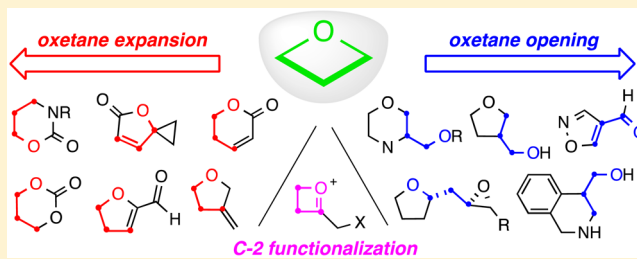


Recent Applications of Oxetanes in the Synthesis of Heterocyclic Compounds

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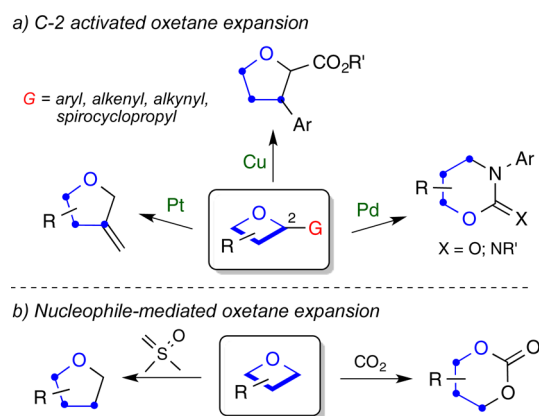
ABSTRACT: Oxetanes are valuable intermediates in organic synthesis, and strategic manipulations of this strained heterocycle continue to emerge. In this Synopsis, recent, distinct approaches to construct heterocyclic systems using oxetanes are described. These include ring expansion, ring opening, and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



Oxetanes are important motifs in some synthetic and natural products¹ and have received considerable attention as versatile elements in drug discovery.² 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 opening³ and functionalization^{2,4} 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-(phenyltetrahydrofuran-2-yl)-2-carboxylate under chiral Cu(II) catalysis (Scheme 2).⁵ This transformation was revisited by Katsuki⁶ and Fu,⁷ using a range of 2-aryloxetanes and chiral bipyridine 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.

Scheme 1. Selected Examples of (a) C-2-Activated and (b) Nucleophile-Mediated Oxetane Expansions in the Synthesis of Heterocycles



Katsuki showcased the utility of the overall insertion in the total syntheses of *trans*-(+)-whisky lactone^{6f} and (–)-avenaciolide,^{6b} where the C2 stabilization came from acetylenic moieties. Njardarson extended this approach to 2-vinyloxetanes reacting with carbenoids to form 3-vinyltetrahydrofurans.⁸

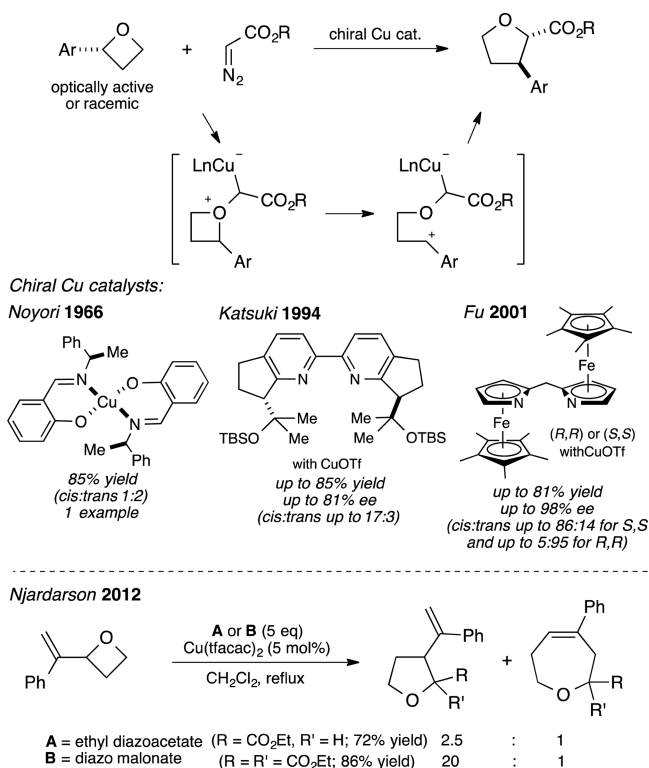
Alper and co-workers utilized vinyl group activation at C2 of oxetanes to access zwitterionic π -allyl-Pd species, which then reacted with heterocumulenes via a net cycloaddition to form 6-membered heterocycles (Scheme 3).⁹ This method was extended to fused-bicyclic vinyl oxetanes, resulting in the stereoselective synthesis of *cis*-fused bicyclic heterocycles.

More recently,¹⁰ 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

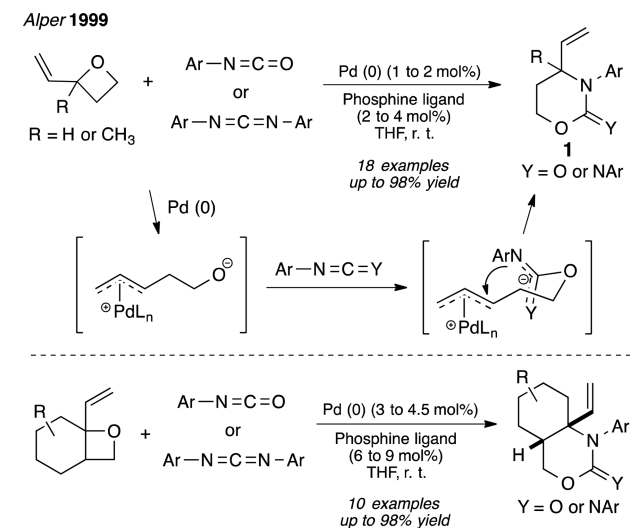
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Scheme 2. Cu(II)-Catalyzed Intermolecular Ring Expansions of Oxetanes with Carbenoids

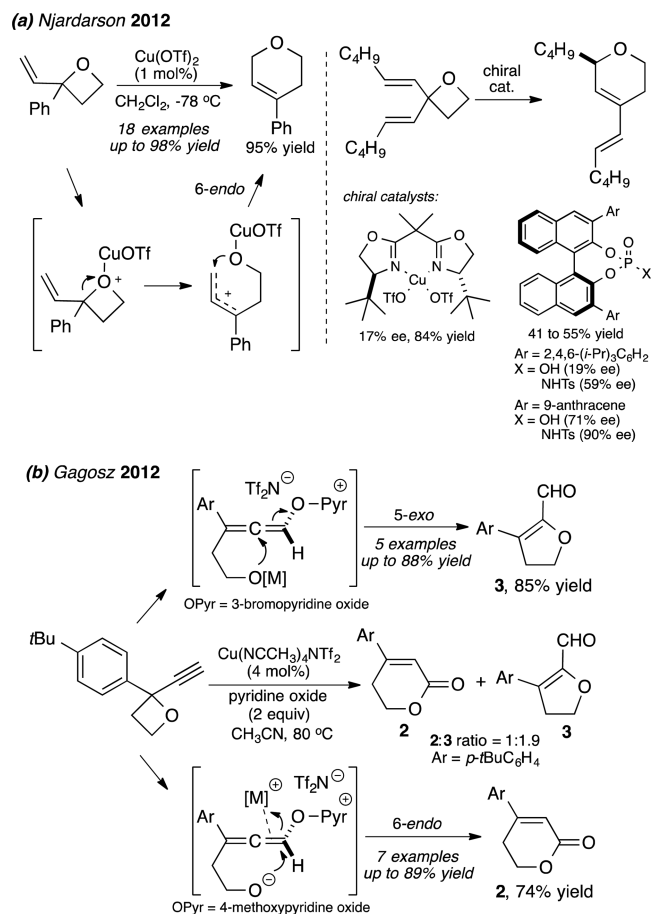


Scheme 3. Pd(0)-Catalyzed Intermolecular Ring Expansion of Vinyl Oxetanes



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 *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

Scheme 4. Cu(II)-Catalyzed Intramolecular Ring Expansion of (a) Vinyl and (b) Alkynyl Oxetanes

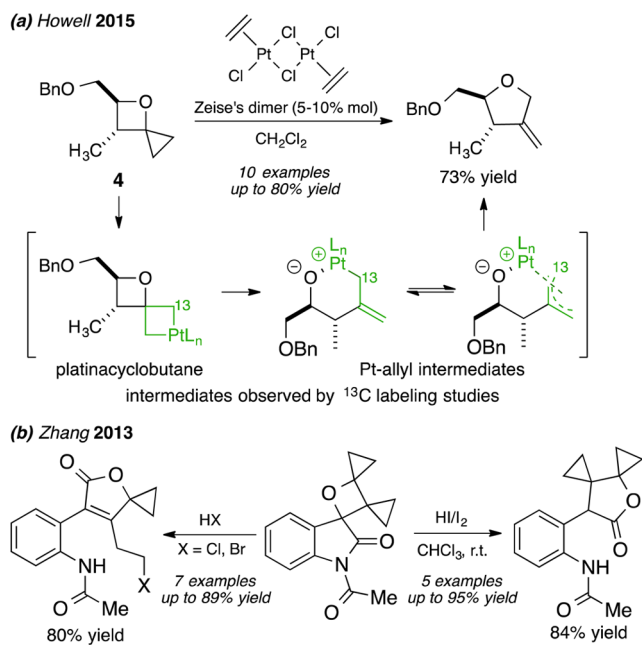


phosphoric acids/amides provided the dihydropyrans in up to 90% ee.

Gagosz and co-workers have cleverly used C2 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 allenylloxypyridinium 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 C2-spirocyclic cyclopropanes can function as useful activators in expansions and rearrangements 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 ¹³C-labeling, coupled with DEPT NMR, confirmed a regioselective insertion of Pt(II) into the distal methylene carbons of the cyclopropane to form a platinumacyclobutane opened, together with the oxetane ring, to form Pt-allyl

Scheme 5. Ring Expansions/Rearrangements of Oxaspirohexanes (Spirocyclopropyl Oxetanes): (a) with Pt Catalysis and (b) Acid-Mediated Reaction



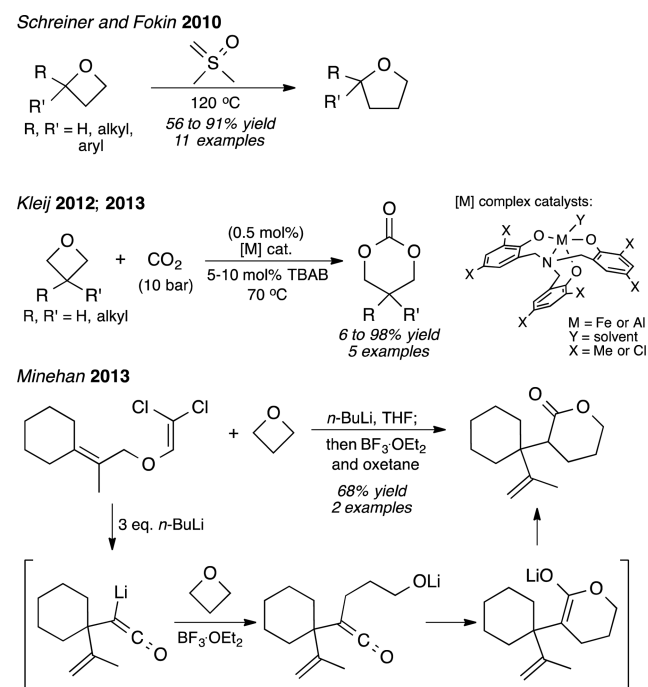
intermediates. Cyclization led to the formation of synthetically useful 3-methylenetetrahydrofurans. To our knowledge, this is the first alkoxy-substituted platinumacyclobutane that has been observed spectroscopically.

In another example of the utility of oxaspirohexane systems, Zhang reported acid-mediated ring expansions of spirocyclopropyl oxetanes (Scheme 5b).¹⁵ 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 S_N2-type ring opening, followed by ring closure with displacement of DMSO, providing C-2 substituted tetrahydrofurans.¹⁶ Kleij and co-workers developed aluminum and iron catalysts for the incorporation of carbon dioxide into oxetanes yielding 6-membered organic carbonates.¹⁷ 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.¹⁸ 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.¹⁹

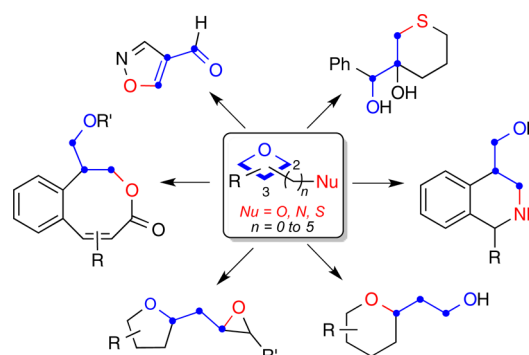
Overall, the ring-expansion reactions described above provide access to new, usefully functionalized heterocycles. In the cases where the oxetanes are readily accessible, the approaches represent efficient access to these systems. While the requirement for C-2 activation limits the scope of some of the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

Scheme 6. Capture of Ring-Opened Oxetanes To Provide Ring-Expanded Heterocycles



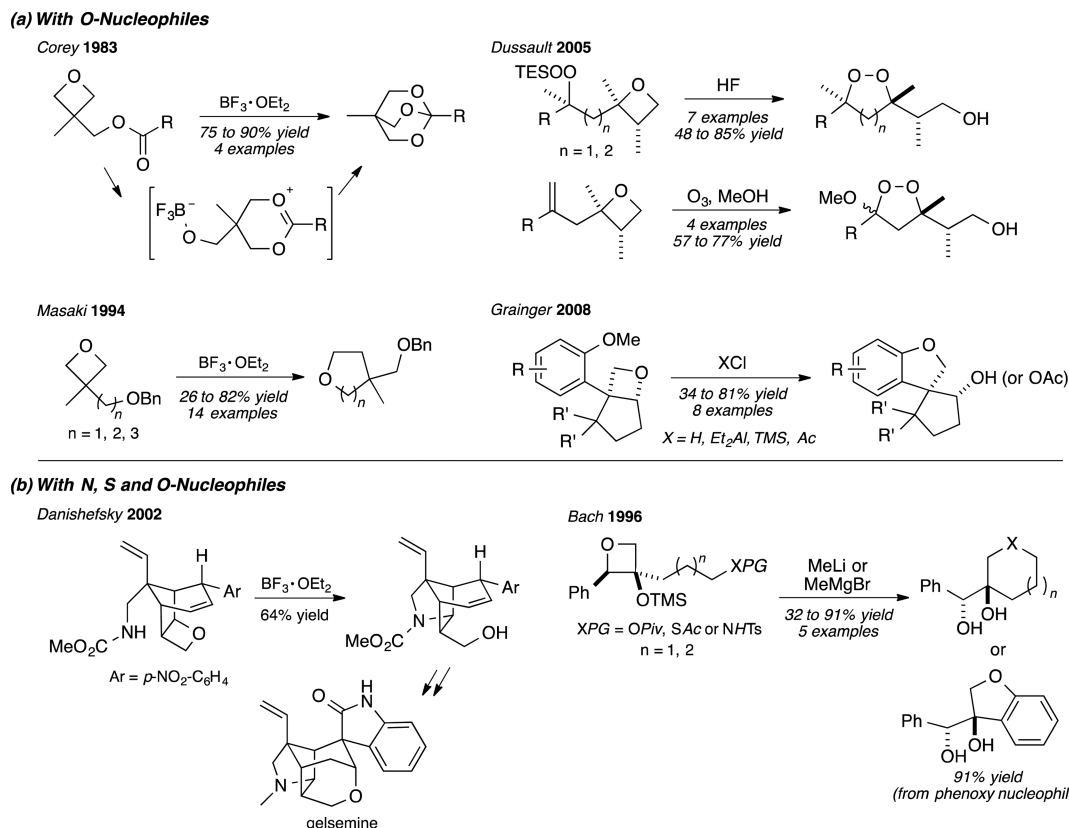
Oxetane Openings. The regio- and stereoselective ring opening of oxetanes with nucleophiles has been well established in organic synthesis as a route to functionalized alcohols. If the nucleophile is a heteroatom within the oxetane-containing molecule, a different heterocyclic system can be constructed in the process of opening the oxetane (Scheme 7). The most

Scheme 7. Selected Oxetane Opening To Construct New Heterocycles



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).²⁰ Subsequently, several other groups demonstrated the use of ethers or peroxides as nucleophiles in intramolecular opening of oxetanes, providing other oxygen-containing heterocycles. Masaki²¹ reported a Lewis-acid mediated process with an oxygen nucleophile, accompanied by transfer of ethereal benzylic and allylic groups, to access several cyclic ethers.²² A general protocol for stereoselective synthesis of 1,2-dioxolanes and 1,2-dioxanes was developed by

Scheme 8. Earlier Reports on Oxetane Opening for the Synthesis of Heterocycles



Dussault through cyclization of oxetane hydroperoxides.²³ Likewise, the Dussault group also found that ozonolysis in methanol of olefin-substituted oxetanes could generate hydroperoxyketal 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.²⁴

Danishefsky showcased an intramolecular oxetane opening strategy using a nitrogen nucleophile in the total synthesis of gelsemine (Scheme 8b).²⁵ Bach developed a base-mediated intramolecular oxetane opening with sulfur, nitrogen, or oxygen, including a phenoxide nucleophile.²⁶

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 enantio-enriched tetrahydrofurans and dihydrobenzofurans (Scheme 9a).²⁷ 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 attempt to extend this methodology to the preparation of optically active C-3 substituted tetrahydropyrans was promising but required longer reaction times. Oxetanes bearing a carbamate nucleophile component provided the corresponding pyrrolidine in good yields, unfortunately, with diminished enantioselectivity. Yadav established a stereospecific formation of tetrahydropyrans through protic acid mediated oxetane opening.²⁸ This was successfully applied to the synthesis of the C1–C17 fragment of salinomycin.

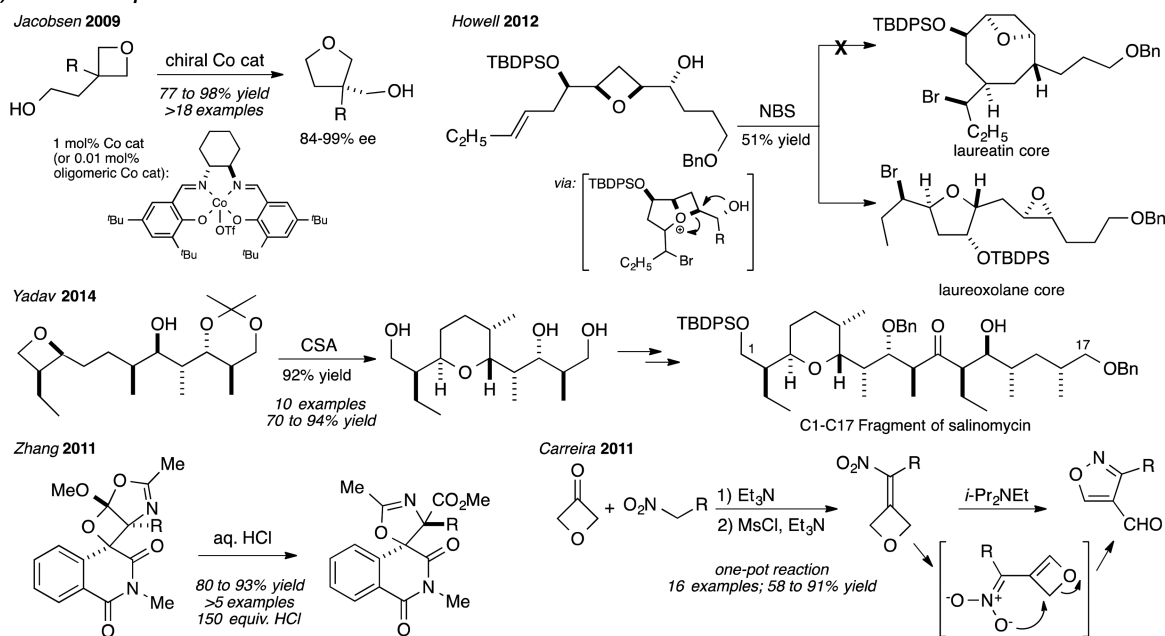
An unusual activation of an oxetane to reaction with an intramolecular OH was seen in our attempt to prepare the natural product, laureatin (Scheme 9a). An NBS-mediated ring opening/cyclization cascade of an oxetane alcohol gave an epoxytetrahydrofuran rather than the expected laureatin core.²⁹ The outcome 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 isoquinolinetriene with oxazoles (Scheme 9a).³⁰ Carreira developed a novel access to isoxazoles from a base mediated rearrangement of nitromethyleneoxetanes, generated in situ from nitroalkanes and oxetan-3-one.³¹ 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.

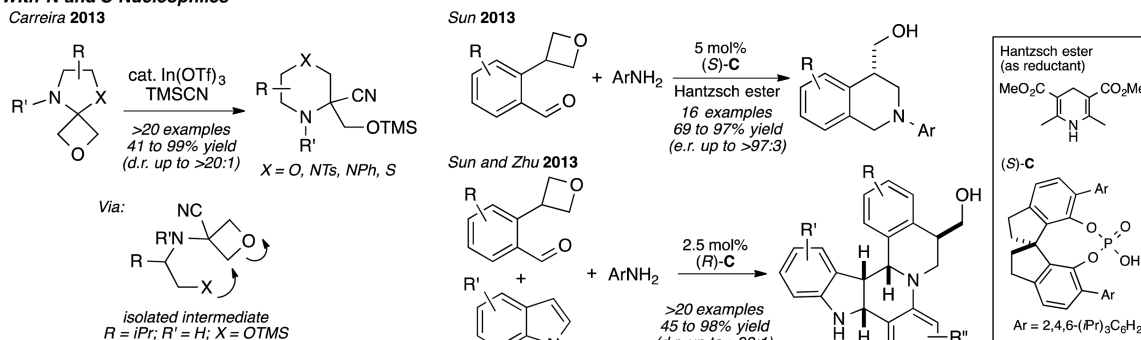
With their ongoing efforts in examining reactivity profiles of oxetanes derived from 3-oxetanones, Carreira and co-workers also developed a facile synthesis of highly functionalized morpholines, piperazines, and thiomorpholines by utilizing an indium-catalyzed ring opening of spirooxazolidine oxetanes with subsequent ring expansion of the oxazolidine (Scheme 9b).³² 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

Scheme 9. Recent Reports on Oxetane Opening for the Synthesis of Heterocycles

(a) With O-Nucleophiles



(b) With N and S-Nucleophiles

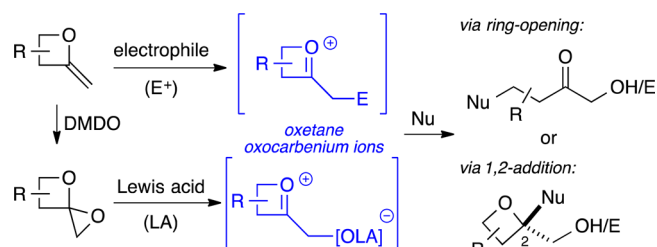


morpholines and related heterocycles with excellent diastereoselectivities.

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.³³ 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.³⁴

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-methyleneoxetanes³⁵ and 1,5-dioxaspiro[3.2]hexanes.³⁶ 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.^{29,35–42} While there have been several functionalization strategies for

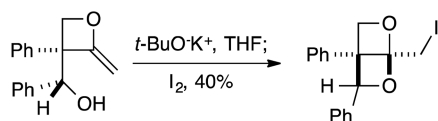
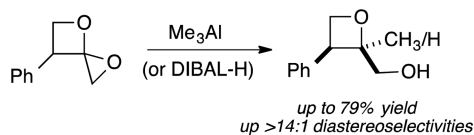
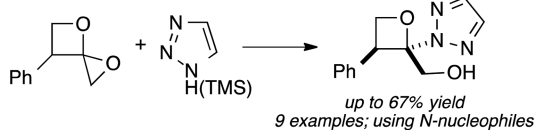
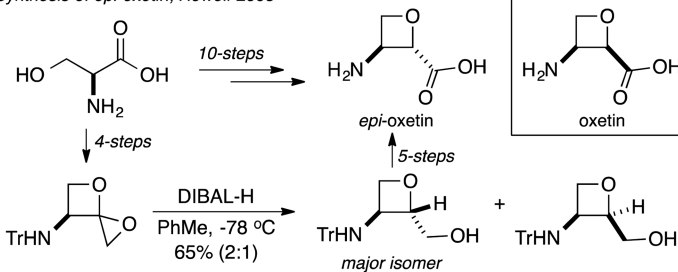
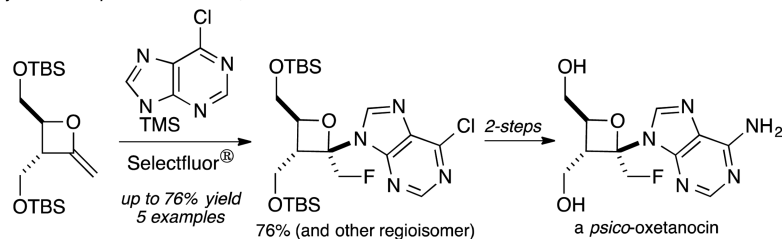
Scheme 10. Generation and Transformations of Oxetane Oxocarbenium Ions



oxetanes,^{2,4} 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).³⁸ In the same year, the generation of oxetane oxocarbenium ions from dioxaspirohexanes was first discovered in their reaction with DIBAL-H or Me₃Al.³⁶ In these reactions, aluminum served as a Lewis acid, generating the

Scheme 11. C-2 Functionalization via Oxetane Oxocarbenium Ions

With *O*-Nucleophiles; Howell 1999With *C* or *H*-Nucleophiles; Howell 1999With *N*-Nucleophiles; Howell 2003 and 2010Synthesis of *epi*-oxetin; Howell 2008Syntheses of *psico*-oxetanocins; Howell 2011

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.^{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.⁴¹ Recently, we developed an F^+ -mediated C-2 incorporation of nucleobases to 2-methyleneoxetanes to access oxetanocin-type frameworks.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.

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Notes

The authors declare no competing financial interest.

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 transnitration 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.

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