azide and N-heteroaromatic bases.\textsuperscript{39,40} The C-2 functionalization of oxetanes with N-heteroaromatic bases appears to be correlated with the pK$_a$ of the nucleophile, with more acidic nucleophiles (pK$_a$ < 10) favoring 1,2-addition while more basic nucleophiles provided mainly ring-opened products.

The ability to generate and capture oxetane oxocarbenium ions from 2-methyleneoxetanes and dioxaspirohexanes has been exploited in the syntheses of C-2 functionalized oxetanes of biological importance (Scheme 11). epi-Oxetin was synthesized from an l-serine derived dioxaspirohexane, which underwent an aluminum-assisted 1,2-addition with hydride to furnish a 2-hydroxymethyloxetane as the key intermediate.\textsuperscript{41} Recently, we developed an F$^+$/mediated C-2 incorporation of nucleobases to 2-methyleneoxetanes to access oxetanocin-type frameworks.\textsuperscript{42} This method was used in the synthesis of the first psico-oxetanocin analogue of the powerful antiviral natural product, oxetanocin A.

In summary, oxetanes are versatile templates for the construction of synthetically valuable heterocyclic compounds. The approaches presented here have found broad applications in organic synthesis, particularly by expanding the medicinal chemist’s toolbox for the synthesis of heterocycles. The increasing number of reports on the preparation of oxetanes and the continued emergence of new transformations involving them suggest that the oxetane moiety will persist as an inspiration for future research in organic synthesis.

\section*{AUTHOR INFORMATION}

\textbf{Corresponding Author}

*E-mail: amy.howell@uconn.edu.

\textbf{Notes}

The authors declare no competing financial interest.

\textbf{Biographies}

Christian Malapit, a M.Sc. graduate of Ateneo de Manila University in the Philippines, joined the Howell group at the University of Connecticut in 2011. His graduate research focuses on the development of transition-metal-catalyzed expansion and opening of strained heterocycles. He is a recipient of a Boehringer Ingelheim Ph.D. Fellowship and spent a year at BI working with Jonathan Reeves on transnitrilation chemistry as part of his Ph.D. program.

After teaching high school, completing Ph.D. (University of Kentucky) and postdoctoral (Northwestern and University of Nottingham) studies, and working in industry (Glaxo in the UK), Amy Howell...
started her academic career at the University of Connecticut, where she has been since 1994. Her group is particularly interested in the synthesis and reactivity of unusual strained heterocycles and in glycolipids that activate NKT cells.

**REFERENCES**


