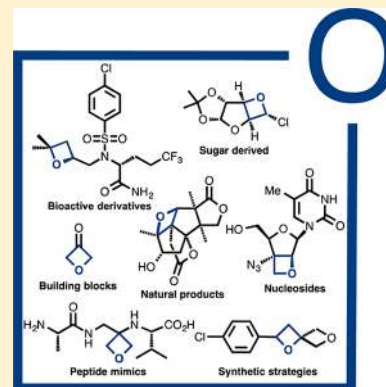


Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry

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ABSTRACT: The four-membered oxetane ring has been increasingly exploited for its contrasting behaviors: its influence on physicochemical properties as a stable motif in medicinal chemistry and its propensity to undergo ring-opening reactions as a synthetic intermediate. These applications have driven numerous studies into the synthesis of new oxetane derivatives. This review takes an overview of the literature for the synthesis of oxetane derivatives, concentrating on advances in the last five years up to the end of 2015. These methods are clustered by strategies for preparation of the ring and further derivatization of preformed oxetane-containing building blocks. Examples of the use of oxetanes in medicinal chemistry are reported, including a collation of oxetane derivatives appearing in recent patents for medicinal chemistry applications. Finally, examples of oxetane derivatives in ring-opening and ring-expansion reactions are described.



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1. INTRODUCTION

Oxetanes, as strained cyclic ethers, present a fascinating combination of stable motifs for medicinal chemistry and reactive intermediates for further synthesis. These features make them attractive motifs for an ever-increasing range of applications in the chemical sciences. In medicinal chemistry, oxetanes have received enormous interest as replacement groups for *gem*-dimethyl and carbonyl groups with improved

Received: April 28, 2016

physicochemical properties. The small, polar nature of the heterocycle has led to its incorporation as a pendant motif to improve “druglike” properties, in particular solubility, and also to offer intellectual property advantages. As a result, these units have been widely adopted in medicinal chemistry programs in recent years. These recent studies have relied on both established synthetic methods and development of numerous new methodologies for oxetane synthesis and incorporation. Accordingly, a number of novel methods have been developed to access oxetane-containing compounds. At the same time, there have been significant advances in utilizing the reactivity of oxetanes in the synthesis of complex molecules. The strain in the small ring facilitates opening with nucleophiles, rearrangements, and ring expansions. Here, we review and collate the synthetic methods and reactivity of oxetanes, as well as commenting on the relevance to medicinal chemistry programs. Advances up to late 2015 are included, concentrating on more recent developments but also detailing older work that still remains powerful in the synthesis of varied oxetane derivatives.

Section 2 will introduce structural features of the oxetane ring and properties that the ring can impart in a medicinal chemistry context. The following sections then examine oxetane synthesis through ring-closing approaches, with the cyclization step forming a C–O or C–C bond (section 3), and (formal) [2+2] cycloadditions forming both C–C and C–O bonds (section 4). Selected transformations of oxetane-containing products are discussed in each section to illustrate the stability of the ring to chemical transformations, as are selected applications of biologically active products. Section 5 examines strategies available for the incorporation of intact oxetane motifs, including the use of Carreira’s oxetan-3-one and other small oxetane-containing building blocks that maintain the small ring. This section also includes a survey of the use of these building blocks in medicinal chemistry applications, with selections covering primary literature and also patent literature. Section 6 continues the functionalization of intact oxetane derivatives through metalation. Section 7 focuses specifically on 2-*exo*-methylenioxetanes and their synthesis and functionalization, in both ring-opening reactions and methods that maintain the ring structure leading to functionalized oxetane derivatives. Section 8 reviews ring-opening and ring-expansion reactions of oxetanes, where the four-membered ring is modified to generate new structural types. Readers are also directed to other notable and complementary reviews incorporating varied aspects of oxetane chemistry from Carreira and co-workers,^{1,2} Abe,³ D’Auria and Racioppi,⁴ De Kimpe and co-workers,⁵ Mahal,⁶ Malapit and Howell,⁷ Sun and co-workers,⁸ and others.^{9–11} The extensive use of oxetane motifs in other fields, including polymer chemistry as a monomer^{12–18} and a cross-linker^{19,20} and, for example, in catalytic reaction with CO₂ to generate cyclic carbonates,^{21–27} is outside the scope of this review and will not be considered.^{28–30}

2. PROPERTIES AND NATURAL OCCURRENCE OF OXETANES AND THEIR INFLUENCE ON BIOLOGICALLY RELEVANT PHYSICOCHEMICAL PROPERTIES

2.1. Physical Properties of Oxetanes

Oxetane itself is a four-membered ring containing an oxygen atom with an inherent ring strain of 106 kJ·mol^{−1} [epoxides 112 kJ·mol^{−1}; tetrahydrofurans (THFs) 25 kJ·mol^{−1}].^{31,32} The ring adopts an essentially planar structure with a puckering angle of

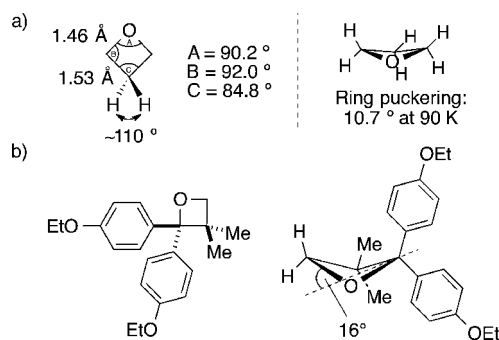


Figure 1. Structural properties of oxetane and puckering of the substituted oxetane ring in EDO.

only 8.7° at 140 K (10.7° at 90 K) as indicated in an X-ray crystal structure of the parent heterocycle (Figure 1a).^{33,34} The planar structure minimizes the strain in the ring, and due to the presence of the heteroatom, there are considerably fewer gauche interactions, which are reduced by puckering, than in cyclobutane (cf. 30° puckering for cyclobutane).³⁵

The introduction of substituents onto the oxetane ring can increase the unfavorable eclipsing interactions, resulting in a more puckered conformation. For example, X-ray crystallographic investigations showed that the puckering angle of the biodegradable insecticide EDO was 16° (Figure 1b).³⁶ The carbon–oxygen bond length in unsubstituted oxetane is 1.46 Å and the carbon–carbon bond length is 1.53 Å, which results in bond angles of 90.2° (C–O–C), 92.0° (C–C–O), and 84.8° (C–C–C), by X-ray at 90 K.³⁴ The strained C–O–C bond angle exposes the oxygen lone pair of electrons, allowing the oxetane to act as an excellent hydrogen-bond acceptor as well as Lewis base.³⁷ As required for hybridization in small rings, there is increased p-character to the bonds in the ring, and exocyclic substituents have increased bond angles. The increasing s-character of the oxygen lone pairs as the ring size of the cyclic ether decreases does not have a significant influence on the H-bonding ability until three-membered epoxides. Consequently, oxetanes form more effective H-bonds than other cyclic ethers.^{38,39} Similarly, oxetanes compete as H-bond acceptors with the majority of carbonyl functional groups (aliphatic ketones, aldehydes, and esters),^{40,41} with only amides providing better acceptors.^{42,43} These structural features are important for many of the advantageous properties of substituted oxetanes.

2.2. Oxetanes in Natural Products

The oxetane ring appears in relatively few natural product structures, but when it is present, there is important biological activity that is often reliant on the ring (Figure 2). Perhaps the most well-known example is paclitaxel, or Taxol, first isolated in 1971 from the stem bark of the western yew (*Taxus brevifolia*) and used in cancer chemotherapy.⁴⁴ Taxol acts by binding to microtubules and stabilizing them during cell division.⁴⁵ Computational studies concluded that the oxetane acted as a conformational lock, rigidifying the structure,⁴⁶ or alternatively as a hydrogen-bond acceptor.⁴⁵ Although lower activity was observed when the oxetane was replaced with related alternative ring structures,^{45,47,48} very recent studies have shown that the oxetane is not in fact essential for biological activity.⁴⁹ In the purported biosynthesis of taxol, cyclization occurs via an enzyme-mediated epoxy ester/oxetane ester rearrangement mechanism. Three separate mechanisms for this transformation have been proposed: a neutral-concerted

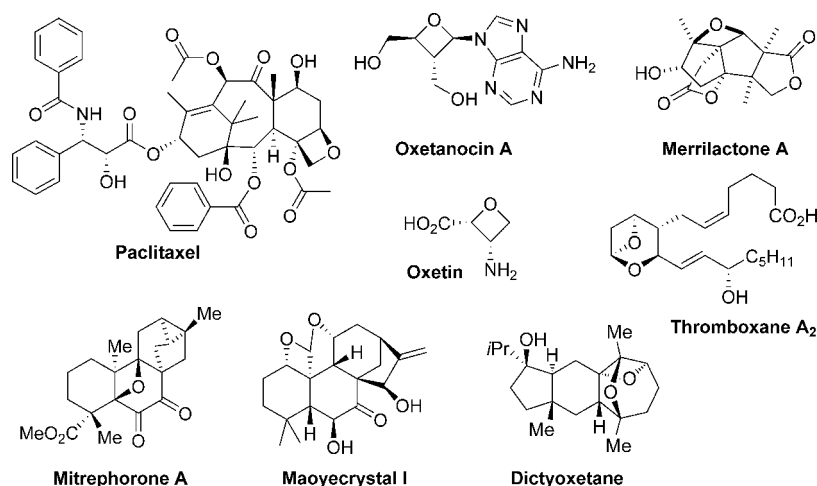


Figure 2. Oxetane-containing natural products.

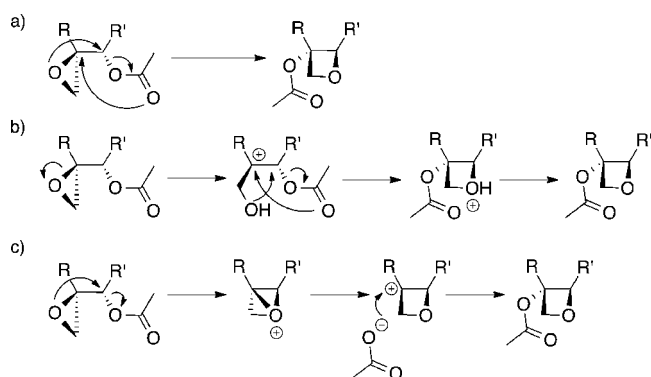


Figure 3. Three proposed pathways for biosynthesis of the oxetane ring of taxol.

pathway (Figure 3a),⁵⁰ an acid-catalyzed route (Figure 3b),⁵¹ and a dissociative pathway (Figure 3c).⁵² Computation studies by Willenbring and Tantillo⁵³ were unable to find evidence to conclusively distinguish among the three mechanisms.

Various other oxetane-containing compounds have been isolated from natural sources. Oxetanocin A was first isolated from the soil bacteria *Bacillus megaterium* and inhibits the *in vivo* replication of human immunodeficiency virus (HIV).⁵⁴ Oxetin was isolated from a broth of *Streptomyces* sp. OM-2317 and has antibacterial and herbicidal effects.⁵⁵ It was reported to inhibit *Bacillus subtilis* and *Piricularia oryzae* in minimal media, as well as showing herbicidal activity, inhibiting glutamine synthetase from spinach leaves. Both maoyecrystal I and mitrephorone A were shown to be cytotoxic.^{56,57} Thromboxane A₂ has prothrombotic properties, and the oxetane is very short-lived in the body due to the acetal structure.⁵⁸ Merrillactone A was first isolated in 2000 from the pericarps of the *Illicium merrillianum* plant and was shown to stimulate the growth of rat neurons.⁵⁹ Dictyoxetane is a marine diterpene isolated from the brown alga *Dictyota dichotome* whose biological properties are currently not understood.⁶⁰ This pentacyclic structure has been subject to a synthetic model study targeting the unusual tricyclic heterocyclic portion.⁶¹ Finally, bradyoxetin, produced by the soil bacterium *Bradyrhizobium japonicum*, has two pendant oxetane rings.⁶²

2.3. Oxetanes as Replacement Groups

In 2006, Carreira, Rogers-Evans and co-workers^{63–65} (Hofmann-La Roche) published a highly influential report on the use of 3,3-disubstituted oxetanes as replacement groups for *gem*-dimethyl groups in medicinal chemistry (Figure 4). *gem*-

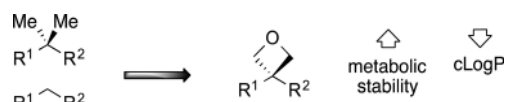


Figure 4. 3,3-Disubstituted oxetanes as replacement group for *gem*-dimethyl.

Dimethyl groups have commonly been used in medicinal chemistry to block metabolically vulnerable methylene sites. However, their introduction results in an increase in lipophilicity, which itself may have adverse effects on the pharmacokinetic properties of a compound.⁶⁶ This work exploited the similar molecular volume of the oxetane and *gem*-dimethyl groups^{67,68} to propose the oxetane motif as a considerably more polar equivalent of a *gem*-dimethyl group with the same spacial arrangement. The replacement afforded a reduction in lipophilicity (cLogP), which can give an associated reduction in metabolic liability.

To probe the effect of the replacement of a *gem*-dimethyl unit with an oxetane, the *t*-butyl group of a model compound, **1**, was replaced with a methyl-substituted oxetane, **2** (Figure 5).⁶³ The parent compound chosen was both lipophilic and amphiphilic, but it became considerably more polar and more soluble upon introduction of oxetane. In addition, the metabolic stability was improved as indicated by reduced intrinsic clearance rates (CL_{int}; microliters per minute per

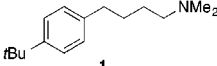
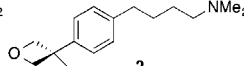
	Parent compound	Addition of the oxetane motif
		
Lipophilicity logD (logP)	2.5 (5.0)	0.8 (3.3)
Solubility (μg mL ⁻¹)	< 4	4400
hCL _{int} (min ⁻¹ mg ⁻¹ μL)	16	0
mCL _{int} (min ⁻¹ mg ⁻¹ μL)	420	43

Figure 5. Effects of replacing a *gem*-dimethyl group with oxetane.

milligram) measured in human (h) and mouse (m) liver microsomes. Oxetane-containing compound **2** was also shown to be have reduced hERG (human ether-a-go-go-related gene) inhibition (hERG IC₅₀ 35 μ M for **2** vs 7.5 μ M for **1**) due to the reduction in lipophilicity.^{63,65}

The strong σ -electron-withdrawing properties of the oxetane ring were shown to attenuate the basicity of nearby amines. Through an “oxetane scan”, the greatest effects were seen when the oxetane was in α -position to the amine, but interestingly, a decrease of 0.3 pK_a unit was still observed when the oxetane was in δ -position to the amine compared to the parent compound (Figure 6). The chemical stability of these compounds, including **2**–**6**, was shown to be high in aqueous buffers over the pH range 1–10 for 2 h at 37 °C.⁶³

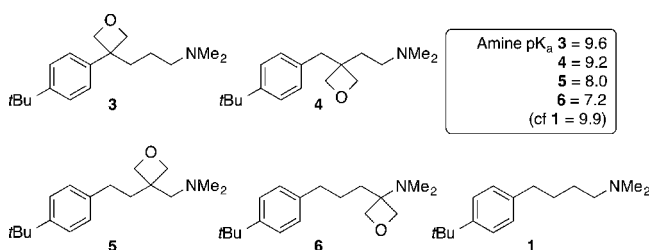


Figure 6. Effect of oxetane motif on amine basicity.

In a subsequent series of papers, Carreira and co-workers^{1,2,65,69} investigated various properties of oxetanes as replacement groups, resulting in a number of advantageous changes. In particular, the use of oxetanes as replacements for carbonyl groups has been of considerable interest due to similar dipoles and H-bonding properties (Figure 7).⁶⁹ Whereas



Figure 7. Comparison between carbonyl and oxetane functional groups, representing similar arrangement of lone pairs and change in size.

carbonyl compounds (aldehydes, ketones, and esters) are vulnerable to enzymatic attack and α -deprotonation/epimerization of stereogenic centers, oxetane derivatives are stable to

both of these concerns. As a replacement, the main difference between an oxetane and carbonyl motif is the length of the group. Fujishima et al.^{70,71} employed this strategy and the increased size of the oxetane to improve the binding affinity of 1,25-dihydroxyvitamin D₃ analogues for bovine thymus vitamin D receptor.

Carreira and co-workers⁶⁹ studied the physicochemical and biological properties of various matched pairs of oxetane-containing spirocyclic compounds and their corresponding carbonyl-containing heterocycle derivatives (Table 1). In both the pyrrolidine and piperidine derivative pairs, **7/8** and **9/10**, incorporation of the oxetane ring decreased solubility. However, opposing effects on lipophilicity were observed. On the other hand, metabolic stability was considerably improved for oxetane spirocycles **8** and **10** compared to **7** and **9** in terms of the intrinsic clearance rate.

Morpholine rings are often incorporated into drug scaffolds to improve aqueous solubility, but they can also undergo undesirable oxidative metabolism. Due to similar structural properties, the spirocyclic oxetane motif **12** was suggested as a morpholine replacement. When compared to morpholine **11**, spirocyclic oxetane **12** had increased aqueous solubility and decreased lipophilicity while remaining metabolically stable toward oxidation (Table 1). In recent years, Carreira and co-workers have also reported spirocyclic structures as structural analogues of heterocycles, including piperazine⁷² as well as piperidine and thiomorpholine analogues,⁷³ and other spirocyclic small-ring heterocyclic systems targeting drug discovery.^{74–78}

In 2008, Duncton et al.⁷⁹ examined the stability of a series of oxetane derivatives on incubation with human liver microsomes in the presence of glutathione and nicotinaide adenine dinucleotide phosphate (NADPH), to screen for reactive metabolites (Figure 8). Glutathione conjugates were observed for fewer than half the derivatives tested, which was interpreted as providing evidence that the oxetan-3-yl chemotype could be attractive for medicinal chemistry.

In 2013, Carreira and co-workers⁸⁰ explored the effects of structural modification of thalidomide and lenalidomide. Infamously, while the *R*-isomer of thalidomide functions as an anti-emetic and sedative, the *S*-isomer is a teratogen. Crucially, these readily interconvert under physiological conditions. When the imide C=O was replaced by an oxetane, an increase in solubility and decrease in lipophilicity, and no

Table 1. Physicochemical and Biological Properties Demonstrating the Effects of Replacing a Carbonyl Group with an Oxetane Ring^a

R =						
	7	8	9	10	11	12
Solubility (μ g mL ⁻¹)	4000	1400	4100	730	8000	24000
Lipophilicity logD (logP)	1.2 (1.6)	1.0 (2.0)	-0.1 (-0.1)	0.7 (1.5)	1.5 (1.6)	0.5 (1.2)
hCL _{int} (min ⁻¹ mg ⁻¹ μ L) ^a	120	6	100	2	9	3
mCL _{int} (min ⁻¹ mg ⁻¹ μ L) ^a	88	22	580	27	8	7
pK _a	7.5	8.3	6.1	8.1	7.0	8.0

^aIntrinsic clearance rates were measured in human (h) and mouse (m) liver microsomes.

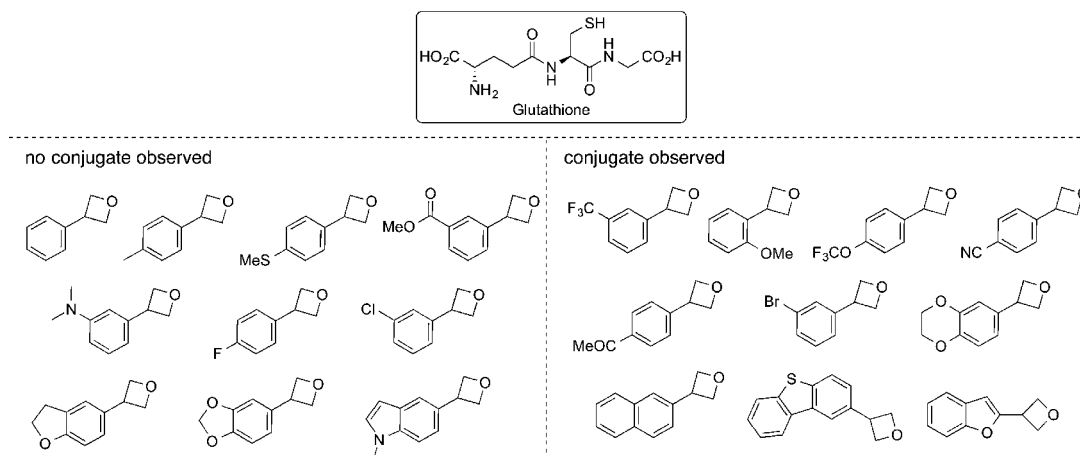


Figure 8. Examples of oxetanes tested with human liver microsomes and glutathione.

Table 2. Comparison of Physicochemical Properties of Thalidomide and Oxetanthalidomide

	Thalidomide	Oxetanthalidomide 13
Solubility ($\mu\text{g mL}^{-1}$)	29	78
Lipophilicity (logD)	0.24	0.00

unfavorable difference in the intrinsic clearance rates in human microsomes, was observed (Table 2).⁸⁰ Oxetanthalidomide **13** was shown to be configurationally stable to racemization in human blood plasma after an incubation period of 5 h, thereby showing that oxetanes as replacements of carbonyl groups can alleviate epimerization at adjacent stereocenters.

Dowling et al.⁸¹ at AstraZeneca compared 3-aminooxetane motifs with other small rings through a series of matched pairs (Figure 9). It was found that introduction of oxetane lowered

	R	logD			
X	Y				
Cl	H	2.2		3.1	nd
Me	H	1.6		2.4	2.9
Me	F	1.5		2.3	3.0
cPr	H	2.2		2.8	nd
cPr	F	2.1		3.0	nd

Figure 9. Matched-pair analysis of logD for 5-anilinopyrazolo[1,5-a]pyrimidine inhibitors of CK2 kinase.

logD by ~ 0.8 unit in comparison to aminocyclopropane and aminocyclobutane derivatives. In addition, the oxetane derivative significantly decreased the fraction of compound bound by human plasma proteins, increased metabolic stability (rat liver microsome and hepatocyte), and reduced hERG ion channel binding.

While 3-substituted oxetanes have now been relatively well explored in this manner and have been exploited accordingly (see section 5), there remain fewer examples and little data on other oxetane substitution patterns being examined in any detail in this context. The most notable study that compared oxetane substitution patterns, from Stepan et al.⁸² (Pfizer), studied the effect of different carbocyclic and oxygen heterocyclic derivatives on a series of N-substituted arylsulfonamides. Progression from carbocyclic rings to six- and five-membered oxygen heterocycles and eventually oxetane rings gave an improvement in metabolic stability without reduction in potency (Figure 10). Across THF derivatives, the 3-substituted example was more stable to human liver microsomes (HLM) than the 2-substituted derivative; similarly, the 3-monosubstituted oxetane was more stable than the 2-monosubstituted derivative. Metabolite identification studies, which initially identified N-alkyl substituents as metabolically labile, were able to identify sites of oxidative metabolism. For the 2-monosubstituted oxetane derivative, the compound underwent ring scission, forming hydroxy acid and diol metabolites. For the 3-monosubstituted oxetane derivative, the major metabolic route was oxidation of the bridging methylene carbon leading to N-dealkylation. Incorporation of *gem*-dimethyl substitution at the oxetane 4-position gave the most stable derivative (CL_{int} $25.9 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$), whereas a *gem*-dimethyl group at the 3-position afforded a considerably

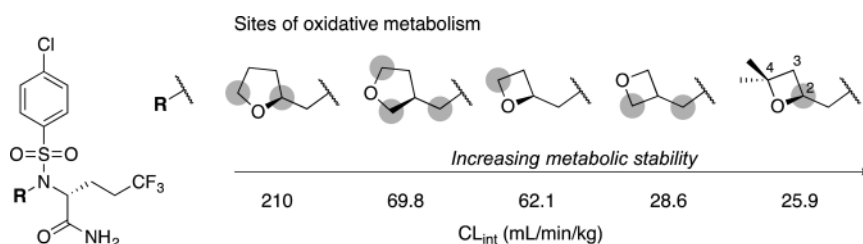


Figure 10. Comparison of metabolic stability of N-substituted arylsulfonamides. $\text{CL}_{\text{int,app}}$ is total intrinsic clearance obtained from scaling in vitro HLM half-lives.

less stable example ($CL_{int} > 293 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$). This study concluded that introduction of an oxetane could increase the overall drug likeness of molecules. Further studies examining oxidative metabolism showed this was largely due to CYP3A4 and that metabolic stability was directly linked to intrinsic lipophilicity.^{83,84} As such, oxetane derivatives benefited from their increased polarity compared to other cyclic ethers.

Bull and co-workers⁸⁵ have reported studies into the chemical and metabolic stability of 2-sulfonyloxetanes, which were designed as novel fragments for fragment-based drug discovery. Selected compounds were shown to be stable across the pH range 1–10, with half-lives in the region of 4–5 days at 25 °C. Similarly, the intrinsic clearance of 2-(2-pyridylsulfonyl)-oxetane was investigated in rat hepatocytes and shown not to present a metabolic liability. Oxetane δ -amino acid scaffolds, synthesized by Wessel and co-workers^{86–88} at Roche, were used to generate an oxetane-based library of oxadiazoles and triazoles.⁸⁹ Typical physicochemical properties were calculated for the oxetane library, and found to be within desirable ranges for medicinal chemistry (Figure 11). Metabolic properties, in

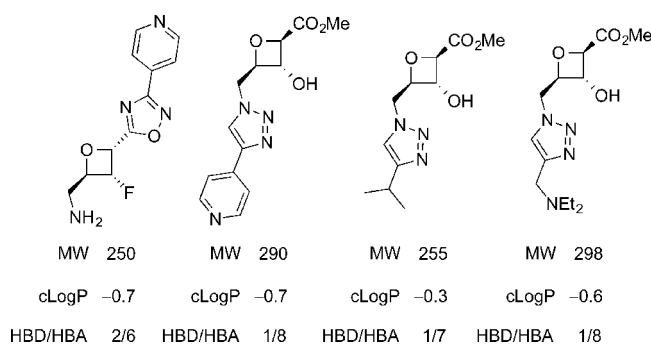


Figure 11. Examples from Wessel's oxetane library.

particular the oxetane derivatives' susceptibility toward degradation in human and mouse microsomes, were evaluated for a selection of substrates. All oxadiazoles tested displayed medium to low clearance in either human or mouse microsomes.

Wipf and co-workers^{90,91} recently developed an oxetane-containing neutral solubilizing group by adapting an oxetanyl dimethyl sulfoxide (DMSO) derivative that had proved effective as an additive to enhance aqueous solubility of small organic molecules. The oxetanyl sulfoxide motif was incorporated into poorly soluble drugs or drug candidates, particularly those containing an ionizable group (Figure 12).⁹⁰ For example, carboxylic acids were transformed into oxetanyl sulfoxide ester derivatives, and amines, used as the hydrochloride salt to improve solubility, were converted into the

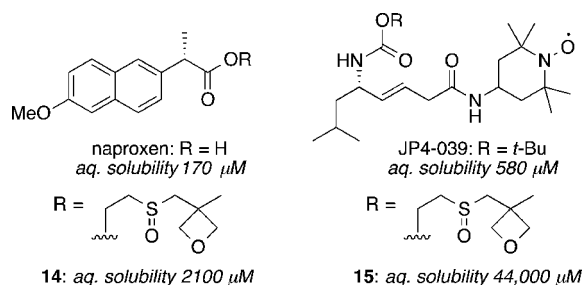


Figure 12. Wipf's oxetane-containing neutral solubilizing group.

corresponding oxetanyl sulfoxide carbamates. For a naproxen derivative, oxetanyl sulfoxide derivative 14 showed a >10-fold increase in solubility and also a significant increase in cell permeability. A similar increase in solubility was achieved by converting free amines to oxetanyl sulfonyl carbamates. A bioactive mitochondrial-targeted nitroxide, JP4-039, currently in development, saw a very large (76-fold) solubility increase when the *t*-butyl carbamate was converted into oxetanyl sulfoxide derivative 15.

These studies and the presence of oxetanes in biologically active compounds have established the oxetane motif as an intriguing structure in medicinal chemistry. Introduction of an oxetane can beneficially influence solubility, metabolic stability, and lipophilicity of a compound as well as influence the basicity of proximal amines. The small polar core may provide the possibility to increase steric bulk without increasing lipophilicity.⁶³ As a result of these desirable properties, oxetanes have recently received significant interest from the pharmaceutical industry, often being employed as bioisosteres and to improve the physicochemical properties of druglike compounds (see section 5 particularly).^{92–94} Recent trends in medicinal chemistry have sought to incorporate motifs that are more sp^3 -rich, that reduce planarity and improve solubility and other physicochemical properties, without a significant increase in molecular weight;^{95–97} the small, polar oxetane motif may offer opportunities toward these goals (this section and section 5). The defined three-dimensional "scaffolding" properties of oxetanes have been exploited as sugar mimics (sections 3.1.4 and 7), and oxetanes have been investigated as amide replacements in unnatural peptides (section 3.1.2 and section 5.1). The subsequent sections will cover the synthesis of varied oxetane derivatives, with examples of the exploitation of the property changes brought about through oxetane incorporation, and also the reactivity of oxetane derivatives.

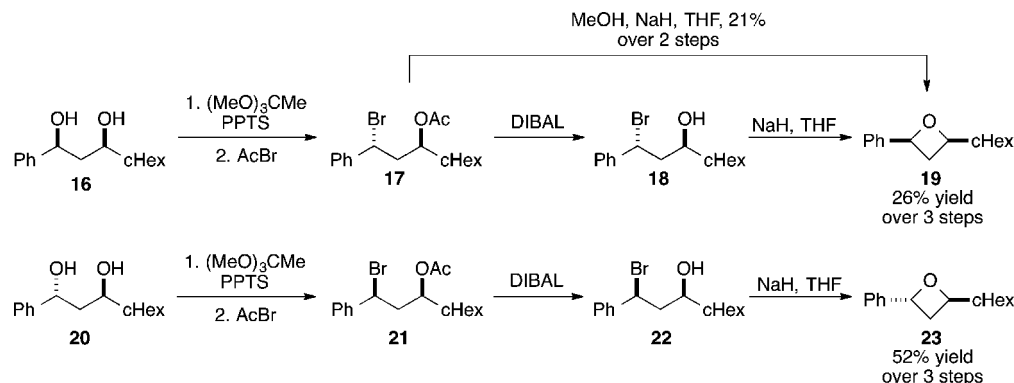
3. SYNTHESIS OF OXETANE DERIVATIVES BY INTRAMOLECULAR CYCLIZATION

The inherent ring strain in oxetane products makes cyclization a fundamental synthetic challenge, and the kinetics of cyclization to form four-membered saturated cyclic ethers are significantly slower than for three-, five-, and six-membered analogues.⁹⁸ Hence anions and good leaving groups are commonly required to achieve acceptable yields for the cyclization of functionalized acyclic precursors to oxetane derivatives. The most common disconnection forms the C–O bond through an intramolecular etherification reaction, which has been achieved by several approaches (section 3.1), complemented by few but increasing C–C bond-forming methods (section 3.2).

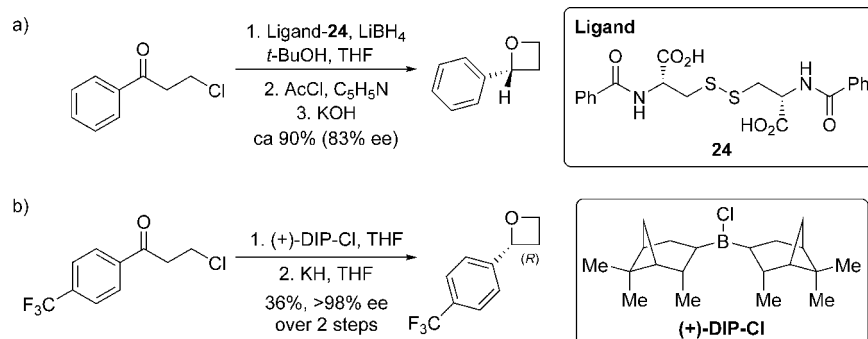
3.1. Cyclization through C–O Bond Formation

3.1.1. Intramolecular Etherification. Williamson etherification describes a general approach to ether synthesis by a base-mediated nucleophilic substitution reaction between an alcohol and an aliphatic carbon center in a 1,3-relationship for oxetane synthesis. Intramolecular cyclization generally provides the desired oxetane products; however, the yields can be modest due to undesirable side reactions, such as Grob fragmentation of the halo-alkoxide into an aldehyde and an alkene.^{99,100} Consequently, intramolecular Williamson etherification as a method for oxetane synthesis is rather substrate-dependent. This approach was first used for the synthesis of oxetane in 1878 by Reboul¹⁰¹ and remains most commonly

Scheme 1. Stereocontrolled Synthesis of Oxetanes 19 and 23 from the Corresponding Diols



Scheme 2. Asymmetric Synthesis of 2-Aryloxetanes by Use of a Chiral Catalyst



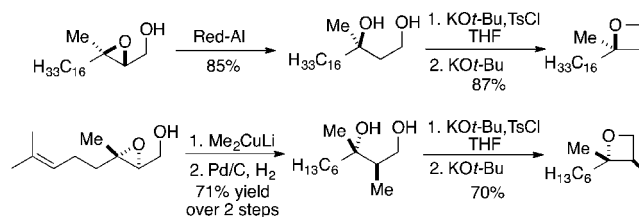
employed in the synthesis of complex oxetane-containing structures.^{102–105}

Nelson and co-workers^{106,107} reported a stereocontrolled synthesis of 2,4-substituted oxetanes from 1,3-diols (Scheme 1). The syn- and anti-diols **16** and **20** were synthesized from the same aldol precursor by stereoselective reduction.^{108,109} Selective synthesis of acetoxybromides **17** and **21** from the 1,3-diols was achieved with inversion of stereochemistry by conversion to the ortho esters followed by treatment with acetyl bromide. The required 1-hydroxy-3-bromo relationship present in intermediates **18** and **22** was established by use of diisobutylaluminum hydride (DIBAL) to cleave the acetyl group. Intramolecular cyclization to oxetanes **19** and **23** was then achieved with complete inversion of stereochemistry by use of sodium hydride in THF, resulting in overall retention of stereochemistry (through double inversion at the benzylic center) over three steps from the 1,3-diol. Interestingly, with a methyl in the 3-position of the oxetane product, a mixture of diastereoisomers was observed, which was speculated to be due to formation of a benzylic cation (not shown). A one-pot procedure for conversion of **17** to **19** was also developed, removing the need for DIBAL reduction, by addition of 1 equiv of MeOH and excess base.

An important enantioselective synthesis of oxetanes was reported in 1986 by Soai et al.¹¹⁰ Three examples of enantioenriched 2-aryl-substituted oxetanes were prepared through enantioselective reduction of β -halo ketones followed by Williamson ether cyclization promoted by KOH. Enantiomeric excesses of 79–89% were achieved by enantioselective reduction with a chiral reducing catalyst, generated in situ from lithium borohydride and chiral ligand **24**. Acetylation followed by subsequent ring closure afforded oxetanes without racemization (Scheme 2a).

More recently, Lo and Fu¹¹¹ demonstrated the preparation of enantioenriched oxetanes by the same approach from enantioenriched γ -chlorohydrins. These were, in turn, synthesized from β -chloroketones via an asymmetric reduction with (+)-B-chlorodiisopinocampheylborane [(+)-DIP-Cl; Scheme 2b].¹¹² The cyclization used KH, and while the yield was moderate, the enantiomeric excess (ee) was retained. Dussault et al.¹¹³ reported the preparation of enantioenriched oxetanes via cyclodehydration of enantioenriched 1,3-diols, generated from 2,3-epoxy alcohols by ring opening with sodium bis(2-methoxyethoxy)aluminum dihydride (RedAl) or dimethyl cuprate (Scheme 3). The use of KOtBu in THF for both monotosylation and cyclization gave the oxetanes in high yield, either as a one-pot reaction or through isolation of the monotosylate.

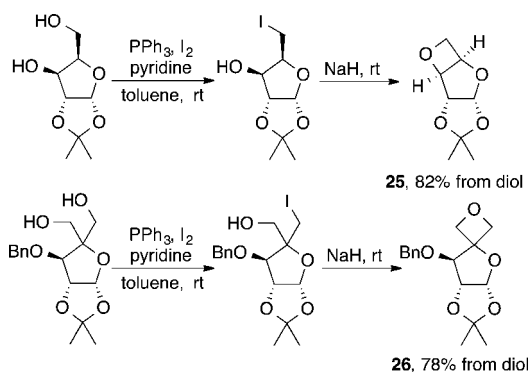
Scheme 3. Stereocontrolled Synthesis of Oxetanes from Epoxy Alcohols



In 2006, Mandal and co-workers¹¹⁴ reported one-pot synthesis of a variety of cyclic ethers, including oxetanes, using a Williamson etherification protocol. Starting from the desired diol, conversion of the primary alcohol to the iodide through an Appel reaction, followed by treatment with base, generated oxetanes **25** and **26** in 82% and 78% yield,

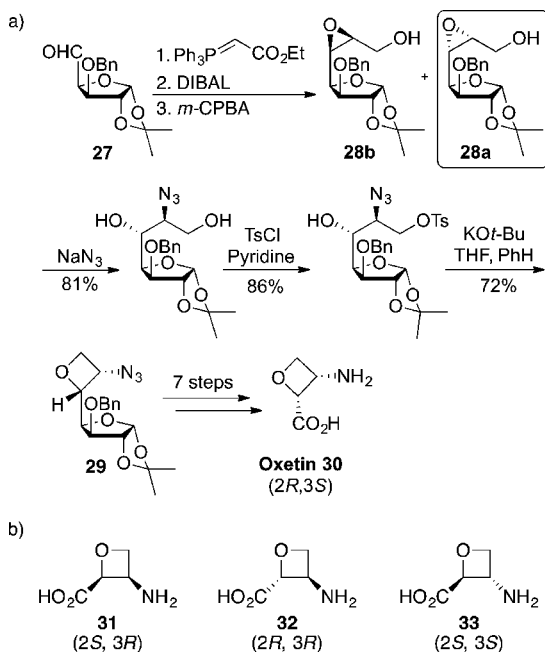
respectively (Scheme 4). [See sections 3.1.3 and 3.1.4 for oxetane-containing sugar derivatives and nucleoside analogues.]

Scheme 4. Synthesis of Oxetanes 25 and 26 through an Iodination–Williamson Etherification Pathway



The first synthesis of oxetin employed a traditional Williamson etherification with a tosylate leaving group to give the oxetane ring motif with the desired stereochemistry. Omura and co-workers¹¹⁵ synthesized the natural product and its three stereoisomers, using a sugar as a chiral auxiliary (Scheme 5a).

Scheme 5. (a) Synthesis of the Natural Product Oxetin from D-Glucose and (b) Unnatural Stereoisomers

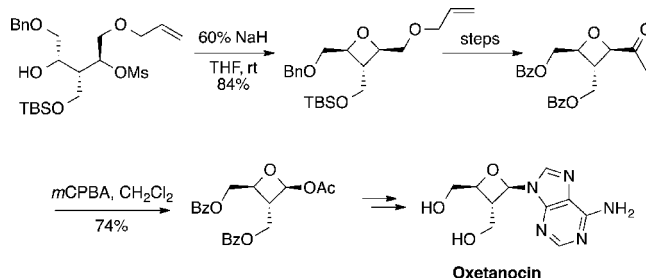


From aldehyde 27,¹¹⁶ a Wittig reaction afforded both cis- and trans-alkenes with poor selectivity (1.3:1 cis/trans), but they could be separated by chromatography. Reduction of the ester moiety with DIBAL accessed both allylic alcohols in good yields, and epoxidation of the cis-allylic alcohol with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave both possible stereoisomers of epoxide 28a/b. Regio- and stereoselective ring opening of epoxide 28a with NaN₃ afforded a single product with an excellent 81% yield. Selective tosylation of the primary alcohol, followed by Williamson etherification with KO^tBu, afforded oxetane 29 in good yield. Functional group manipulation afforded the natural product 30, which was

purified by ion-exchange chromatography. The remaining three stereoisomers 31–33 (Scheme 5b) were all prepared by the same synthetic route. Subsequently, all four stereoisomers of oxetin were tested against *B. subtilis*, but only the natural product oxetin 30 showed any activity.

Synthesis of oxetanocin was achieved by Yamamura and co-workers¹¹⁷ by use of Williamson etherification for the oxetane-forming step (Scheme 6). A sodium hydride-mediated

Scheme 6. Synthesis of Oxetanocin by Use of Williamson Etherification for the Key Cyclization Step



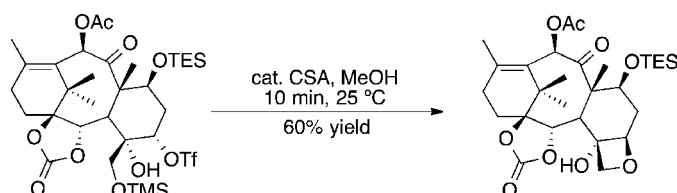
cyclization was utilized to synthesize the oxetane scaffold of oxetanocin in a good yield of 84% with a mesylate leaving group. Interestingly, the 2-hydroxymethyl substituent could be replaced at C2 with adenine over a sequence of steps involving conversion to the methyl ketone and Baeyer–Villiger oxidation to form the 2-acetate derivative,¹¹⁸ followed by displacement with protected adenine.

Total syntheses of taxol have primarily formed the oxetane ring midway through the sequence by an intramolecular Williamson etherification (Scheme 7).^{119–129} The majority of total syntheses use base-mediated approaches for formation of the oxetane on similar intermediates, with the leaving group commonly being either a mesylate, triflate, or halide. Interestingly, mild acidic conditions with catalytic camphorsulfonic acid (CSA) enabled oxetane formation in the sequence of Nicolaou et al.,¹²¹ delivering the desired oxetane in just 10 min. The intermediate of Danishefsky et al.¹²⁷ differed considerably as the oxetane was introduced in step 13 of 49, considerably earlier than, for example, in the work of Nicolaou et al.¹²¹ (step 31 of 37) or in the total synthesis of Wender et al.¹¹⁹ (step 40 of 44). Danishefsky stated that this strategy would be important for an analogue program. Treatment with ethylene glycol at reflux allowed the cyclization to occur, and it was speculated by Danishefsky et al.¹²⁷ that this transformation involved a hypervalent silyl ether to trigger the displacement of the required triflate. Wender et al.¹¹⁹ and Kuwajima and co-workers¹²³ both utilized a halide leaving group, which allowed conversion to the oxetane in good yields of 95% and 86%, respectively, in a single step. A base-mediated cyclization step with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is a common and enduring approach, with Holton et al. (1994),^{125,126} Kuwajima and co-workers (2000),¹²³ Takahashi and co-workers (2006),¹²⁰ and Nakada and co-workers (2015)¹²⁹ all using closely related conditions from very similar intermediates (for Nakada's recent example, see Scheme 7). In all cases the proximity of the required leaving group to the primary alcohol allowed the etherification reaction to proceed in good yield under a variety of conditions. Various synthetic studies have been reported on taxol mimics.^{130–132}

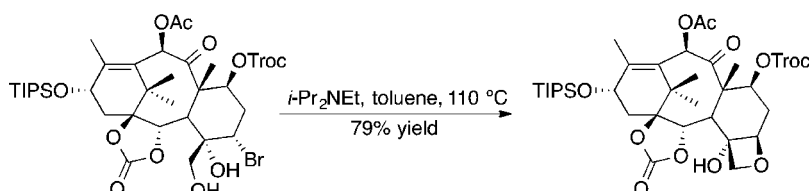
In 2009, Fan and co-workers¹³³ reported oxidative cyclization of malonate Michael adducts with chalcones to selectively

Scheme 7. Selected Examples of the Oxetane-Forming Step in Taxol Total Syntheses

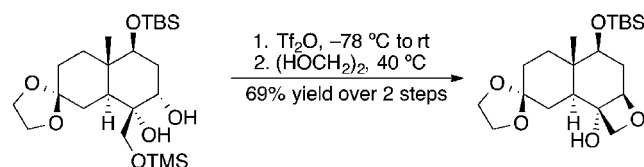
Nicolaou, 1994



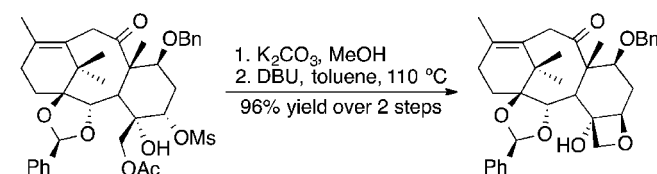
Wender, 1997



Danishefsky, 1996

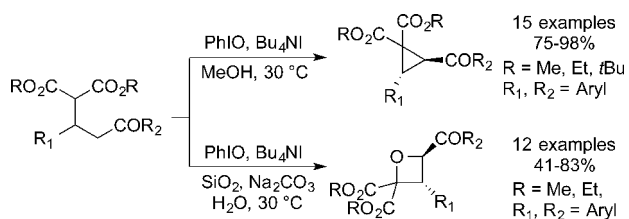


Nakada, 2015



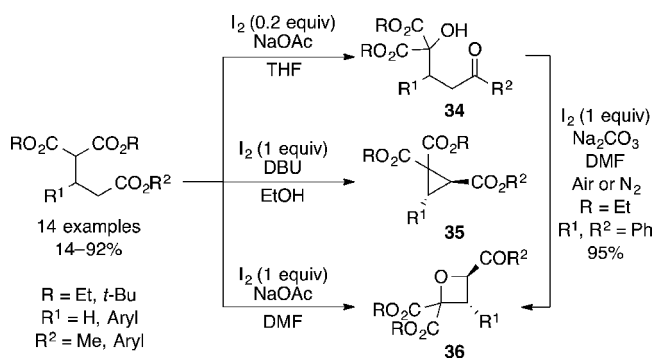
access cyclopropanes and oxetane derivatives with high diastereoselectivity (Scheme 8). Cyclization was observed

Scheme 8. Solvent-Controlled Synthesis of Cyclopropanes and Oxetane Derivatives from Michael Adducts of Malonates



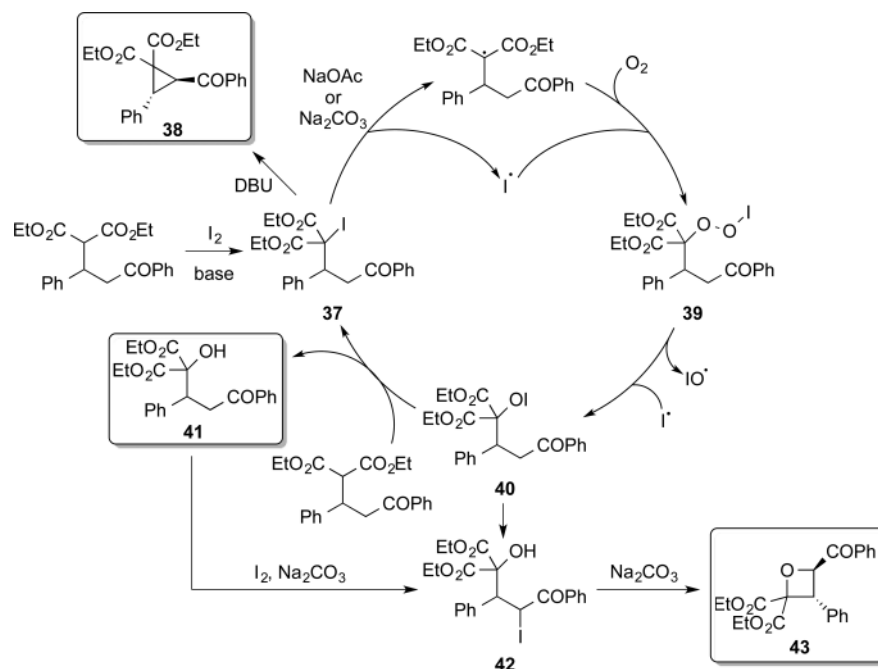
only when iodosobenzene (PhIO) and tetrabutylammonium iodide (Bu₄NI) were utilized. During optimization, cyclopropanes were synthesized in shorter reaction times when alcoholic solvents were used. Conversely, when the reaction was conducted in an open-air system with water, the oxetane was formed as the major product. Substrates bearing electron-rich aryl groups gave improved yields and selectivity for oxetane products, as did addition of SiO₂ and Na₂CO₃.

Two years later, Yang and co-workers¹³⁴ reported a similar iodine-mediated conversion of Michael adducts of malonates with enones to either α -hydroxymalonate derivatives (34), cyclopropanes (35), or oxetanes (36) with high diastereoselectivity (Scheme 9). The oxygen atoms in α -hydroxymalonates 34 and oxetanes 36 were derived from atmospheric O₂, and

Scheme 9. Selective Synthesis of α -Hydroxymalonates, Cyclopropanes, and Oxetane Derivatives from Michael Adducts

substoichiometric amounts of I₂ (0.2 equiv) could be used. Each of the three reactions proceeded well when both R₁ and R₂ were aryl groups, with the nature of substituents on the aryl ring having no significant impact on the reaction.

A radical mechanism was proposed that involved initial iodination of the Michael adduct to give key intermediate 37 (Scheme 10). This intermediate could undergo a DBU-mediated cyclization in the absence of O₂, to give cyclopropane 38, or cleavage of the C–I bond and reaction with oxygen and an iodine radical, to give iodoperoxide 39 and then hypoiodide 40. Iodine abstraction with the starting material would give α -

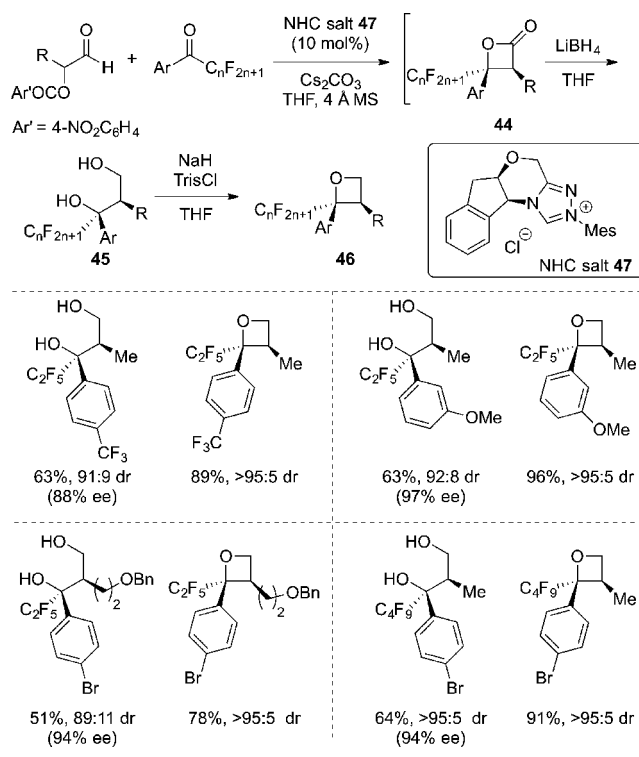
Scheme 10. Proposed Mechanism for Conversion to Cyclopropane, α -Hydroxymalonate, and Oxetane Products

hydroxymalonate **41** and regenerate key intermediate **37**. Treatment of **41** with I₂ and Na₂CO₃ would give iodide **42**, and a simple Williamson etherification would afford oxetane **43**. Alternatively, intramolecular electrophilic attack of the hypoiodide would also give iodide **42**, with a final C–O bond-forming step.

Recently, Smith and co-workers¹³⁵ developed an enantioselective formal [2+2] cycloaddition to form highly substituted, fluorinated β -lactones **44** from fluorinated ketones and α -aroyloxyaldehydes, using chiral N-heterocyclic carbene (NHC) catalyst **47**. Reduction to diols **45** with LiBH₄ and activation of the primary alcohol with TrisCl, followed by Williamson etherification, afforded the substituted fluorinated oxetanes **46** with excellent diastereomeric ratio (dr) and ee (Scheme 11).

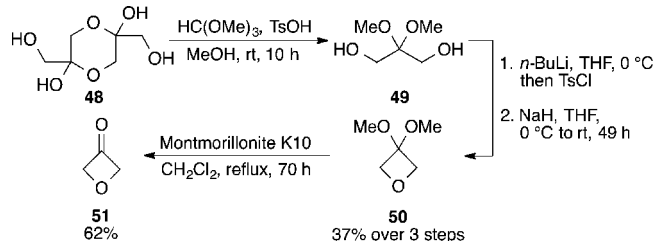
Following Carreira's studies on the properties of 3-substituted oxetanes (see section 2), there has been considerable interest in developing approaches to functionalized 3-substituted oxetanes. Carreira's approach used oxetan-3-one, the chemistry of which is covered in section 5 of this review. Carreira and co-workers⁶³ developed a four-step synthesis of the cyclic ketone that involved an intramolecular cyclization to form the oxetane (Scheme 12). Dihydroxyacetone dimer **48** was converted into the corresponding dimethylketal **49**. Monotosylation with TsCl followed by deprotonation with NaH prompted the intramolecular cyclization, forming oxetane **50**. Acidic cleavage of the ketal provided oxetan-3-one **51** in a yield of 62%. This motif has been widely used as a building block to prepare oxetane derivatives and is now commercially available from many suppliers.

Use of solid-phase synthesis for preparation of 3,3-disubstituted oxetanes **53** and **55** was reported by Hailes and co-workers¹³⁶ in 2005. Polystyrene and a novel PEG 3400 resin were used with a sulfone linker. Polymer-bound precursors were synthesized from polymer-bound sulfonyl chlorides and the desired diols **52** and **54**, with bead staining providing evidence for incorporation. Cyclization with sodium hydride proved unsuccessful, but treatment with KOtBu resulted in

Scheme 11. Synthesis of Oxetanes via NHC-Catalyzed Formal [2+2] Cycloaddition of Fluorinated Ketones and α -Aroyloxyaldehydes

much improved yields over two steps when compared to solution-based synthesis for both resins and substrates used (Scheme 13a).

Vigo et al.¹³⁷ reported the synthesis of 3,3-disubstituted oxetanes with hydroxy, amino, and carboxylic acid residues suitable for further functionalization. From diol **56**, through a route of cyclization, nucleophilic substitution, and then

Scheme 12. Synthesis of Oxetan-3-one by Intramolecular Cyclization

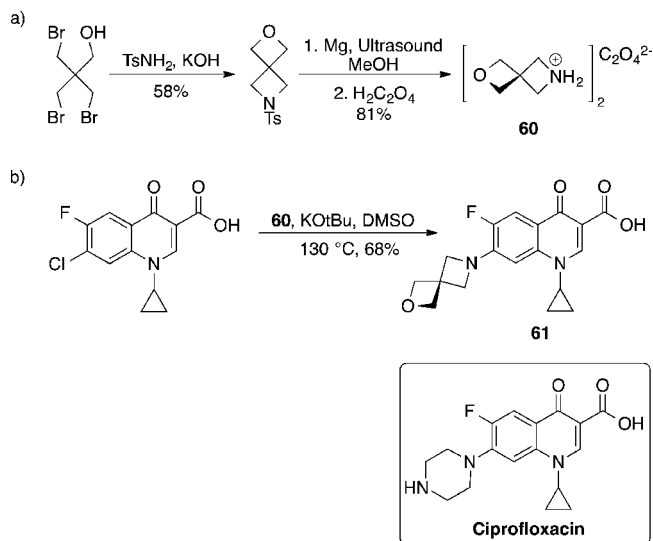
functional group manipulation, a variety of functionalized oxetanes were prepared (Scheme 13b).

Development of a three-step route from diol **57** via cyclic carbonate **58** allowed access to 3-benzyloxetane **59** in moderate yield (Scheme 13c).¹³⁷ Previous cyclization strategies and functional group manipulation had proved unsuccessful for this synthesis.

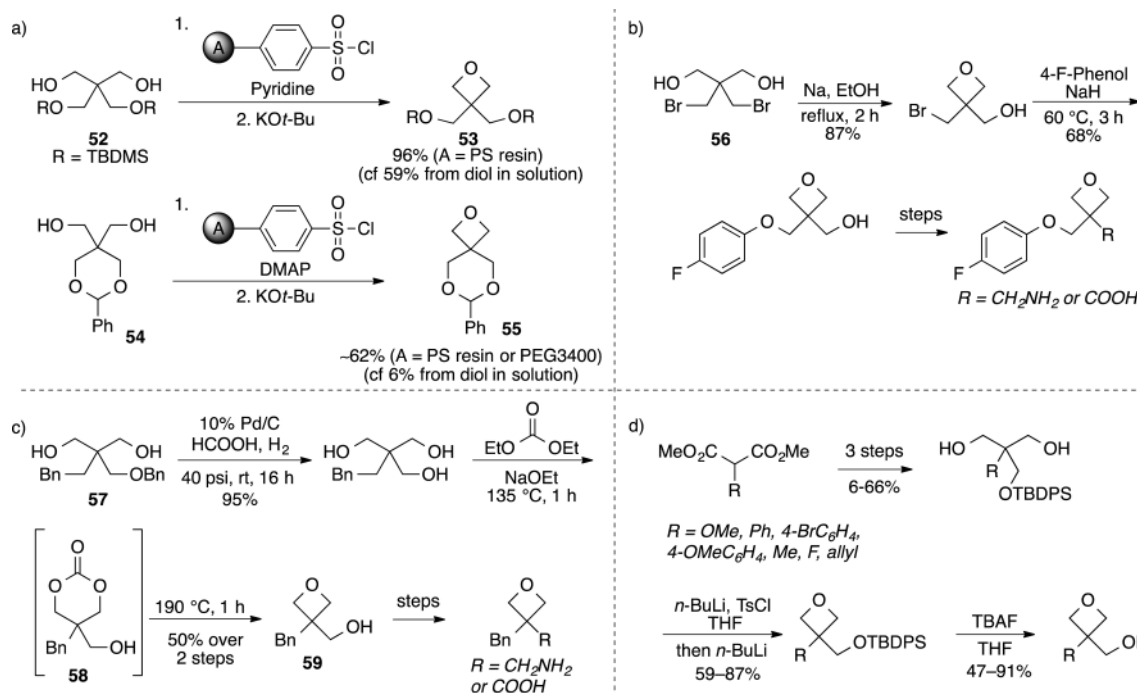
Further examples of medically relevant 3,3-disubstituted oxetanes were reported in 2014 by Boyd and Davies¹³⁸ (AstraZeneca). 3,3-Disubstituted oxetanes were synthesized from the relevant substituted dimethyl malonates with installation of a protected hydroxymethyl group, double ester reduction to the diol, tosylation, base-mediated cyclization, and finally removal of the silyl protecting group with tetra-*n*-butylammonium fluoride (TBAF; Scheme 13d). Yields for the Williamson etherification were reported between 59% and 87%. Scope included various substitution at the 3-position with aryl, allyl, alkyl, and halide substituents tolerated.

Synthesis of a large number of spirocyclic oxetanes has been examined in recent years, often by Williamson etherification in particular incorporating a 3-linked oxetane. An excellent review from Carreira and Fessard² on this subject appeared in 2014; we will not replicate their material here but only highlight a small selection of examples. Synthesis and biological testing of

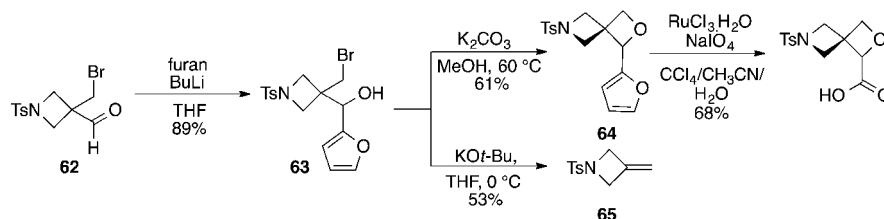
an analogue of ciprofloxacin **61** containing a spirocyclic oxetane motif is an excellent demonstration of both the synthetic strategy that has been widely employed for this class of compounds and the potential application of spirocyclic oxetanes in medicinal chemistry.^{69,73} Spirocyclic building block **60** was synthesized in two steps from 3-bromo-2,2-bis(bromomethyl)propan-1-ol (Scheme 14a). Synthesis of

Scheme 14. Spirocyclic Building Block 60 and Use in a Ciprofloxacin Analogue

ciprofloxacin analogue **61** was achieved in a yield of 68% by use of KOtBu in DMSO at 130 °C (Scheme 14b). Oxetane analogue **61** was then compared against an azetidine analogue and the parent ciprofloxacin in a number of biological assays. Comparable activities were seen for the two spirocyclic

Scheme 13. Synthesis of 3,3-Disubstituted Oxetanes from Diols

Scheme 15. Preparation of Spirocyclic Oxetane Azetidines

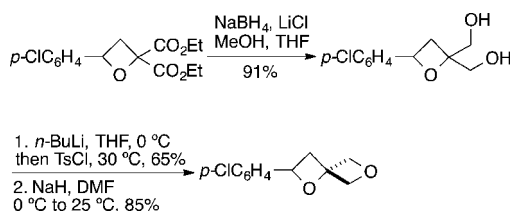


analogues, and additionally there was no observable metabolism in human microsomal assays.

Carreira and co-workers⁷⁴ also reported the synthesis of 2-substituted spirocyclic oxetane azetidines (Scheme 15). The addition of furyllithium to azetidine aldehyde **62**, synthesized in three steps from tribromopentaerythritol, afforded cyclization precursor **63** with the required 1,3-relationship between the alcohol and electrophilic carbon. Cyclization to the desired spirocyclic oxetane **64** occurred successfully under mild basic conditions (K_2CO_3 in MeOH). This work highlighted how the conditions employed for cyclization can be important in determining the reaction outcome; when $KOtBu$ in THF was used, Grob fragmentation occurred to give 3-*exo*-methylenazetidine **65** in a 53% yield. The likelihood of Grob fragmentation occurring appeared to depend on the thermodynamic stability of the olefin formed. Additionally, both the solvent and base utilized have an effect on the probability of Grob fragmentation occurring.¹³⁹

Recently Davis and Bull¹⁴⁰ prepared an unusual bis-spirocyclic oxetane derivative (Scheme 16). Reduction of an

Scheme 16. Preparation of a Bis-spirocyclic Oxetane Derivative

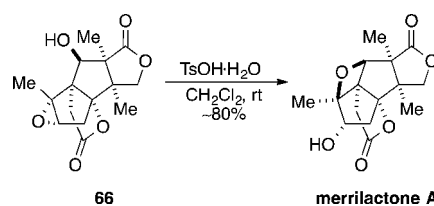


oxetane diester to the diol with $LiBH_4$ proceeded in high yield. Treatment with $BuLi$ and $TsCl$, followed by a second treatment with $BuLi$ in a separate step, formed the second oxetane ring.

Epoxides have also been used as leaving groups for the synthesis of oxetanes via intramolecular etherification. Kato and co-workers^{141,142} demonstrated the synthesis of oxetanocin analogues involving base-mediated ring opening of *cis*-epoxides of homoallylic epoxides by KOH to afford oxetanes (61–66% yield) along with the THF product (3.5:1 to 14.5:1 ratio, oxetane/THF). Interestingly, *trans*- and terminal epoxides gave only the THF product. Additionally, stoichiometric tributyltin methoxide was used by Chung et al.¹⁴³ in 1996 for ring opening of a terminal epoxide by a hydroxy group to give 4-[(benzyloxy)methyl]oxetan-2-ylmethanol in 32% yield. Subsequently, Carreira and co-workers⁶⁹ used this methodology for synthesis of a bridged bicyclic morpholine; it was also used elsewhere.¹⁴⁴ This disconnection has also been achieved under acidic conditions. In 2002, Birman and Danishefsky¹⁴⁵ first devised this Payne-type rearrangement from the relevant α -epoxide to yield the desired oxetane motif as a last step in the synthesis of merrilactone A. Treatment of α -epoxide **66** with

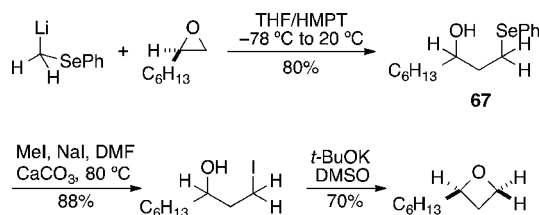
tosic acid in dichloromethane at room temperature yielded merrilactone A with the correct stereochemistry. These conditions have been replicated as the final step in a number of merrilactone A syntheses, yielding approximately 80% in all reports (Scheme 17).^{146–150}

Scheme 17. General Procedure for Synthesis of the Oxetane Ring in Merrilactone A via Payne Rearrangement-type Mechanism



3.1.2. Epoxide Ring Opening/Ring Closing. Epoxides can be ring-expanded to oxetanes: as a variant of the Williamson etherification, the cyclization precursor has been accessed by opening an epoxide with nucleophiles bearing leaving groups. In 1980, Servin and Krief¹⁵¹ opened epoxides (2-hexyloxirane, 2-hexyl-2-methyloxirane, or 2-methyloxirane) with a selenomethylithium reagent in THF/HMPT at -78 °C, which was then warmed to 20 °C to afford ring-opened hydroxyselenide **67** (Scheme 18). These intermediates were

Scheme 18. Oxetane Formation through Epoxide Opening with Selenoalkyllithium

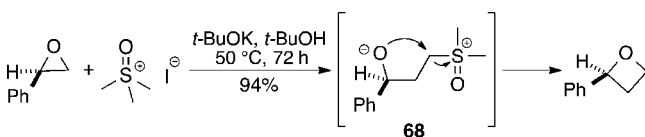


converted to halides that could be cyclized with a base such as $KOtBu$ or $MeMgBr$ to access the oxetane. Selenoethyl- and selenopropylithium were also successful to introduce additional Me/Et groups at the oxetane C4 position.

In 1983, Okuma et al.¹⁵² reported a similar method to access the oxetane cyclization precursor by ring opening of epoxides with a sulfoxonium ylide generated in situ from trimethyloxosulfonium iodide. Attack of a 2-substituted or 2,2-disubstituted epoxide with the sulfur ylide accessed the ring-opened intermediate **68**, which subsequently cyclized directly in the same reaction flask with release of dimethyl sulfoxide to afford 2-substituted oxetanes in excellent yields of 83–99% (Scheme 19). Aromatic and alkyl substituents were tolerated; however,

examples were limited to Ph, *p*-ClC₆H₅, Me, or H substituents and an example with cyclohexanone.

Scheme 19. Oxetane Formation through Epoxide Opening with Trimethyloxosulfonium Ylide



Okuma et al.¹⁵² demonstrated that by increasing the equivalents of trimethyloxosulfonium iodide, the oxetane motif could be accessed from the corresponding carbonyl compound through initial formation of the epoxide followed by ring opening. A related method was reported that used the sodium anion of an NTs-sulfoximine.^{153,154} Fitton et al.¹⁵⁵ expanded the scope of oxetanes accessed through this method to incorporate alkyl substituents that could be further manipulated to access a range of oxetane derivatives. Treating monosubstituted epoxides with dimethyloxosulfonium methylide resulted in oxetanes **69** in good yields (Table 3). The useful

Table 3. Expanded Scope of Oxetanes Accessed through Epoxide Ring Opening with Trimethyloxosulfonium Ylide

entry	R	yield (%)
1	CH ₂ OCH(CH ₃)OC ₂ H ₅	70
2	CH ₂ OCH ₂ CH=CH ₂	65
3	CH ₂ OC ₆ H ₅	83
4	CH ₂ CH ₂ CH=CH ₂	56
5	CH(OC ₂ H ₅) ₂	59

2-hydroxymethyloxetane motif was formed in 74% yield following acetal deprotection (from entry 1, Table 3), and the vinyl derivatives (entries 2 and 4) successfully underwent bromination with Br₂ or epoxidation with *m*-CPBA.

Fokin and co-workers¹⁵⁶ modeled the ring expansion of an unsubstituted epoxide computationally at the density functional theory MP2 level of theory, utilizing a polarizable continuum model to account for solvent effects and determining that formation of the oxetane ring from an epoxide required 13–17 kcal·mol^{−1} activation energy; therefore, moderate heating was required. Subsequent ring-expansion barriers were calculated for oxetane to THF at 25 kcal·mol^{−1} and THF to tetrahydropyran (THP) at 38 kcal·mol^{−1}. For 2-methyl- and 2,2-dimethyloxirane, the methylenation of epoxides with

dimethylsulfoxonium methylide was modeled and shown to proceed via an S_N2 transition structure and was sensitive to epoxide substitution. Experimental findings were consistent with computational results, whereby enantioenriched chiral oxetanes were accessed from enantioenriched epoxides with full retention of enantiomeric purity (Table 4). 2-Alkyl- and 2,2-dialkylepoxides had similar reactivity when treated with dimethylsulfoxonium methylide; however, the 2,3-disubstituted epoxide was unreactive, resulting in only trace amounts of product (Table 4, entry 5). Consecutive ring expansion was performed, treating chiral oxetanes with dimethylsulfoxonium methylides to form chiral tetrahydrofurans (THFs), also with conservation of ee. Recently, Carreira and co-workers⁷⁵ applied this approach to *N*-Boc-azetidin-3-one, where this transformation was successful in the generation of a spirocyclic azetidine-oxetane. Aggarwal and McGarrigle and co-workers¹⁵⁷ reported the cyclization of a related intermediate to form a 2,2-disubstituted oxetane through conjugate addition of a hydroxy malonate to a vinyl sulfonium salt, forming an ylide, which underwent proton transfer and cyclization.

Shibasaki and co-workers¹⁵⁸ developed a powerful one-pot enantioselective synthesis of 2,2-disubstituted oxetanes involving an asymmetric Corey–Chaykovsky epoxidation reaction, followed by ring expansion of the resulting chiral epoxides to chiral oxetanes. Excellent levels of ee were obtained, with reinforcing enantioinduction leading to partial kinetic resolution and amplified ee. The starting methyl ketone **70** was treated with 1.2 equiv of dimethyloxosulfonium methylide, 5 mol % catalyst **71**, and phosphorus oxide additive **72** in the presence of molecular sieves to afford the corresponding chiral epoxide, which was then treated with a further equivalent of the sulfur ylide and 15 mol % catalyst and additive to compensate for the slow reaction rate (Scheme 20). Chiral 2,2-disubstituted oxetanes were accessed in good to excellent yields of 58–88% with up to 99.5% ee, employing both alkyl and aryl methyl ketones. When ethyl ketones such as propiophenone were employed, the epoxide intermediate was produced in 88% ee; however, the subsequent ring expansion provided the oxetane in 91% ee with only a 26% yield, demonstrating that the reaction was sensitive to ketone substitution.

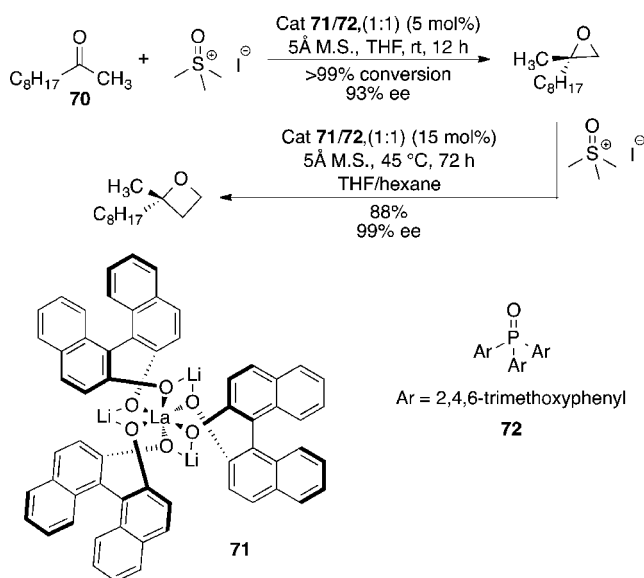
3.1.3. Synthesis of Oxetanes from Sugar Derivatives.

Saccharides have been used extensively as starting materials for the synthesis of oxetanes, due to the repeating 1,3-functionality and the opportunity to access enantioenriched and diastereomerically defined oxetanes.¹⁵⁹ Similarly, these starting materials have been used in the synthesis of small oxetane-containing natural products, though typically this approach can be lengthy. In this manner, sugars have been used extensively by Fleet and co-workers^{160,161} as starting materials for the synthesis of enantioenriched oxetanes through ring contraction

Table 4. Assessing Chiral Oxetanes from Ring Expansion of Chiral Epoxides with Dimethylsulfoxonium Methylide

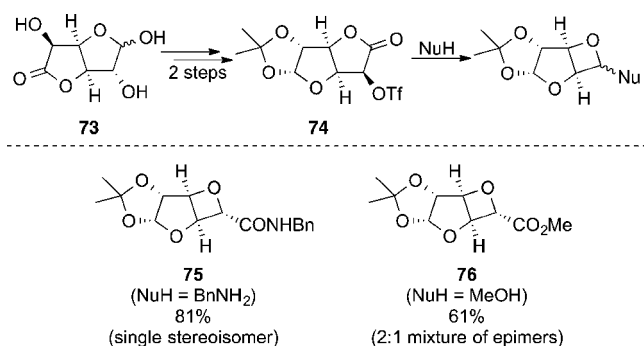
entry	R	R ¹	R ²	R ³	conditions	yield (%)	ee (%)
1	C ₆ H ₅	H	H	H	NaH, DMSO, 70 °C	85	>98
2	<i>n</i> -hexyl	H	H	H	<i>t</i> -BuOK, <i>t</i> -BuOH, 80 °C	91	>98
3	H	CH ₂ OCH ₂ Ph	H	H	<i>t</i> -BuOK, <i>t</i> -BuOH, 80 °C	80	>98
4	C ₆ H ₅	Et	H	H	NaH, DMSO, 110 °C	88	>98
5	C ₆ H ₅	H	H	Me	<i>t</i> -BuOK, <i>t</i> -BuOH, 120 °C	trace	nd

Scheme 20. Asymmetric Synthesis of 2,2-Disubstituted Oxetanes via One-Pot Sequential Addition of Sulfur Ylides to Ketones



of the triflates of α -hydroxy- γ -lactones (Scheme 21). These were formed from the corresponding α -hydroxy- γ -lactones,

Scheme 21. Sample Ring Contraction of α -Hydroxy- γ -lactone Triflates

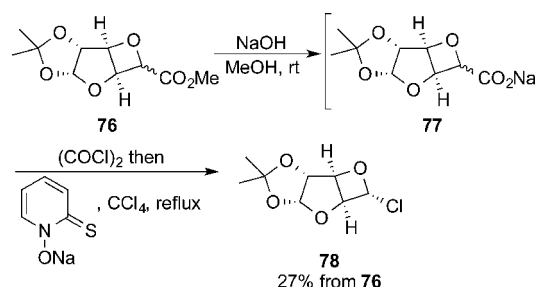


which are in turn prepared from compounds derived from sugars.^{162–164} Certain nucleophiles attack the lactone carbonyl, leading to ring opening of the lactone, followed by displacement of the triflate to form the oxetane. When lactone 74, derived from glucuronolactone 73, was treated with benzylamine or K_2CO_3 in methanol, ring contraction occurred to form oxetanes 75 and 76, respectively, in good yield.¹⁶¹

Only one stereoisomer was formed with benzylamine with a yield of 81%, and no reaction was observed when OTf was replaced with OMs. On the other hand, an epimeric mixture was observed when K_2CO_3 in methanol was used (61%, ratio 2:1), with the major product having retention of configuration at the oxetane C2 position due to epimerization prior to oxetane formation. Treatment of ester oxetane 76 with benzylamine and hydrazine hydrate afforded the corresponding amide oxetanes, and reduction was achieved by use of $LiAlH_4$; both reactions proceeded without epimerization.¹⁶¹

The synthesis of an unusual but stable α -chlorooxetane 78 was achieved by Fleet et al.¹⁶⁶ through a Barton modification of the Hunsdiecker reaction (Scheme 22).¹⁶⁵ Ester 76 was

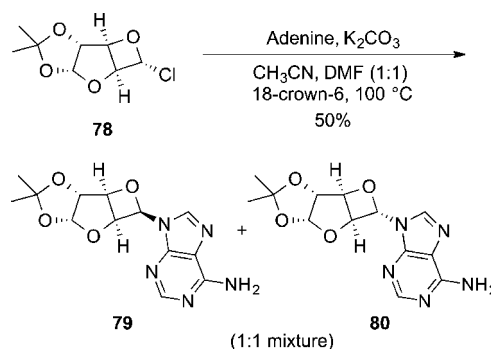
Scheme 22. Synthesis of α -Chlorooxetane 78 through Barton Modification of the Hunsdiecker Reaction



converted to the chloride with a yield of 27% through hydrolysis to the sodium carboxylate 77, formation of the acid chloride, and reaction with *N*-hydroxypyridine-2-thione sodium salt under reflux in CCl_4 . The structure of this fascinating chlorooxetane was proven by an X-ray crystal structure.¹⁶⁶

In subsequent work, Fleet et al.¹⁶⁷ showed that α -chlorooxetanes could be converted into oxetane nucleoside analogues through displacement of the chloride with adenine (Scheme 23). A separable 1:1 mixture of C2-epimers 79 and 80 was obtained, which may indicate nucleophilic displacement had significant S_N1 character.

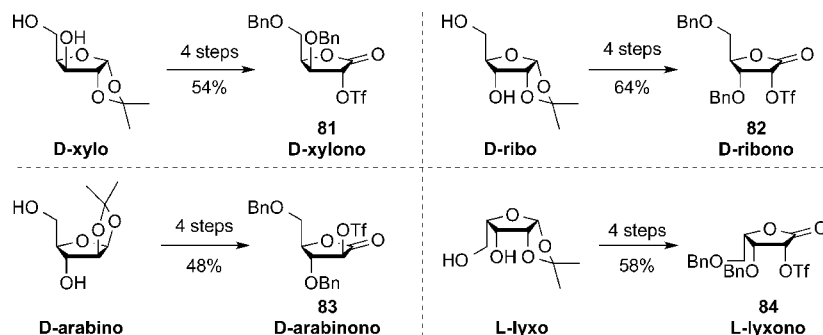
Scheme 23. Synthesis of Oxetane Nucleoside Analogue from α -Chlorooxetane 78



A few years after the reaction with bicyclic lactones, Fleet and co-workers¹⁶⁸ expanded the scope of ring contraction of α -hydroxy- γ -lactones to all four diastereoisomers of 3,5-di-*O*-benzylpentono-1,4-lactones. These lactones were prepared from 1,2-*O*-isopropylidene-pentofuranose sugars (Scheme 24). Triflates 81–84 were prepared in four steps from the readily available diols of *D*-xylo, *D*-ribo, *D*-arabino, and *L*-lyxo sugars with yields between 48% and 64%.

Ring contraction was conducted on each example under previously reported conditions (dry K_2CO_3 in anhydrous MeOH), affording methyl oxetane-2-carboxylates 85–88 in yields of 70%–82% (Table 5). Interestingly, for *D*-xylono and *D*-arabinono triflates 81 and 83, the expected inversion of configuration occurred, whereas for *D*-ribono and *L*-lyxono triflates 82 and 84, retention of configuration at C2 of the lactone resulted. The major product of each ring contraction has a trans relationship between the C2 and C3 substituents on the oxetane ring. No deuterium incorporation was observed when the reaction was conducted in methanol- d_4 , which implied that the stereochemical outcome of these reactions was not a consequence of equilibrium of the oxetane products.

Scheme 24. Synthesis of Triflate Lactones 81–84 from Pentofuranose Sugars

Table 5. Synthesis of Oxetanes 85–88 by Ring Contraction^a

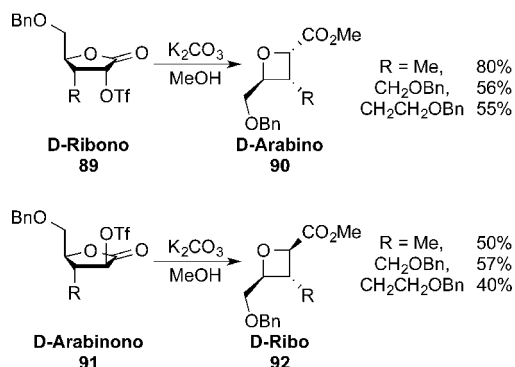
Yield of Product (%)				
	85	86	87	88
Triflate				
D-xylo (81)	79 (inv) ^a	-	-	-
D-ribo (82)	-	73 (ret) ^b	-	9
D-arabino (83)	-	70 (inv) ^a	-	-
L-lyxono (84)	-	-	80 (ret) ^a	-

^aInv = inversion of configuration at C2 upon cyclization. ^bRet = retention of configuration upon cyclization.

Unfavorable interactions during S_N2 ring closure in the open-chain 4-hydroxy-2-*O*-triflate esters when the substituents of the resulting oxetane are *cis*-configured were cited as a possible reason for this stereochemical outcome. Epimerization of the hydroxy triflate intermediate therefore occurs more rapidly than cyclization, which favored the *trans* configuration.

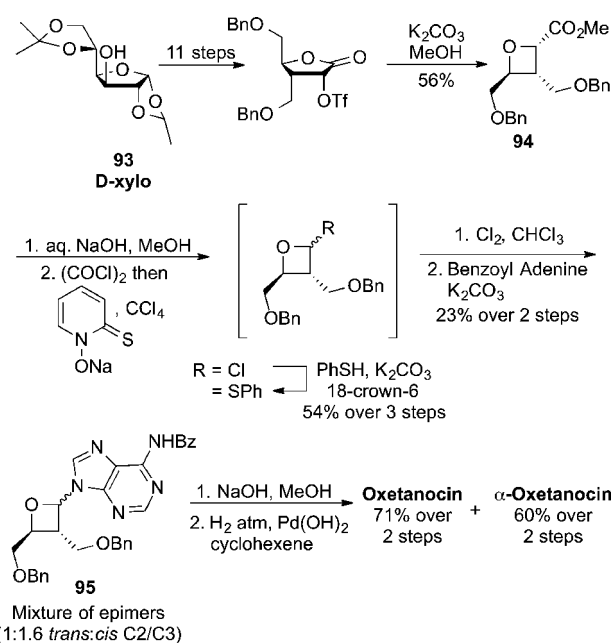
Fleet and co-workers¹⁶⁹ later demonstrated that ring contraction occurred with C3-deoxy 3-substituted oxetane products (Scheme 25). In this case, inversion of configuration was observed for both D-ribono (89) and D-arabinono (91)

Scheme 25. Synthesis of 3-Alkyloxetanes 90 and 92



substrates upon ring contraction. Yields for 3-alkyloxetanes 90 and 92 were generally lower than those for previously reported 3-ether-substituted oxetanes due to the increased tendency of alkyl triflate lactones to undergo elimination reactions rather than ring contractions.

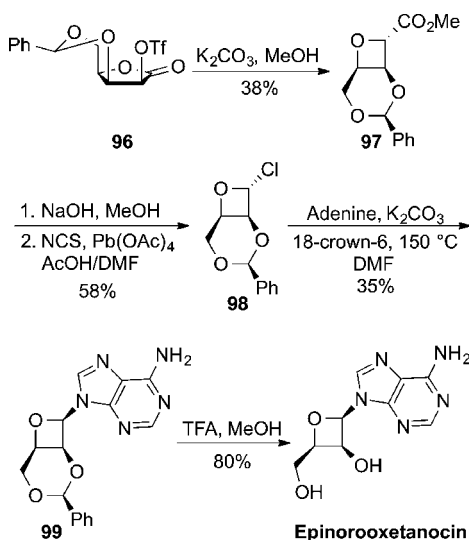
This ring contraction strategy enabled synthesis of the natural product oxetanocin and its α -epimer (Scheme 26).¹⁷⁰

Scheme 26. Synthesis of Oxetanocin and Its α -Epimer

From the triflate lactone, derived from D-xylo 93, ring contraction with K₂CO₃ in MeOH afforded oxetane 94 with inversion of configuration. The epimer of oxetane 94 could be formed from the same triflate lactone in three steps; treatment with sodium trifluoroacetate and MeOH gave the inverted α -hydroxy- γ -lactone (D-arabinonolactone), followed by conversion to the triflate and ring contraction. Radical decarboxylative chlorination gave an unstable α -chlorooxetane, which was immediately trapped as the sulfide with PhSK to be purified. Regeneration of the α -chlorooxetane was conducted with Cl₂ in CHCl₃, followed by addition of benzoyl adenine to give protected adenine oxetane 95 as an epimeric mixture in 23% yield. Separation and subsequent deprotection afforded oxetanocin and α -oxetanocin in 71% and 60% yields, respectively.

Through an almost identical route, Fleet and co-workers¹⁷¹ synthesized both epimers of norooxetanocin in 15 steps from diacetal glycoside. Both α - and β -norooxetanocin were inactive against HIV-1 (up to a concentration of $100 \mu\text{g}\cdot\text{mL}^{-1}$).¹⁷² In an improved sequence, epinorooxetanocin was prepared from lactone triflate **96**, itself prepared in two steps (Scheme 27).¹⁷²

Scheme 27. Synthesis of Epinorooxetanocin



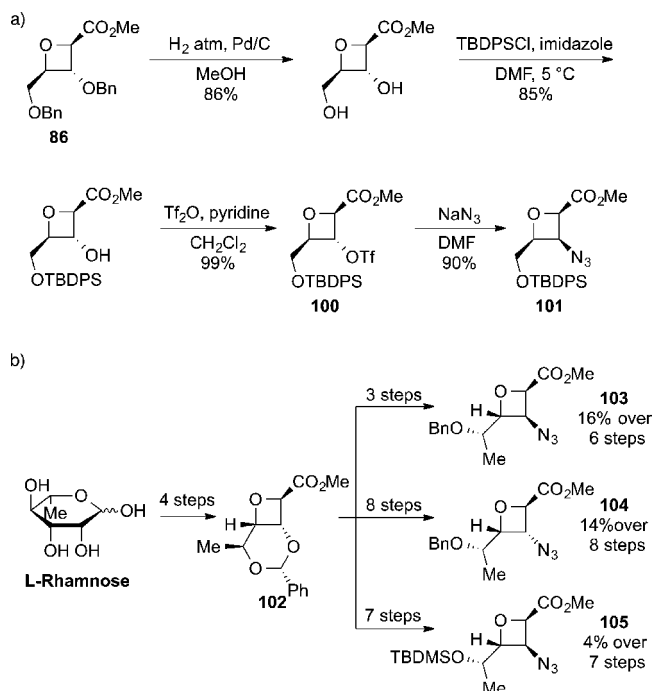
Ring contraction under standard conditions afforded oxetane **97**. To access α -chlorooxetane **98**, hydrolysis of the ester, followed by treatment with *N*-chlorosuccinimide (NCS) and lead tetraacetate, gave a single stereoisomer in 58% yield. The chloride was displaced with adenine to give nucleoside oxetane **99** as a single epimer, which was subsequently deprotected with trifluoroacetic acid (TFA), affording epinorooxetanocin with an 80% yield. In vitro studies of epinorooxetanocin showed significant activity against HIV-1 ($\text{IC}_{50} = 0.5\text{--}1.5 \mu\text{g}\cdot\text{mL}^{-1}$), which was similar to the activity of oxetanocin ($\text{IC}_{50} = 0.5\text{--}1.5 \mu\text{g}\cdot\text{mL}^{-1}$).

In 1992, Saksena et al.¹⁷³ developed the use of mesylate and tosylate groups for ring contraction under aqueous hydrolytic conditions to form oxetanecarboxylic acids with high yields. Gumina and Chu¹⁷⁴ used the conditions reported by Saksena in their synthesis of the enantiomer of oxetanocin. They achieved this in 16 steps, starting from *L*-xylose with an overall yield of 2.8%, in a route otherwise similar to that reported by Fleet and co-workers.¹⁷⁰

Oxetanes constructed by these strategies have provided important building blocks for further functionalization to provide enantioenriched oxetanes with varied substitution patterns, especially at the 3- and 4-position of the oxetane ring. In sections 3.1.3.1 and 3.1.3.2, we report some of the transformations that may be valuable in accessing functionalized oxetane derivatives and for applications in medicinal chemistry.

3.1.3.1. C3 Functionalization and Applications of Oxetanes Derived from Sugars. Fleet and co-workers¹⁷⁵ showed that oxetane 2-esters could undergo a variety of transformations at C3, particularly nucleophilic displacements. Deprotection of the benzyl protecting groups in oxetane **86** proceeded by hydrogenolysis with H_2 and Pd/C with a good yield of 86% (Scheme 28a). After selective silylation of the primary hydroxy group, the secondary alcohol at the C3

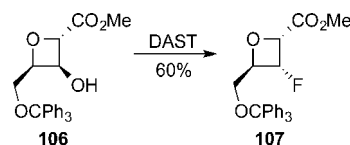
Scheme 28. Synthesis of Azidooxetanes



position of the oxetane ring could be converted to the triflate with TiF_4 , and triflate **100** could be displaced with inversion by a variety of nucleophiles. Initially this was achieved by use of NaN_3 to form oxetane **101**, and no competing elimination reactions were observed. Oxetane **102**, prepared from *L*-rhamnose in four steps,^{176,178} was used to access a range of 3-azidooxetanes **103–105** in a similar manner through reduction of the acetal protecting group, triflate formation, and $\text{S}_{\text{N}}2$ displacement with NaN_3 (Scheme 28b).^{177–179} A similar sequence was conducted with *D*-xylose.¹⁷⁷

3-Hydroxyoxetane **106** was converted to a single isomer of fluorooxetane **107** through the use of diethylaminosulfur trifluoride (DAST), which proceeded with inversion (Scheme 29).¹⁷⁵ Recently, Wessel and co-workers⁸⁶ used DAST in the

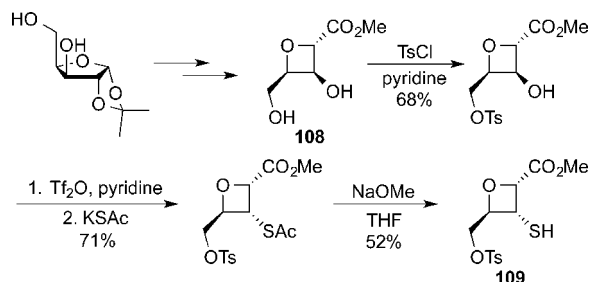
Scheme 29. Synthesis of Fluorooxetane **107** by Use of Diethylaminosulfur Trifluoride



synthesis of 3-fluorooxetane δ -amino acids as interesting new rigid scaffolds for use in medicinal chemistry. Fleet and co-workers¹⁷⁵ converted fluorooxetane and azidooxetane derivatives to analogues of oxetanocin, and while the azido analogue showed significant antiviral activity against HIV-1 ($\text{IC}_{50} = 6 \mu\text{g}\cdot\text{mL}^{-1}$), it was less than the activity of oxetanocin itself.

In 1997, Sakya et al.¹⁸⁰ synthesized oxetane-3-thiols from oxetane **108** (Scheme 30). Selective tosylation of the primary alcohol occurred with good yield. This tosyl group could not be displaced by either NaN_3 or amines; instead, retro-aldol and decomposition products were isolated. However, the secondary alcohol could be converted to thiol **109** through triflate

Scheme 30. Synthesis of Oxetanethiol 109



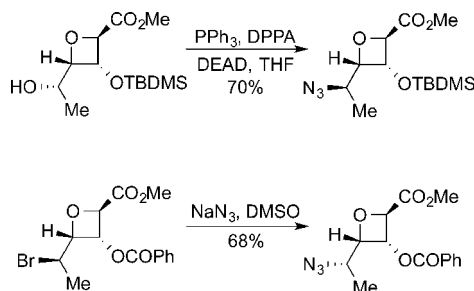
formation followed by displacement with KSac, selective for the secondary triflate, and deprotection.

These oxetanethiols were subsequently used in synthesis of a variety of oxetane carbapenems **110** and to determine their antibacterial structural activity relationship against both Gram-positive and Gram-negative bacteria (Table 6). The oxetane carbapenems tended to have less activity against Gram-positive bacteria (such as *Staphylococcus aureus*) compared with the broad-spectrum antibiotic imipenem,¹⁸¹ but they showed similar activity against Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). Oxetane carbapenem **110a** was also shown to be more stable to hydrolysis by hog kidney dehydropeptidase (DHP) than imipenem.

3.1.3.2. C4 Functionalization and Applications of Oxetanes Derived from Sugars. Oxetane derivatives have been developed as isosteres for dipeptides.¹⁸² Toward this aim, Fleet and co-workers¹⁸³ incorporated an azide group at the C4 position by two routes: a Mitsunobu reaction with PPh₃, diethyl azodicarboxylate (DEAD), and diphenylphosphoryl azide (DPPA) and also a displacement reaction of an alkyl bromide using sodium azide (Scheme 31).

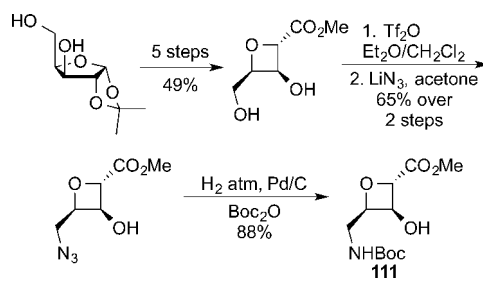
Toward novel oxetane amino acids, Wessel and co-workers^{86,87} from Roche reported that the azide moiety could be incorporated through displacement of a triflate (Scheme 32). These primary azides were subjected to hydrogenolysis

Scheme 31. Synthesis of Alkylazido oxetanes



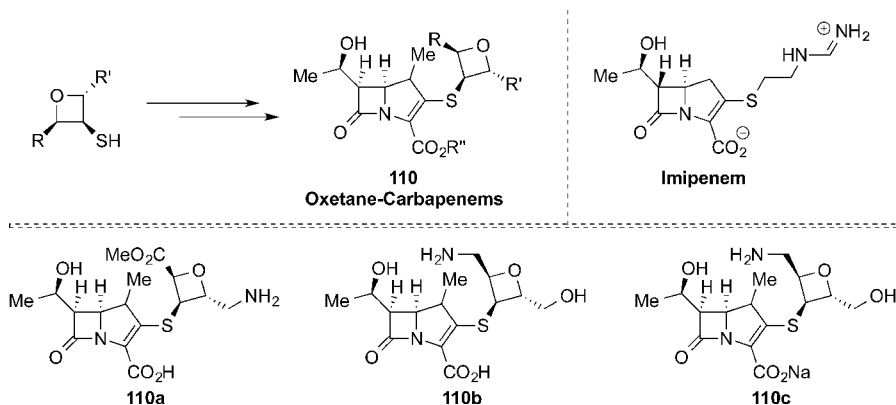
followed by in situ protection with Boc₂O to give protected primary aminooxetane **111** in good yields.

Scheme 32. Synthesis of a Protected Amino Acid Oxetane



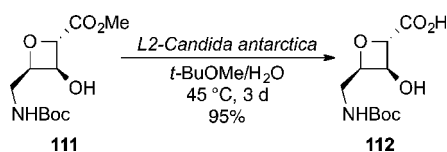
Wessel and co-workers⁸⁶ achieved hydrolysis of the methyl esters using 1 N LiOH in THF with quantitative yield, and it could also be achieved enzymatically with pig liver esterase (Scheme 33). Acidic aqueous workup led to degradation of oxetane **112**; therefore, the reaction was screened in micro-aqueous reaction systems (organic solvents with a small amount of water added). It was shown that lipase L2 from *Candida antarctica* provided the best activity, and oxetanecarboxylic acid **112** could be isolated by filtering off the enzyme followed by evaporation of the solvent. This enzymatic hydrolysis was conducted on a gram scale, and an excellent

Table 6. Structure–Activity Relationships of Oxetane Carbapenems



organism	strain	minimum inhibitory concn (μg·mL ⁻¹)			
		imipenem	110a	110b	110c
<i>E. coli</i>	ATCC 25922	0.12	0.25	0.12	0.12
<i>P. aeruginosa</i>	ATCC 27853	2	128	16	64
<i>S. aureus</i>	ATCC 28213	≤0.06	1	0.12	0.12
relative hydrolysis to hog DHP		100	<1		

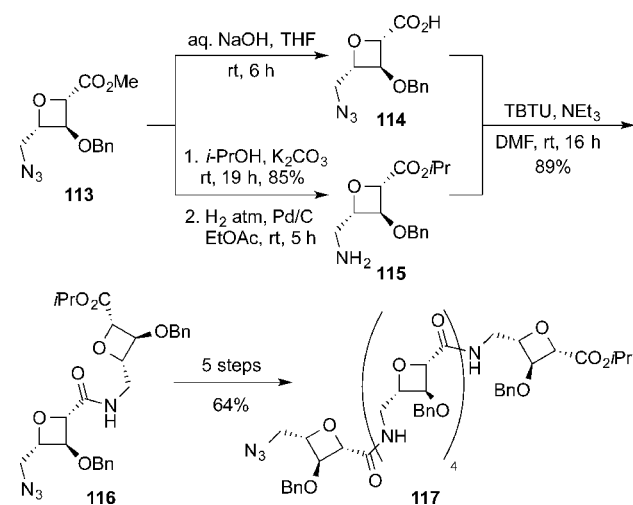
Scheme 33. Hydrolysis of Oxetane Ester by Use of *Candida antarctica* Lipase L2



yield was obtained. A related oxetane monomer was incorporated into a β -turn region of cyclodecapeptide gramicidin S, which caused a well-defined cyclic hairpin structure in solution.¹⁸⁴

While investigating the preferred secondary structures of homooligomers of oxetane amino acids,¹⁸⁵ oxetane-azido ester scaffolds were converted to β -amino acid monomers and coupled to form a range of β -amino acid oligomers (dimers, tetramers, and hexamers). For example, the δ -2,4-*cis*-oxetane azido ester scaffold **113** underwent hydrolysis to afford oxetane acid **114**. Fleet showed that transesterification to the isopropyl ester allowed for successful hydrogenolysis of the azide to the free amine **115** in good yields. This transesterification avoided intramolecular lactamization and oligomerization, which was observed with hydrogenolysis of methyl ester **113**.¹⁸⁶ Treatment of these two monomers with TBTU [*N,N,N,N'*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate] gave oxetane dimer **116** in 89% from isopropyl ester oxetane **115**. This dimer was subjected to the same iterative process, and homooligomers up to the hexamer were successfully synthesized. Hexamer **117** was built up over five steps with a very good yield of 64% from dimer **116** (Scheme 34).

Scheme 34. Synthesis of Oxetane Hexamer 117



Conformational analysis of these oxetane β -amino acid oligomers by IR and NMR spectroscopy, involving nuclear Overhauser effect (NOE), total correlation (TOCSY), and rotating-frame nuclear Overhauser effect (ROESY) spectra, indicated that well-defined secondary structures were adopted in solution.^{185,187} The major conformation was dictated by an internal 10-membered hydrogen-bonded motif, which is comparable to a conventional α -amino acid peptide β -turn. On the other hand, the *trans*-oxetane amino acid oligomers did not show any defined secondary structures. By contrast, *trans*-oxetane amino acid oligomers with a bulky 3-(*tert*-butyldimethylsilyl)oxy (3-OTBS) substituent did display a

defined conformation in chloroform and 2,2,2-trifluoroethanol, enforced through steric interactions without the influence of H-bonding.¹⁸⁸ Cyclic tetrameric derivatives have also been prepared.¹⁸⁹

Oxetanes have also been incorporated as side chains in β -amino acids for the synthesis and conformational analysis of the foldamers they might adopt in solution.¹⁹⁰ Novel oxetane β^3 -amino acids **119a,b** were prepared from sugar-derived diol **118** in 14 steps with overall yields of 1.4% and 3.7%, respectively (Scheme 35). Oxetane formation was achieved via Williamson etherification with NaH in THF. The amine stereocenter was introduced by an aza-Michael addition. Oxetane β^3 -amino acid **119a** was incorporated into tri- and penta- α,β -peptides under standard peptide coupling conditions¹⁹¹ with L-Ala derivatives. Conformational analysis by NMR, molecular dynamics, and circular dichroism indicated the presence of a well-defined folded conformation that involved hydrogen bonding.

3.1.4. Synthesis of Oxetane-Containing Nucleoside Analogues. Nucleoside analogues have been developed as effective classes of novel antiviral and cancer therapeutics. Their mode of action stems from an ability to disrupt nucleotide metabolism and DNA replication, thus leading to apoptosis.^{192,193} Examples include idoxuridine, the first marketed antiviral nucleoside for treatment of herpes simplex virus;¹⁹⁴ zidovudine (AZT),¹⁹⁵ approved in 1987 as a treatment for HIV; and more recently entecavir¹⁹⁶ (approved in 2005) and sofosbuvir¹⁹⁷ (approved in 2013) as treatments for hepatitis B and C, respectively (Figure 13).

Toxic side effects and development of resistance to existing therapies^{198,199} means there has been a continued drive in this area to find novel nucleoside-based therapeutics with optimal physicochemical properties. Several groups in recent years have investigated incorporation of oxetanes, in addition to other functionalities, toward this goal.²⁰⁰ Wengel and co-workers,²⁰¹ in 1998, evaluated the thermal stabilities of duplexes comprising several oxetane-containing modified oligonucleotides (ONs) against the complementary single-stranded DNA and RNA. The synthesis of the desired bicyclic oxetane-containing nucleoside **121** was completed in 12 steps from the known ulose **120** in overall 8.5% yield, with the key cyclization step being intramolecular etherification between the secondary alcohol and primary mesylate group. This was achieved in 93% yield over the mesylation and cyclization steps (Scheme 36). Subsequent steps allowed synthesis of the corresponding 3'-*O*-phosphoramidite building block **122** for incorporation into ONs.

Several modified 14-mer ONs were synthesized along with a 9-mer variant, and the thermal stabilities of their duplexes with single-stranded DNA and RNA were determined by melting-point analysis and compared to that of unmodified ON (Table 7).²⁰¹ It was found that the majority of modified 14-mer ONs resulted in decreased thermal stability against both DNA and RNA, with lower melting points being reported. However, 5'-X₁₃T was the notable exception, showing a significant increase in thermal stability against both DNA and RNA (Table 7, entry 7). Additionally, the 9-mer example showed small increases in thermal stability against the reference ON (Table 7, entry 8 vs entry 9), thus demonstrating the potential in incorporating an oxetane into ONs in order to deliver superior physical properties.

In 2001, Nielsen and co-workers²⁰² published a study exploring the anti-HIV activity of a conformationally restricted nucleoside analogue of AZT featuring an oxetane motif.

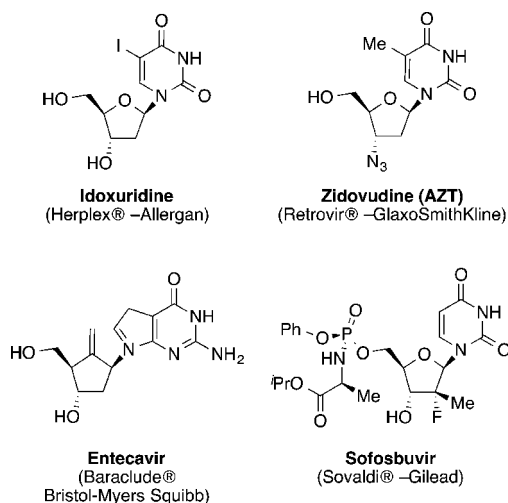
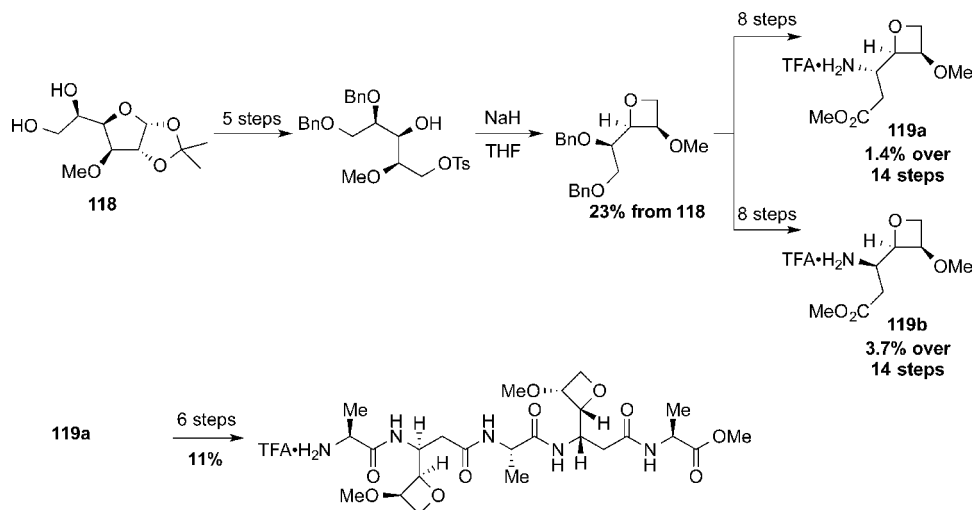
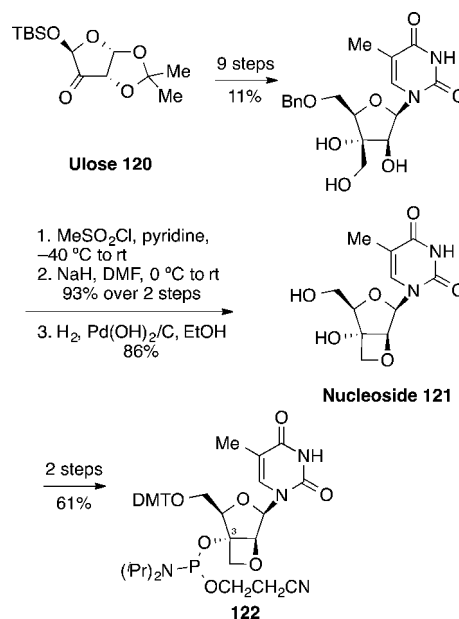
Scheme 35. Synthesis of Novel β^3 -Amino Acids and Penta- α,β -peptide

Figure 13. Examples of marketed nucleoside antivirals.

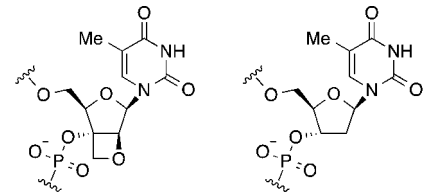
Starting from the cheap and readily available D-arabinose, both anomeric configurations of the desired oxetane-containing nucleoside, **124a,b**, were synthesized in 12 steps (Scheme 37). A modified Corey–Link reaction furnished an α -azido methyl ester stereoselectively, which was followed by stereoselective reduction of a ketone, ester reduction, and conversion to the mesylate to give oxetane precursors **123a,b**. Sodium hydride-mediated etherification delivered the oxetane functionality. However, when the antiviral activity of both anomeric configurations **124a,b** was then tested against HIV-1 in MT-4 cell lines, in both cases, no anti-HIV activity was observed at 300 μ M.

In 2004, Sharma and Nielsen²⁰³ reported the synthesis of oxetane-containing [3.2.0]bicycloarabinonucleoside **129**, of interest for potential in antisense and antigene technology, from alkene **125** (Scheme 38). The key step of the synthesis involved oxidative cleavage of the terminal alkene to give alcohol **126** by use of in situ formed RuO_4 (from $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ and NaIO_4). In the second step of this oxidative cleavage, addition of NaBH_4 reconverted the α -ketol (formed from overoxidation) back to the diol as well as reducing any active Ru species. After protecting group manipulation, thymine was used to displace the acetate at the anomeric center.

Scheme 36. Synthesis of Oxetane Nucleoside Phosphoramidite **122** from Ulose **120**

Deprotection of the benzoyl and acetyl protecting groups followed by mesylation afforded dimesylate **127**. Selective hydrolysis of the primary sulfonate ester of the primary mesylate, followed by Williamson etherification, afforded oxetane bicycle **128**. Benzyl deprotection gave oxetane **129**.

Chattopadhyaya and co-workers^{204,205} explored the synthesis and antisense effects of 1',2'-locked oxetane-containing nucleosides. Extensive studies on the effects of replacing either thymine or cytosine residues in antisense oligonucleotide (AON)–RNA duplexes with nucleoside **130** or **131**, respectively, were performed, with a focus on examining the effect on RNase H cleavage (Figure 14). With nucleoside **130**, singly, doubly, and triply modified AON–RNA duplexes were found to be similarly good substrates for RNase H as the unmodified duplex. The modified duplexes also exhibited improved protection toward endonuclease, with stability increasing with increasing levels of modification. The modifications led to a loss in thermodynamic stability, which

Table 7. Melting Point Experiments To Determine Thermal Stability of Modified Oligonucleotides^a


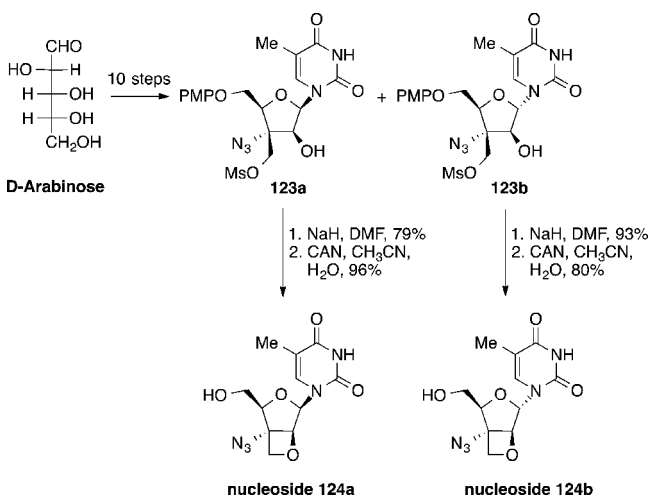
Monomer "X" derived from 122 **Thymidine Monomer "T"**

entry	oligonucleotide	<i>T_m</i> (°C)	
		ssDNA duplex	ssRNA duplex
1	5'-T ₁₄ ^b	36.0	34.0
2	5'-T ₇ XT ₆	36.0	33.5
3	5'-T ₆ X ₂ T ₆	34.5	33.0
4	5'-T ₆ XTXT ₅	35.5	32.5
5	5'-T ₃ X ₄ T ₅	31.5	37.0
6	5'-T ₃ (TX) ₄ T ₃	35.5	31.5
7	5'-X ₁₃ T	58.0	49.0
8	5'-GTGATATGC ^b	26.0	26.5
9	5'-GXGAXXGC	34.5	34.5

^aThermal stability is compared to that of the unmodified reference oligonucleotide and is measured at 260 nm in medium-salt buffer: 1 mM ethylenediaminetetraacetic acid (EDTA), 10 mM Na₃PO₄, and 140 mM NaCl, pH 7.2. Concentration of each strand was 2.5 μM. G = 2'-deoxyguanosine monomer; A = 2'-deoxyadenosine monomer; C = 2'-deoxycytidine monomer; *T_m* = melting point, determined as maximum of the first derivative of absorbance vs temperature curve.

^bReference oligonucleotide.

Scheme 37. Overall Synthetic Strategy for Synthesis of Nucleosides 124a,b



could be improved by introduction of a dipyrrophenazine (DPPZ) moiety.²⁰⁴ For nucleoside 131, singly and doubly modified AON–RNA duplexes were again found to be good substrates for RNase H. Michaelis–Menten kinetics indicated catalytic activity close to that of the native duplex. Target affinity for AON–RNA duplexes modified with nucleoside 131 was significantly improved compared to those modified with nucleoside 130.²⁰⁵

In 2005, Chattopadhyaya and co-workers²⁰⁶ developed routes to oxetane-containing 1',2'-locked nucleosides from protected furanose derivatives. The oxetane ring-forming step

Scheme 38. Synthesis of Bicyclic Oxetane 129 from Sugar-Derived Alkene 125

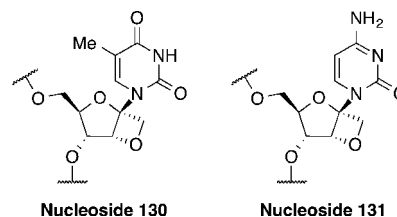
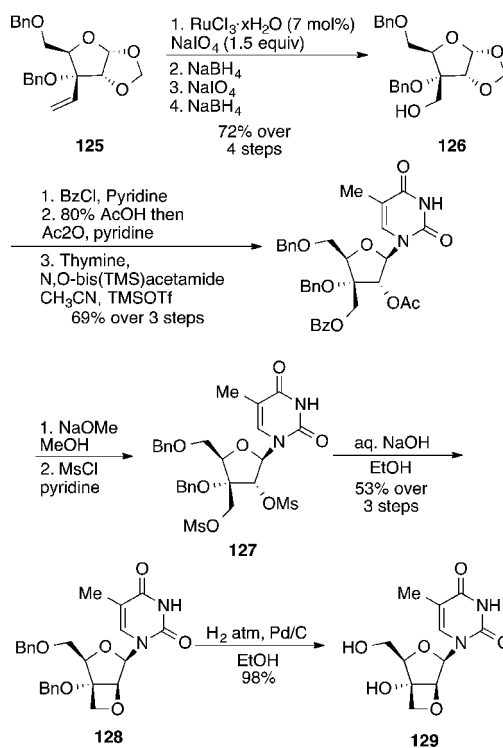
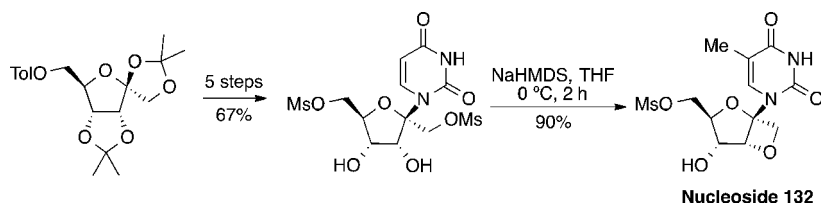


Figure 14. Structures of 1',2'-locked oxetane-containing nucleosides 130 and 131.

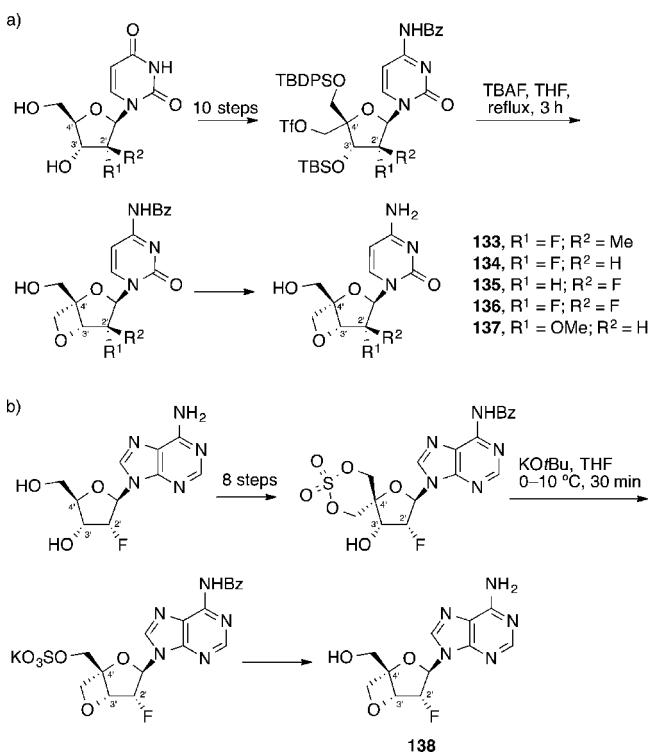
involved base-mediated Williamson etherification with either a mesyl or tosyl leaving group: for example, the synthesis of uracil derivative 132 is shown in Scheme 39. Synthesis of guanine and adenine derivatives was achieved via a similar strategy, which allowed the synthesis of oxetane-containing nucleosides on a multigram scale.²⁰⁶ In 2014, Komsta et al.²⁰⁷ prepared uridine and guanosine 1',2'-locked oxetane derivatives, with anti-HCV activity; a 1',2'-oxetane guanosine 6-triphosphate derivative was found to be a modest inhibitor of HCV NS5B polymerase (IC₅₀ = 10 μM).

Interest in nucleosides including an oxetane moiety as antivirals for treatment of hepatitis C virus (HCV) has led to a number of studies being published in this area. The synthesis and anti-HCV activity of 3',4'-oxetane nucleosides was reported by Du and co-workers²⁰⁸ in 2010. Initially, six examples of the nucleoside with a 4'-hydroxymethyl group were synthesized (133–137), with varying groups known to be compatible with anti-HCV activity at the 2'-position. Synthesis of the cytosine-based analogues was achieved in 12 steps from the corresponding uridine nucleosides (Scheme 40a), whereas the adenine example 138 was synthesized in 10 steps directly from 2'-deoxy-2'-β-fluoroadenosine (Scheme 40b). In both cases, the key ring-forming cyclization was a base-mediated displacement

Scheme 39. Synthesis of 1',2'-Locked Oxetane Nucleoside



Scheme 40. Synthesis of Cytosine and Adenine Oxetane-Containing Nucleoside Analogues



of a triflate (Scheme 40a) or a cyclic sulfate group (Scheme 40b).

When subjected to the subgenomic replicon assay, none of the oxetane derivatives showed significant antiviral activity compared to several related non-oxetane-containing analogues. This lack of activity was postulated to be due to an inability of the modified nucleosides to be anabolized to the triphosphate derivative, an essential step for antiviral efficacy. Therefore, the triphosphate derivatives of **134**–**136** were prepared and their activity relating to inhibition of HCV polymerase (NS5B) was explored and compared to that of a known inhibitor, PSI-6130. In this case, inhibition of HCV polymerase was observed, albeit at higher concentrations than PSI-6130 (Table 8),²⁰⁸ demonstrating that phosphorylation might be the inhibiting factor for activity in whole-cell replicon studies.

In 2014, both Du et al.²⁰⁹ and Jonckers et al.²¹⁰ published anti-HCV data for nucleosides furnished with a pendant oxetane group at the 2'-position. The study by Jonckers et al.²¹⁰ indicated disappointing results for 4'-hydroxymethyl derivatives **142**–**144**, as significantly reduced inhibition of HCV replication was seen compared to other derivatives in a luciferase assay in Huh-7 replicon cells (Table 9).

In a similar study by Du et al.,²⁰⁹ several 2'-oxetane derivatives were compared, unfavorably, to the 2'-tetrahydro-

Table 8. Inhibition of HCV Polymerase (NS5B) Activity in Vitro by Oxetane-Containing Triphosphate Nucleosides Compared to Known Inhibitor PSI-6130

nucleoside	IC ₅₀ (μM)
139	30.96 ± 4.75
140	78.91 ± 5.68
141	32.76 ± 5.36
PSI-6130	5.37 ± 0.50

Table 9. Selected Results Comparing the Anti-HCV Activity of Oxetane-Containing Nucleoside Derivatives to That of a Cyclopropane Analogue

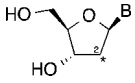
nucleoside	EC ₅₀ (μM)
142	>98
143	17.1
144	7.3

furan derivatives in a luciferase-based genotype 1b replicon assay in Lunet cells (Table 10). Only one example, **143**, indicated any anti-HCV activity, and this was significantly lower than the best 2'-tetrahydrofuran example. In the two studies, different anti-HCV activities were calculated for nucleoside **143**; this was likely due to the different assays used in the studies.

In both studies, by Du et al.²⁰⁹ and Jonckers et al.,²¹⁰ a prodrug strategy was successfully exploited to bypass the restrictive phosphorylation steps. In the study by Jonckers et al.,²¹⁰ 25 phosphoramidate derivatives were prepared from the 4'-hydroxymethyl derivative, by use of *N*-methylimidazole (Scheme 41). The anti-HCV activity of each compound was investigated, and generally very promising EC₅₀ values in the low micromolar range were observed. Additionally, cytotoxicity up to a 98 μM concentration was observed in only one compound.

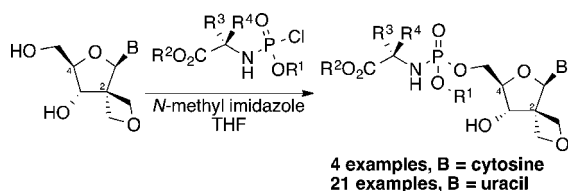
Du et al.²⁰⁹ also prepared a number of prodrug derivatives **151** and **152** (via an analogous method to that shown in Scheme 41) with similarly positive results against a HCV replicon assay using ET-Lunet cells (Table 11). Once again, no cytotoxicity was observed up to concentrations of 100 μM. As with the 2010 study of Du and co-workers,²⁰⁸ triphosphate derivatives **153** and **154** were also prepared. These examples

Table 10. Anti-HCV Activity of Pyrimidine Nucleosides



Nucleoside	B	*	EC ₅₀ (μM)
142	Uracil		>100
145	Uracil		>100
143	Cytosine		56.6
146	Cytosine		>100
147	Uracil		>100
148	Uracil		14.9
149	Cytosine		>100
150	Cytosine		>100

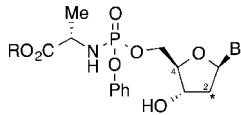
Scheme 41. Synthesis of Oxetane-Containing Nucleoside Prodrugs



demonstrated more promising results than the corresponding tetrahydrofuran-containing analogues and the 4'-hydroxymethyl derivatives against NSSB polymerase and its S282T mutant (Table 12).²⁰⁹

Prasad and co-workers²¹¹ identified oxetanoribonucleosides as potentially interesting antiviral agents, and in 2014 they developed a synthesis of C-4'-spiro-oxetanoribonucleosides utilizing a diastereoselective Novozyme-435-catalyzed deacylation step. In just seven moderate- to high-yielding steps, both thymine and uracil spiro-nucleoside derivatives **155** and **156** could be formed (Scheme 42).

3.1.5. Oxetane Synthesis through Electrophilic Halocyclization of Alcohols. Intramolecular haloetherification has been shown to be a viable strategy for the synthesis of oxetanes but has received relatively little investigation. Throughout the 1980s and early 1990s, a variety of 4-exo-trig electrophilic cyclizations to form oxetanes were discovered largely by use of *N*-bromosuccinimide (NBS) and often with constrained structures. In 1980, Ehlinger and Magnus²¹² found that vinyl silane **157** favored an exo cyclization process, giving adamantyloxetane **158** in a very good yield of 92% (Scheme

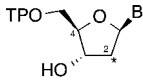
Table 11. Anti-HCV Activity Data for Prodrug Nucleoside Analogues^a


151, B = uracil, R = *i*-Pr
152a-d, B = cytosine, R = Me

Nucleoside	*	EC ₅₀ (μM)
151		16.7
152a		16.7
152b		28.5
152c		28.3
152d		20.6

^aStudied by Du et al.²⁰⁹.

Table 12. Anti-HCV Activity Data for Triphosphate-Containing Nucleosides

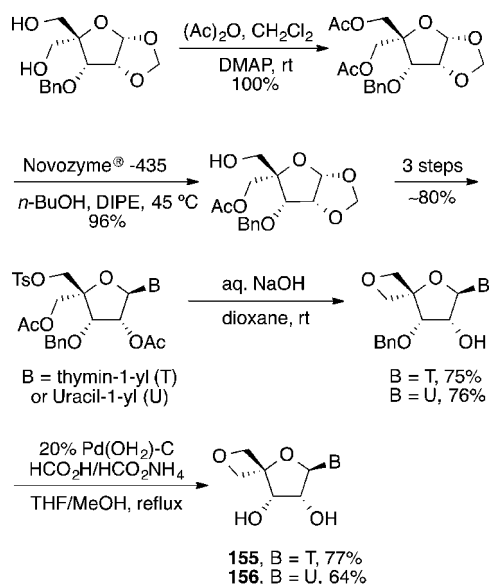
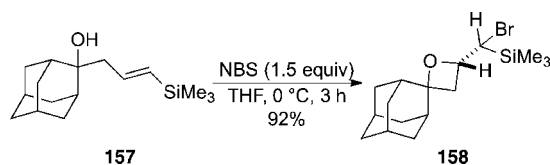
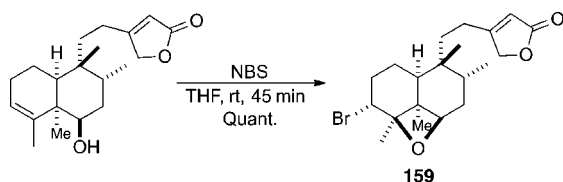


153a-b, B = uracil
154a-d, B = cytosine

Triphosphate	*	IC ₅₀ (NS5B) (μM)	IC ₅₀ (S282T) (μM)
153a		39.4	>100
154a		8.48	>100
154b		>100	n/a
153b		>100	n/a
154c		45.3	>100
154d		>100	n/a

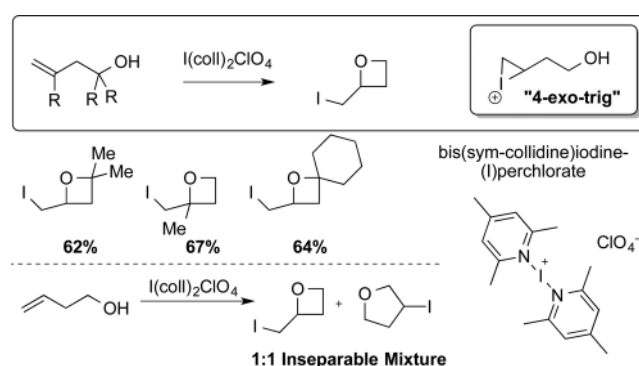
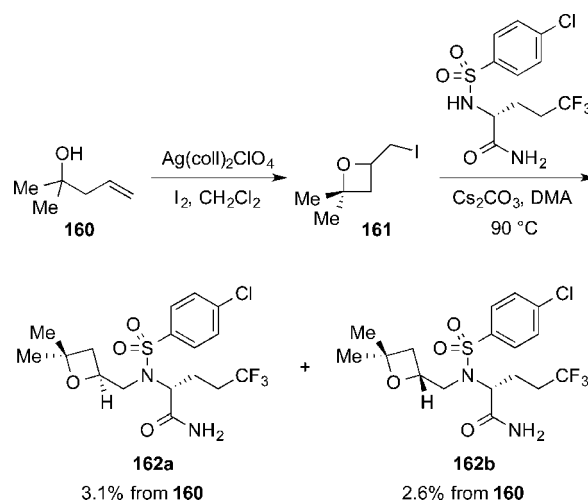
43). The THF that would result from endo cyclization, the desired product in this study, was not observed. A few years later, in the process of determining the stereochemistry of *cis*-clerodane diterpenes, Manabe and Nishino²¹³ formed oxetane **159** in quantitative yield by use of NBS (Scheme 44). The same reaction was used by Paquette et al.²¹⁴ in the synthesis of a [5.9.5] tricyclic system closely related to jatrophatriene.

In the late 1980s, bis(*sym*-collidine)iodine perchlorate [I(coll)₂ClO₄] reagent was used to synthesize β-iodooxetanes by a 4-exo-trig cyclization.²¹⁵ This reagent, which was generated in situ from iodine and bis(*sym*-collidine)silver(I) perchlorate,

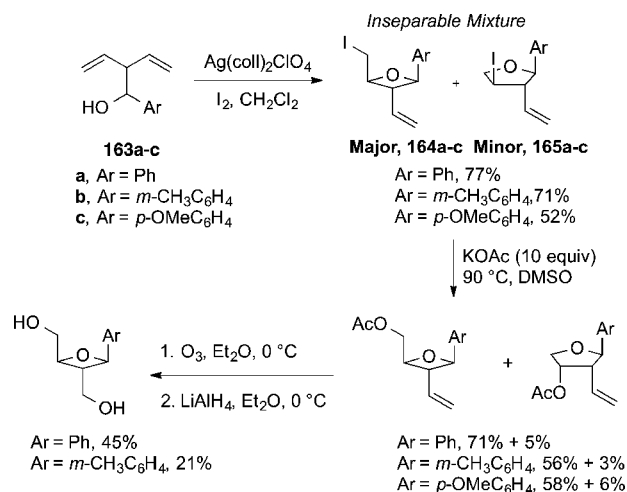
Scheme 42. Seven-Step Synthesis of C-4'-Spiro-oxetanoribonucleosides 155 and 156**Scheme 43. Synthesis of Adamantylloxetane through NBS-Mediated 4-exo-trig Cyclization****Scheme 44. Synthesis of Oxetane-Containing Diterpene Derivative**

could provide three- to seven-membered ring ethers by use of unsaturated alcohols. Four oxetane examples were demonstrated, which indicated that tertiary alcohols helped the exo cyclization, though relatively high yields were also achieved if the double bond was substituted (Scheme 45). The methyl group altered the charge distribution on the iodonium intermediate, which made it more electrophilic at the C3 position. Finally, when an unsubstituted unsaturated alcohol was used, an inseparable 1:1 mixture of oxetane and THF was observed (no yield given). Stepan et al.⁸² used this approach to develop the γ -secretase inhibitors discussed in section 2. Oxetane **161** was formed from alcohol precursor **160**, and the crude material was used to form the alkylated sulfonamide products, obtained in low yields (Scheme 46).

Jung and Nichols²¹⁶ used this 4-exo-trig haloetherification cyclization strategy to synthesize racemic oxetanocin A analogues, predicting that the aryl and vinyl groups on the alcohol substrate **163** would be enough to promote oxetane formation. Cyclization from alcohols **163a–c** occurred via in situ formation of bis(collidine)iodine(I) perchlorate from the silver salt to afford good yields and selectivity (oxetane/THF)

Scheme 45. Synthesis of Iodo-Substituted 2-Alkyloxetanes via 4-exo-trig Cyclization**Scheme 46. Synthesis of γ -Secretase Inhibitor 162 via Iodonium-Mediated Oxetane Cyclization**

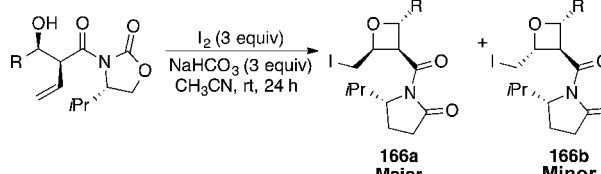
for each substrate (Scheme 47). Trans-substituted oxetanes **164** were the major products, as determined by NOESY experiments, but reductive deiodination of **164a** with LiAlH_4 indicated that all four possible isomeric oxetane products formed in a ratio of 10:2:1.5:1. Oxetanes **164** and the respective THFs **165** could be separated after displacement of the alkyl

Scheme 47. Accessing Oxetanocin A Analogues via Iodonium-Mediated Oxetane Cyclization

iodide with acetate; ozonolysis followed by reduction gave oxetanocin A analogues.

In 1997, an asymmetric variant of this process was achieved through incorporation of an oxazolidinone auxiliary.²¹⁷ With the Evans auxiliary a variety of substituted alcohols underwent the cyclization successfully, and only oxetane products **166** were observed. However, the oxetane bearing a phenyl group readily decomposed (Table 13). Interestingly in a previous

Table 13. Iodine-Mediated Cyclization of Enantioenriched Oxetanes through Incorporation of an Evans Auxillary

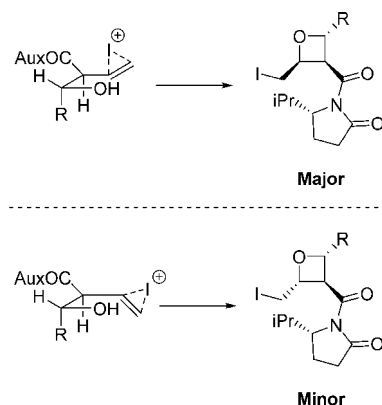


entry	R	yield 166 (%)	ratio a:b
1	Me	63	>98:<2
2	Et	90	82:18
3	<i>i</i> Pr	77	81:19
4	Ph	85	^a

^aDecomposition occurred in this case.

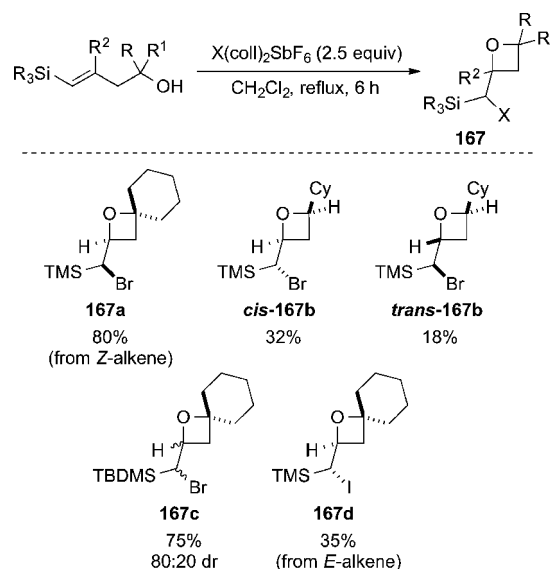
study, use of methyl esters preferentially gave THF products.²¹⁸ Good facial selectivity was observed in the cyclization step, proposed to be due to minimizing a 1,3-transannular interaction between the iodomethyl and R groups in the developing oxetane ring. The selectivity went down as the size of R increased, suggesting the transition state to the major product may experience allylic strain ($A^{1,3}$ strain) between the terminal vinyl hydrogen and imide group (Scheme 48).

Scheme 48. Possible Transition States Explaining the Facial Selectivity of Cyclization



Exo cyclization of vinylsilanes was later investigated by Rousseau and co-workers²¹⁹ (Scheme 49). The nature of the counterion in the halide reagent was important, with best results obtained with hexafluoroantimonate. Tertiary alcohols that were unsubstituted on the double bond gave only one diastereoisomer (**167a**) upon reaction with the bromonium reagent $\text{Br}(\text{coll})_2\text{SbF}_6$, and *Z*- and *E*-alkenes gave different oxetane diastereoisomers. When secondary alcohols were used, mixtures of *cis*- and *trans*-2,4-disubstituted oxetane isomers were obtained (**167b**). Substituents on the $\text{C}=\text{C}$ double bond led to mixtures of diastereomers (**167c**), which could not be

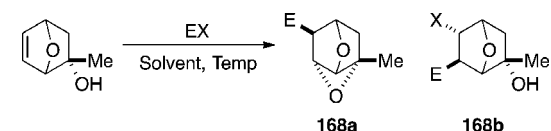
Scheme 49. Electrophilic Halocyclization of Functionalized Vinylsilanes



identified. Finally, reactivity of the iodonium salt, $\text{I}(\text{coll})_2\text{SbF}_6$, was investigated but a reduced yield was obtained (**167d**).

Similar transformations have been reported by exo cyclization using electrophilic S and Se reagents to generate oxetanes. The electrophilic addition of PhSe, by use of PhSeCl, and etherification was first reported as an unwanted side reaction in the synthesis of a *cis*-hydrindenone, a bicyclic natural product scaffold.²²⁰ Arjona et al.²²¹ shortly afterward reported electrophilic addition using both PhSeCl and PhSeI with a variety of 7-oxanorbornenic substrates. The use of PhSeCl was more effective at promoting etherification and gave oxetane **168a** as the major product, whereas the use of PhSeI gave the addition of chloride as the major product. Improved selectivity and yields for the oxetanes could be achieved if the temperature of the reaction was lowered, though tertiary alcohols were required to gain high yields for cyclization (Table 14).²²²

Table 14. Investigations into Electrophilic Cyclization of a 7-Oxanorbornenic Substrate

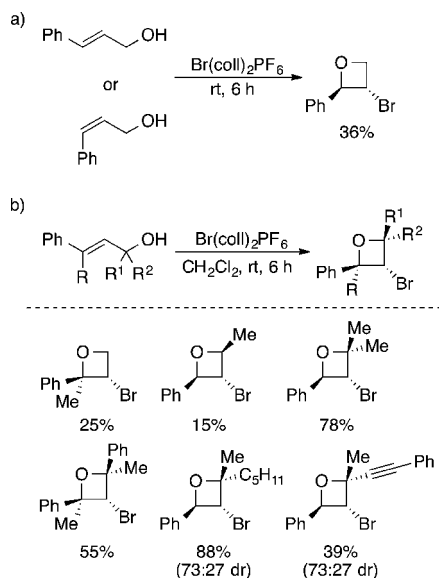


entry	electrophile (EX)	solvent	temp (°C)	yield 168 (%)	ratio a:b
1	PhSeCl	CHCl_3	rt		4:1
2	PhSeCl	CH_2Cl_2	−50	93	1:0
3	PhSeCl	CHCl_3	rt		1:4
4	PhSeCl	CH_2Cl_2	−78	84	9:1

Synthesis of four-membered rings from a 4-endo-trig cyclization is much less common than a 4-exo-trig cyclization, due to the strain in the transition state. However, Homsí and Rousseau²²³ showed that oxetanes (as well as other four-membered rings) could be synthesized in reasonable yields from cinnamic alcohols through a 4-endo-trig cyclization by use of bis(collidine)bromine(I) hexafluorophosphate (Scheme 50a). The *E*- and *Z*-alkenes gave the same oxetane, with the

stereochemistry determined to be trans due to a coupling constant of 6 Hz (expected to be larger for cis).

Scheme 50. Oxetane Synthesis via 4-endo-trig Halselectrophilic Cyclization^a



^a(a) Initial result with cinnamic alcohols. (b) Substrate scope accessing highly substituted oxetanes.

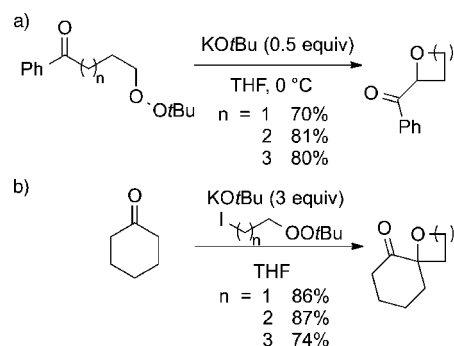
Examination of the influence of substituents on cyclization revealed that primary and secondary alcohols mainly gave low yields of oxetanes and significant degradation, and tertiary alcohols gave oxetanes in good yields (Scheme 50b).^{223,224} A tertiary alcohol with an α -phenyl group led to oxetane formation in moderate yield (55%). When $R \neq R'$, mixtures of diastereoisomers were observed. These oxetanes were further functionalized in order to access oxetane derivatives, for example, through oxidative cleavage of the phenyl group with NaIO₄ and catalytic RuCl₃ (not shown).

3.1.6. Other C–O Bond-Forming Cyclization Approaches. In 2014, Dussault and co-workers²²⁵ reported the synthesis of cyclic ethers through a C–O bond formation with reversed polarity. Unlike the traditional Williamson etherification (oxyanion and electrophilic carbon), carbanions as enolate anions and electrophilic oxygen in the form of a peroxide were used. Cyclization proceeded rapidly in the presence of KOtBu or KH in THF, giving oxetanes, THFs, and tetrahydropyrans (THPs) in high yields (Scheme 51a). The transformation was also achieved in an intermolecular fashion with *t*-butyl iodoalkyl peroxides and cyclohexanone to give the spirocyclic ether derivatives (Scheme 51b).

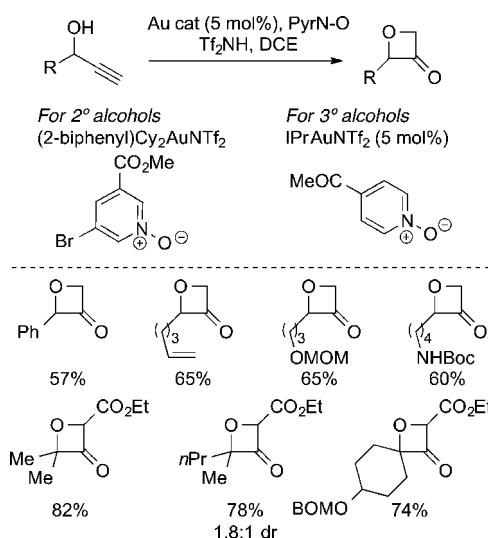
Commonly, oxetan-3-ones have been formed by intramolecular OH insertion of diazo compounds, which has been previously reviewed.^{5,226} In 2010, Zhang and co-workers²²⁷ reported an alternative, whereby a gold carbene was generated from an alkyne that formed oxetan-3-ones from propargylic alcohols in one step, with Au(I) as catalyst (Scheme 52). Functionalized secondary and tertiary propargylic alcohols were successfully employed though they required a slight modification to the catalyst and pyridine *N*-oxide additives.

Sharma and Williams²²⁸ demonstrated the formation of oxetan-3-ones in a two-step sequence from allenes (Scheme 53). Double epoxidation of the allene and then halide or

Scheme 51. Synthesis of Oxetane, Tetrahydrofuran, and Tetrahydropyran Rings through Reverse C–O Bond Formation

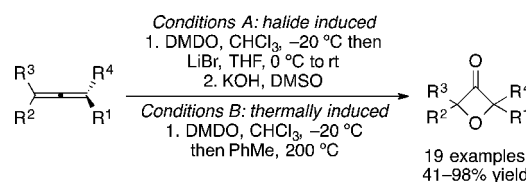


Scheme 52. Au(I)-Catalyzed Cyclization of Propargylic Alcohols to Oxetan-3-ones



thermally induced rearrangement of the spirodiepoxide gave the desired oxetan-3-one analogues. Different conditions for the rearrangement gave different diastereomers as the major product.

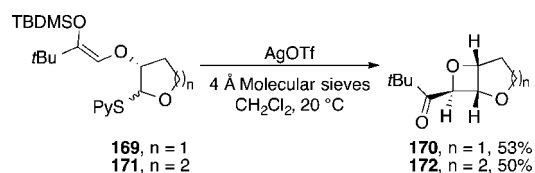
Scheme 53. Synthesis of Oxetan-3-ones in Two Steps from Allenes



3.2. Cyclization through C–C Bond Formation

The formation of oxetanes via C–C bond formation is relatively unexplored, but there are increasing examples of this as an effective and complementary strategy. In the 1990s, Craig et al.^{229,230} reported the use of a C–C bond-forming cyclization for the stereoselective synthesis of bicyclic ketooxetanes **170** and **172** by intramolecular C-glycosidation (Scheme 54). Silver triflate mediated the cyclization of thiopyridyl glycosides **169** and **171** in moderate yields through addition of the silyl enol ether side chains to the generated

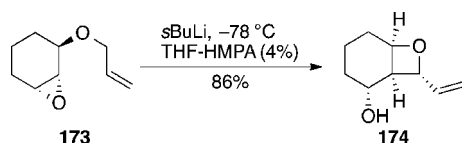
Scheme 54. Intramolecular C-Glycosidation Route to Oxetanes



oxocarbenium intermediate. The stereoselectivity was rationalized as resulting from minimization of unfavorable steric interactions between the bulky nucleophilic side chain and the ring system in the transition state. Extension of this methodology to more complex bicyclic systems from sugar derivatives was achieved by variation of the leaving group and cationic activator, either under the original conditions or with thiophenyl glycosides with tin chloride or ethylaluminum dichloride.^{231,232}

Intramolecular cyclization with epoxide opening through C–C bond formation has been used to form oxetanes. First reported in 1976 by Still,²³³ trans-epoxy allylic ether **173** was treated with *s*BuLi in THF/hexamethylphosphoramide (HMPA) at $-78\text{ }^{\circ}\text{C}$ to form vinyl oxetane **174** regioselectively, via stereospecific cyclization of the resulting allyloxycarbanion (Scheme 55). Formation of the more strained four-membered

Scheme 55. Vinyl Oxetane Formation via Intramolecular Epoxide Ring-Opening Cyclization

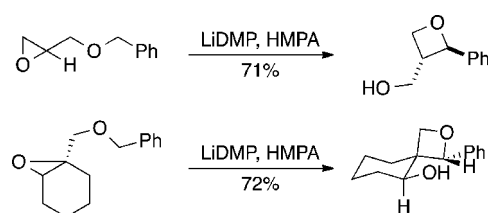


ring over the isomeric five- or six-membered rings was favored due to the lower strain necessary in the transition state to obtain the required alignment of the carbanionic center and the epoxide C–O bond. The trans isomer of **173** was required for intramolecular epoxide ring opening: when the cis isomer was treated with *s*BuLi, 2-cyclohexenol was formed. The addition of 4% HMPA was required to prevent the oxetane ring opening of **174** through further reaction with *s*BuLi.

Bird and Hormozi²³⁴ reported a similar outcome upon treating allyl glycidyl ethers with *s*BuLi in THF/HMPA at $-78\text{ }^{\circ}\text{C}$; the four-membered oxetane or seven-membered oxepane products were favored over the isomeric THF or THP. In general, the oxepane product was favored, but two examples gave the oxetane as the major product due to substituent effects. In 1983, Williams and Grote²³⁵ reported the intramolecular epoxide ring opening of substrates bearing a benzyl substituent to afford various cyclic ethers. For oxetane examples, treatment of epoxides with 3 equiv of lithio-2,4-dimethylpiperidine (LiDMP) and 3 equiv of HMPA in THF at $-78\text{ }^{\circ}\text{C}$, followed by warming to $22\text{ }^{\circ}\text{C}$ for 2 h, resulted in cyclization (Scheme 56). Good stereocontrol was observed, with the phenyl ring preferring orientations that minimized unfavorable steric interactions.

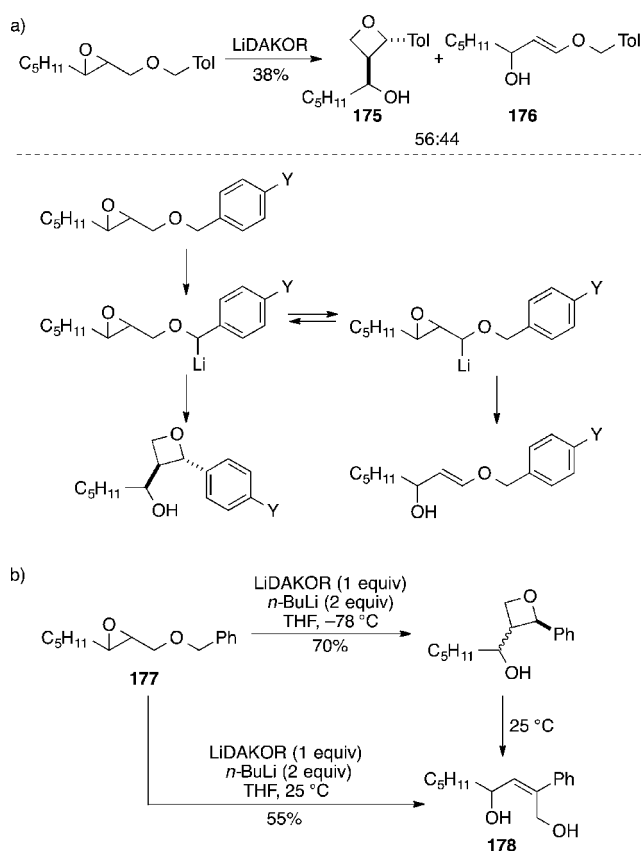
Mordini et al.²³⁶ further explored the reactivity of benzyl epoxides as precursors to access oxetanes by treating benzyl epoxy ethers with 2 equiv of LiDAKOR (lithium diisopropylamine and potassium *tert*-butoxide) in THF at $-50\text{ }^{\circ}\text{C}$ for 15 h. Cyclization of the benzylic anion by attack at the epoxide

Scheme 56. Intramolecular Cyclization of Epoxy Ethers Bearing a Benzyl Substituent



formed 2,3-disubstituted oxetanes with complete anti selectivity between the C2 and C3 substituents, but yields were low due to a competing elimination reaction to form vinyl ethers **176** (Scheme 57a). The electronics of the aryl group were

Scheme 57. Oxetane Formation from Cyclization of Benzyl Epoxides

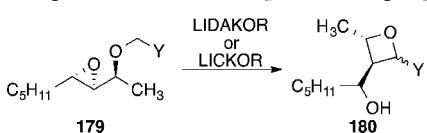


important in determining reaction outcomes. With electron-rich examples, migration of the lithiated anion from the benzylic position occurred, resulting in formation of the vinyl ether product ($Y = \text{OMe, Me, and } t\text{Bu}$). Electron-withdrawing substituents favored oxetane formation unless the anion was too stable; the *p*-nitro substituent gave no reaction. When a phenyl ring was present ($Y = \text{H}$), the oxetane could be accessed as the only product in 70% yield. When benzyloxy ether **177** was treated with LiDAKOR and a large excess of *n*BuLi at higher temperature ($25\text{ }^{\circ}\text{C}$), *Z*-alkene diol **178** was formed due to further reaction with excess base (Scheme 57b).²³⁷ The lithiated oxetane underwent ring opening to form a carbene intermediate, which, following an alkyl 1,2-shift, afforded the observed diol. The same process was reported for more functionalized alkoxymethyl derivatives; all substrates cleanly

converted to the oxetanes in good yields of 50–75% upon treatment of the epoxides with LiDAKOR.²³⁸ Subsequent treatment with *n*BuLi (4 equiv) resulted in diol formation with stereocontrol.

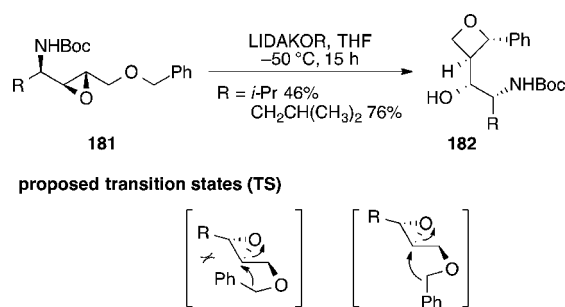
α -Substituted epoxy ethers **179** prohibited migration of the anion, resulting in trisubstituted oxetanes **180** as the sole products.²³⁹ Treating benzyloxy epoxides, prepared by a Sharpless kinetic resolution, with LiDAKOR or LiCKOR (butyllithium and potassium *tert*-butoxide) in THF at $-50\text{ }^{\circ}\text{C}$ resulted in excellent yields of the trisubstituted oxetanes (Table 15, entry 1).

Table 15. Stereoselective Synthesis of Trisubstituted Oxetane through Intramolecular Epoxide Ring Opening



entry	Y	2,3-syn:2,3-anti	yield 180 (%)
1	C ₆ H ₅	13:87	80
2	<i>p</i> -F-C ₆ H ₅	12:88	81
3	CH ₂ =CH	2:98	80
4	C ₆ H ₅ S	78:22	86

Scheme 58. Regio- and Stereoselective Synthesis of Amino Alcohol-Substituted Oxetanes



In 1997, Mordini et al.²⁴⁰ expanded these studies to access amino alcohols bearing an oxetane moiety. Benzyl epoxy ethers derived from valine, leucine, and serine were treated with LiDAKOR at $-50\text{ }^{\circ}\text{C}$ to generate the amino alcohol-substituted oxetanes (Scheme 58). Employing the *E* isomers of **181** resulted in formation of the anti configuration of oxetane **182**. However, when a *Z* isomer of the benzyl epoxy ether derived from serine was employed (protected as an oxazolidine), the

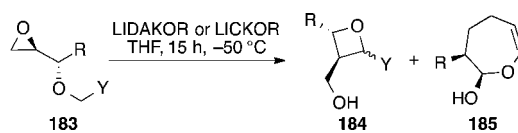
oxetane was formed in 65% yield and a mixture of syn and anti (30:70) configurations was observed.

Trisubstituted oxetanes with a hydroxymethyl substituent could be generated from monosubstituted epoxides. Terminal epoxy α -substituted ethers **183**, upon treatment with LiCKOR or LiDAKOR at $-50\text{ }^{\circ}\text{C}$, afforded **184** (Table 16).²⁴¹ When Y was a phenyl ring or an alkyne, 2-phenyl- or 2-alkynyloxetanes were the major products, demonstrating preferred formation of the four-membered ring over the isomeric THF. The relative stereochemistry of the oxetane products at C2/C3 was determined by consideration of the stereochemistry of epoxy ether substrates and selectivity for the anti configuration of Y and hydroxymethyl substituents (Table 16, entries 1–4). Oxepanes **185** were formed instead when allyl epoxy ethers were employed (Table 16, entries 5–7). Enantioenriched cis-substituted epoxides were also converted to enantioenriched epoxides.²⁴² A synthesis of oxetanocin used this strategy with lithiation of allyl ether and epoxide opening; however, selectivity and yield for the desired oxetane were low.^{243,244}

Fujioka and co-workers²⁴⁵ developed a C–C bond-forming route to highly substituted 2-phosphonatooxetan-3-ones by intramolecular ester condensation (Scheme 59). Cyclization precursors such as **186** were prepared from the corresponding methoxymethyl ether with trimethylsilyl triflate (TMSOTf) and P(OMe)₃, and the cyclization was then promoted with lithium diisopropylamide (LDA) in the presence of tetramethylethylenediamine (TMEDA) to form oxetanone **187**. The phosphonates could then be used in Horner–Wadsworth–Emmons reactions to generate the substituted *exo*-methyleneoxetane **188**. A one-pot process gave similar yields to the two-step procedure.

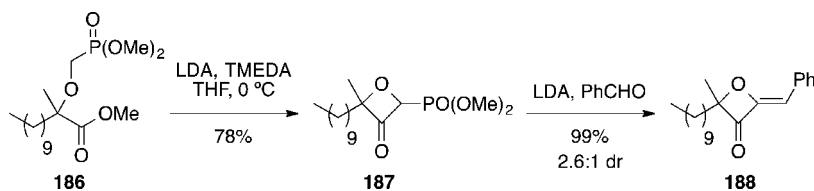
In 2014, Bull and co-workers²⁴⁶ reported an anionic substitution cyclization reaction to form 2-functionalized oxetanes, forming the C2–C3 bond. 2-Sulfonyl oxetanes were targeted as unusual fragments for fragment-based drug discovery but presented unsuitable substrates for C–O bond-forming cyclization approaches.⁸⁵ This prompted more extensive investigation of a C–C bond-forming approach. The required cyclization precursors **189** were accessed in three steps from readily available chloromethyl aryl sulfides. Treatment of aryl sulfones **189** with lithium bis(trimethylsilyl)amide (LiHMDS) resulted in formation of a carbanion, stabilized by the sulfone, which effected cyclization to afford 2-sulfonyl oxetane **190** (Scheme 60). The reaction proceeded in high yield in just 1 h at $0\text{ }^{\circ}\text{C}$ and was successful on a gram scale. The aryl group could be readily varied to build a collection of 2-sulfonyl oxetanes. The sulfonyl oxetane fragments were further

Table 16. Stereoselective Synthesis of Hydroxyoxetanes through Cyclization of Epoxy Ethers

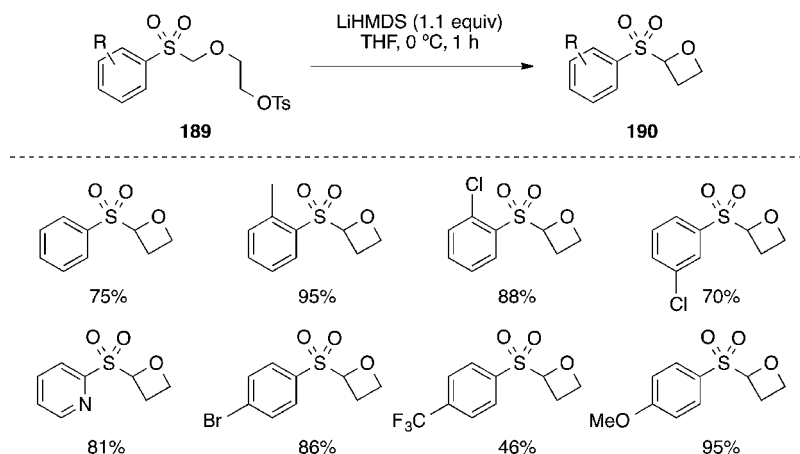


entry	R	Y	184 (syn/anti): 185 (syn/anti)	yield (%)
1	C ₅ H ₁₁	C ₆ H ₅	98 (5/95):2	53
2	CH ₂ OSiMe ₂ tBu	C ₆ H ₅	98 (2/98):2	55
3	C ₅ H ₁₁	CH \equiv C	98 (20/80):2	55
4	CH ₂ OSiMe ₂ tBu	CH \equiv C	98 (15/85):2	50
5	H	CH ₂ =CH	2:98 (98/2)	45
6	C ₅ H ₁₁	CH ₂ =CH	2:98 (98/2)	65
7	CH ₂ OSiMe ₂ tBu	CH ₂ =CH	2:98 (98/2)	53

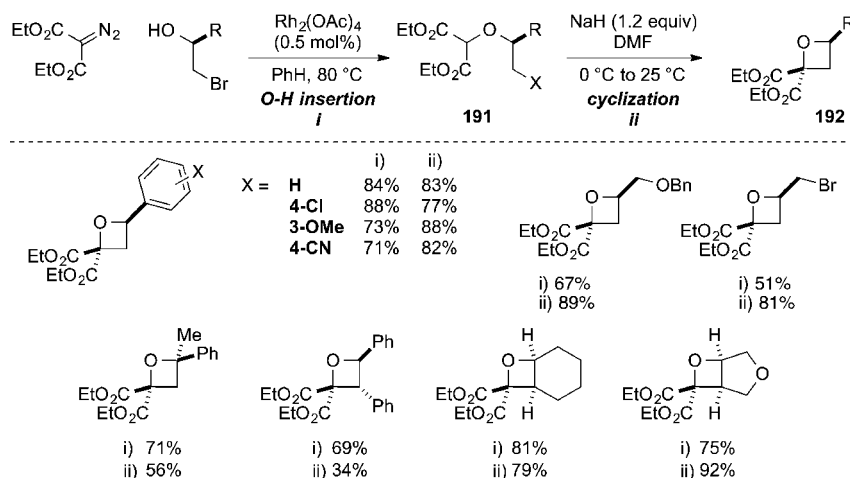
Scheme 59. Synthesis of Oxetan-3-ones by Intramolecular Ester Condensation



Scheme 60. Synthesis of 2-Sulfonyl Oxetanes



Scheme 61. Oxetane Synthesis by O–H Insertion/C–C Bond-Forming Cyclization



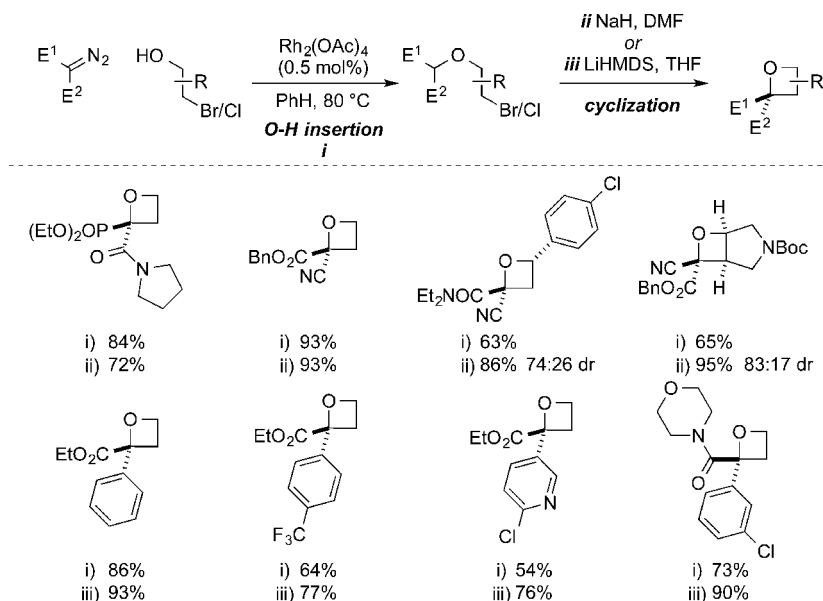
derivatized through deprotonation on the ring, aided by the sulfonyl group (section 6), as well as cross-coupling reactions through the aryl substituent, maintaining the oxetane ring intact.^{246,85} Furthermore, the chemical and metabolic stability of the fragments, relevant to fragment-based drug discovery, was assessed.⁸⁵ This approach to oxetane synthesis was extended to sulfonyl oxetanes, which cyclized under modified conditions upon deprotonation adjacent to the sulfoxide.²⁴⁷

The C–C bond-forming strategy was extended to a two-step approach to 2,2-disubstituted oxetane derivatives.^{140,248} A rhodium acetate catalyzed O–H insertion between ethyl diazomalonate and β -bromohydrins rapidly constructed suitable cyclization precursors **191** (Scheme 61). Cyclization forming the C–C bond [NaH in *N,N*-dimethylformamide (DMF) at 0 °C for 1 h] was very effective to generate 2,2-disubstituted oxetanes **192**. Substituents were incorporated at the 4-position by use of substituted bromohydrins, and the ee of

enantioenriched bromohydrins was transferred to the oxetane product. Varied substituents could be incorporated at the 4-position, and chlorides were also effective as leaving groups. More highly substituted oxetane examples were prepared from tertiary alcohols and 1,2-substituted bromohydrins, including cyclic systems to generate fused oxetanes. These diester oxetane derivatives were further elaborated in order to generate a range of oxetane-containing fragments and building blocks.

The use of other diazo compounds gave a series of novel functionalized oxetane motifs. From the corresponding diazo compounds, varied functional groups were introduced into the oxetane products, including amides, nitriles, phosphonates, and sulfones (Scheme 62).²⁴⁹ More substituted examples were also demonstrated, with low to good diastereoselectivity. Through the use of donor–acceptor diazo compounds, aryl rings could also be introduced onto the oxetane ring. With these examples, deprotonation with LiHMDS in THF gave better conversions.

Scheme 62. Synthesis of Functionalized Oxetanes from Unsymmetrical Diazo Compounds



Ester hydrolysis was again demonstrated, and amide coupling with nitrile- and aryl-substituted examples accessed new amide derivatives.

4. [2+2] AND FORMAL [2+2] CYCLOADDITIONS

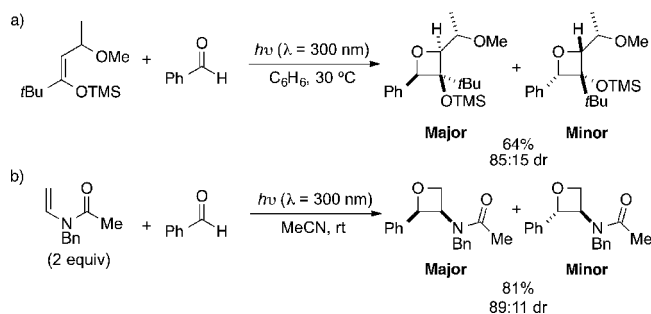
This section will consider recent examples in the synthesis of oxetanes where both the C–C and C–O bonds are formed in a single operation. Given the comprehensive reviews in recent years on the topic of the Paternò–Büchi reaction,^{3,4,250–252} here selected examples of photochemical [2+2] reactions will be presented, including continuous-flow approaches and other formal [2+2] reactions, focusing on recent advances. See section 7 for examples of [2+2] reactions involving allenes to form 2-alkylideneoxetanes.

4.1. Paternò–Büchi [2+2] Photocycloaddition

Over many years, the light-induced Paternò–Büchi reaction between carbonyls and olefins has been exploited for oxetane synthesis. High yields are often achieved for suitable substrates, frequently affording highly substituted oxetanes. Reaction between the alkene and a photoexcited singlet or triplet carbonyl derivative proceeds to the oxetane by either a nonconcerted or concerted pathway. Where the reaction occurs through the triplet-state carbonyl, the reaction is nonconcerted and proceeds through a C,C-biradical intermediate, first forming the C–O bond. However, reaction of the singlet carbonyl is more complex and can occur through either a concerted mechanism or nonconcerted mechanism.^{3,4,253–256} While regio-, site-, and stereoselectivity can be challenging, such selectivities have been achieved, for example, in the extensive work by Bach et al., targeting 3-silyloxy^{257,258} and 3-aminooxetane derivatives^{259–263} (Scheme 63).^{264,265} In this work, reactions were conducted by irradiating aryl aldehydes and silyl enols or *N*-acyl enamines with ultraviolet light, and high diastereoselectivity was obtained, with a *cis* configuration favored between the aryl group and the silyl ether/amine.

Recently, Griesbeck et al.²⁶⁶ have formed fused oxetaneisoxazolines by a Paternò–Büchi reaction of methyl-substituted isoxazoles with aryl aldehydes with high regioselectivity and exo diastereoselectivity. Zhang and co-workers²⁶⁷ reported the

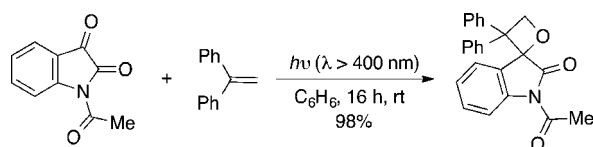
Scheme 63. Synthesis of (a) 3-Silyloxyoxetanes and (b) 3-Aminooxetanes via Paternò–Büchi Photochemical [2+2] Cycloadditions



[2+2] cycloaddition reaction of oxazoles with isoquinoline-1,3,4-trione to form spiroisoquinolineoxetanes, which underwent an acid-catalyzed hydrolysis to give spiroisoquinolineoxazoline products. Furthermore, the Paternò–Büchi reaction has been conducted on designed chiral templates with dihydropyridones,^{268,269} with 8-phenylmenthol as an auxiliary,²⁷⁰ and directed by chiral hydroxy groups.²⁷¹ Additionally, the synthesis of a variety of natural products, for example, oxetanocin²⁷² and merrilactone A,²⁷³ successfully utilized the Paternò–Büchi reaction as the oxetane-forming step.

There are certain substitution patterns around oxetanes that have only been prepared through [2+2] approaches, one such example being 3,3-diaryl-substituted oxetanes. In 2001, Xu and co-workers²⁷⁴ reported the synthesis of a 3,3-diphenyloxetane in 98% yield by a Paternò–Büchi reaction (Scheme 64). Prior to this work 3,3-diaryloxetanes were not known in the literature.

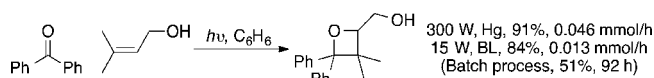
Subsequently, Inoue and co-workers^{275,276} used [2+2] photocycloaddition methods for the synthesis of 3,3-diphenyloxetanes from chiral cyanobenzoates and diphenylethene. Interestingly, the diastereoselectivity was entirely dependent on the mode of excitation (direct excitation of acceptor or selective activation of the charge-transfer band). Noninterconvertible diastereomeric pairs of excited-state complexes were generated with different ratios depending on excitation, and the dr was

Scheme 64. Synthesis of 3,3-Diphenyloxetane by Paternò–Büchi Reaction

carried through to the oxetane products. The mode of excitation was controlled by simply changing the irradiation wavelength.^{275,276}

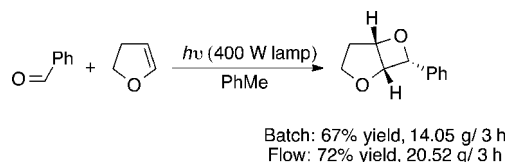
D'Auria and co-workers²⁷⁷ examined the Paternò–Büchi reaction with alkenyl boronates and benzophenone. When pinacol boronate **193** and benzophenone were irradiated in benzene at 310 nm, the product oxetane **194** was observed in a 30% yield (Scheme 65a). Interestingly, when the *N*-methyliminodiacetic acid (MIDA) boronate derivative **196** was submitted to the same conditions, allylic alcohol **197** was observed in 66% yield, resulting from hydrogen abstraction at the allylic position (Scheme 65b). Computational studies indicated that the Paternò–Büchi reaction was likely to proceed via C,C-biradical intermediate **195**. This differed from the previous hypothesis that electron-poor alkenes proceeded mainly by a C,O biradical intermediate. Further computational studies suggested that both observed products were the kinetically favored products and not thermodynamically preferred.²⁷⁷

Photochemical reactions, although often powerful as a synthetic tool, may involve long irradiation times that can lead to reduced yields of the product due to undesired reactions over the extended time period. In recent years, reactions in continuous flow have been described as a strategy to achieve more efficient and uniform irradiation.²⁷⁸ The first example of a [2+2] cycloaddition in a microflow system was published in 2004; enones and vinyl ethers were reacted to give the corresponding cyclobutane, by use of a 300 W mercury lamp and a residence time between 2 and 3.2 h.²⁷⁹ The equivalent reaction on a model substrate in a batch process gave a significantly lower yield (8% vs 88%), demonstrating the potential of this approach.²⁷⁹ Subsequently, this methodology has been applied to the Paternò–Büchi reaction for synthesis of oxetanes. In 2011, Ryu and co-workers²⁸⁰ demonstrated that using either a 15 W black light (BL) or a 300 W mercury lamp in a microflow photoreactor system with a residence time of 1.2 or 4 h converted benzophenone and prenyl alcohol to the desired oxetane in excellent yields of 84% or 91% (Scheme 66).

Scheme 66. First Example of Paternò–Büchi Cycloaddition in Flow

The 15 W black light required an extended residence time to achieve comparable yields, but the energy efficiency was still far superior to the batch process, which yielded only 51% of product after 92 h.²⁸⁰

A single example of a Paternò–Büchi cycloaddition in flow was published by Booker-Milburn and co-workers²⁸¹ in 2014 (Scheme 67). After 3 h, the batch process (run at a 0.3 M

Scheme 67. Example of Paternò–Büchi Cycloaddition in Flow Compared to Batch Process^a

^aBooker-Milburn and co-workers.²⁸¹

concentration) gave 14.05 g of product (67% yield). Under optimized flow conditions at a flow rate of 3 mL·min⁻¹, 20.52 g of product was isolated after 3 h (72% yield), representing an increase in productivity of 50%.

In 2014, Kakiuchi and co-workers²⁸² investigated the Paternò–Büchi reaction, using slug flow technology to increase the efficiency of the system, which involves two interspersed phases in the flow microsystem. Three different modes of flow were investigated and compared to batch reaction: normal flow, slug flow with substrate solution/N₂, and slug flow with substrate solution/H₂O. Both normal flow and slug flow approaches gave a considerable increase in reaction efficiency compared to the batch reaction (Table 17).²⁸² The slug flow approach with substrate solution/H₂O combination gave the highest efficiency. Suggested reasons for the increase in efficiency include light dispersion effects and a stirring effect caused by movement of the second layer, as well as a thin-layer effect leading to a short pathway for irradiation. All conditions gave the same diastereoselectivity.

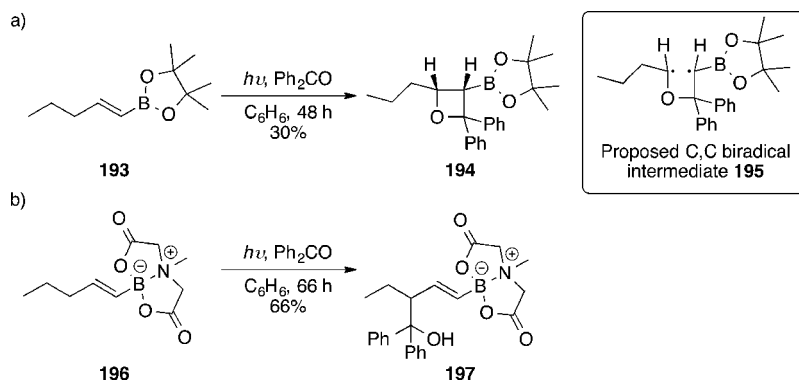
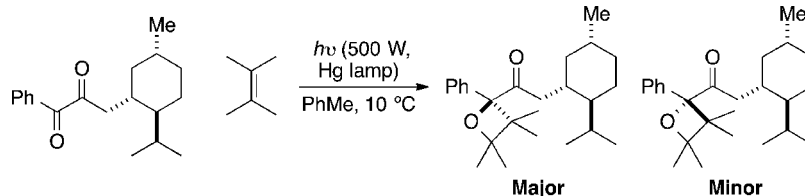
Scheme 65. Photochemical Reactions of Electron-Poor Alkenyl Boronates with Benzophenone

Table 17. Effect of Normal and Slug Flow Conditions on Efficiency of Paternò–Büchi Cyclization



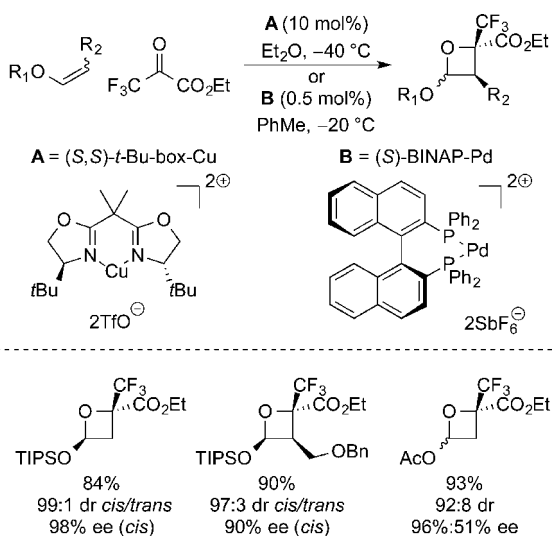
reactor	yield (%)	irradiation time (s)	energy efficiencies	
			%·W ⁻¹ ·h ⁻¹	%·W ⁻¹ ·h ⁻¹ ·cm ⁻²
batch	40	180	1.60	0.561
normal flow	39	30	9.36	0.596
slug flow ^a	45	15	21.6	1.376

^aUsing H₂O and substrate solution.

4.2. Formal [2+2] Cycloadditions

In 2011, Mikami et al.²⁸³ reported a Lewis acid-catalyzed asymmetric formal [2+2] cycloaddition to form 2-trifluoromethyloxetanes from trifluoropyruvate and activated alkenes (Scheme 68). This transformation was achieved by use of

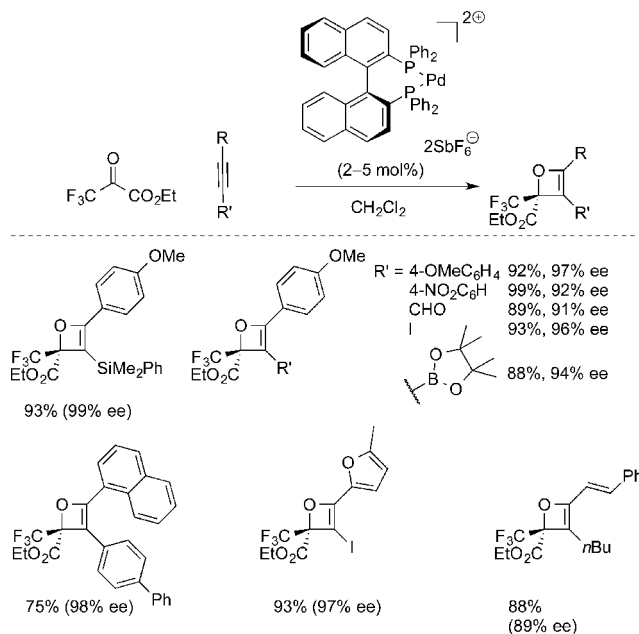
Scheme 68. Synthesis of 2-Trifluoromethyloxetanes via Transition Metal-Catalyzed Formal [2+2] Cycloaddition



either Cu(II) or Pd(II) complexes depending on the vinyl substrate: silyl ethers required Cu–bis(oxazoline) complex **A**, whereas Pd–BINAP complex **B** [BINAP = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl] was required for the less reactive vinyl acetate.

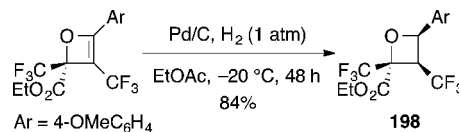
This Lewis acid-promoted strategy was also used to synthesize unusual yet stable oxetene derivatives. Mikami and co-workers^{284,285} demonstrated that alkynylsilanes bearing electron-rich *p*-methoxyphenyl groups underwent the formal [2+2] cycloaddition to afford oxetenes with high ee when a chiral cationic BINAP–Pd complex was used (Scheme 69). Alkynes bearing aliphatic and aromatic groups gave the desired oxetanes in good to excellent yields and ee.²⁸⁴ A variety of other conjugated alkynes were also compatible, including 1-naphthyl-, heteroaryl-, and vinyl-substituted alkynes. Remarkably, an ynamide was also able to undergo this transformation in excellent yield and ee, and the catalyst loading could be lowered to 0.5 mol %. These unusual oxetenes could undergo a variety

Scheme 69. Synthesis of Chiral, Stable Oxetene Derivatives through Formal [2+2] Cycloaddition Mediated by a Chiral BINAP–Pd Complex



of transformations, including reduction of the double bond with Pd/C and H₂ to give oxetane **198** (Scheme 70).²⁸⁴

Scheme 70. Reduction of Trifluoromethylated Oxetene to the Corresponding Oxetane

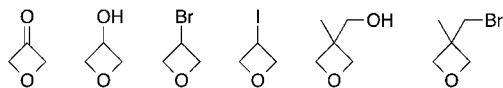


5. SYNTHESIS OF OXETANE DERIVATIVES FROM OXETANE-CONTAINING BUILDING BLOCKS

Partly due to interest in the pharmaceutical industry, a number of oxetane building blocks have recently been developed and become increasingly available. In turn, this has furthered the exploration of oxetanes in drug discovery. An increasing selection of oxetane building blocks, largely 3-substituted examples, are now readily available from commercial suppliers

(Figure 15). Certain examples, particularly modifications of oxetan-3-one, and 3-hydroxyoxetane are inexpensive, yet other

Readily available, inexpensive oxetane building blocks



Less available and costly

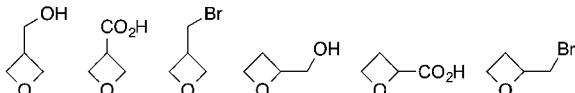
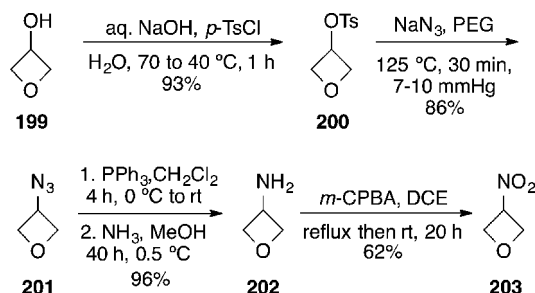


Figure 15. Some commercially available oxetane-containing building blocks.

simple substitution patterns remain very costly, for example, oxetane-3-carboxylic acid.

Reactions of 3-hydroxyoxetane **199** were demonstrated by Baum et al.²⁸⁶ in 1983 via the tosylate, formed by use of aqueous sodium hydroxide and tosyl chloride (Scheme 71).

Scheme 71. Synthesis of 3-Amino- and 3-Nitrooxetane



Reaction of 3-(tosyloxy)oxetane **200** with sodium azide yielded 3-azidooxetane **201** in 86% yield. Subsequent reaction with triphenylphosphine and then ammonolysis with liquid ammonia gave 3-aminooxetane **202** in excellent 96% yield. Oxidation to 3-nitrooxetane **203** was successful with *m*-CPBA. This could be then converted to the 3,3-dinitrooxetane by use of aqueous methanol and tetranitromethane.²⁸⁶

Simple 3-bromo, iodo, and tosylate examples have been shown to be effective electrophiles for N-alkylation, especially on N-heteroaromatic compounds, with nucleophilic substitution occurring at the four-membered ring by an S_N2 mechanism.²⁸⁷ Recent examples include applications in medicinal chemistry and in the preparation of substrates for ring-opening reactions (Scheme 72;^{288,289} also see section 3.1.3.1 for additional examples of similar reactions on more substituted substrates).

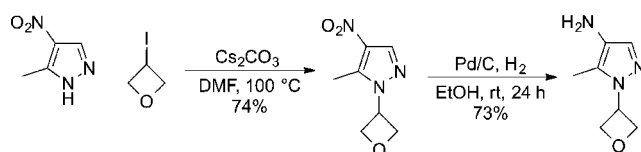
Nonetheless, outside the patent literature, there remain relatively few reactions on these simple substrates that maintain the oxetane ring. An example is oxidation of oxetane-3-methanol to the aldehyde, which has been achieved with Dess–Martin periodinane^{290,291} or PCC.²⁹² This section will give an overview of the transformations available on key oxetane building blocks and provide examples of their use in drug discovery efforts, including a survey of examples from the patent literature.

5.1. Carreira's Oxetan-3-one

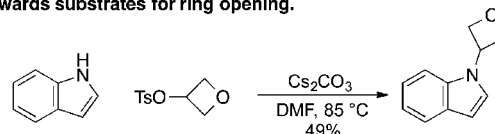
Oxetan-3-one was originally reported in 1973;^{5,287} however, studies from Carreira and co-workers^{63,65} since 2006 have

Scheme 72. S_N2 Reactions on Simple Oxetane Building Blocks^a

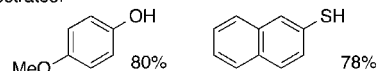
Estrada, towards LRRK2 inhibitors



Sun, towards substrates for ring opening.



example substrates:

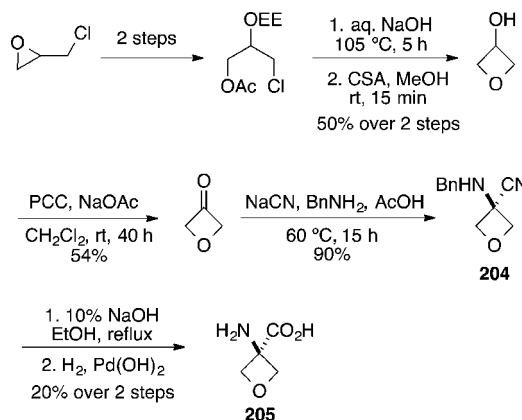


^aEstrada et al.²⁸⁸; Sun and co-workers.²⁸⁹

developed this unit as an attractive electrophilic building block for the incorporation of oxetanes. There have been a large number of examples since, exploiting this ketone in reactions to incorporate an oxetane into a selection of important molecules.

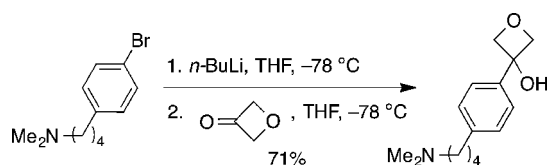
In 1991, prior to Carreira's studies, Kozikowski and Fauq²⁹³ published a route to synthesize oxetane-containing amino acid derivatives as inhibitors for the glycine binding site of the N-methyl-D-aspartate (NMDA) receptor complex (Scheme 73).

Scheme 73. Synthesis of Two Oxetane Amino Acid Derivatives via Oxetan-3-one



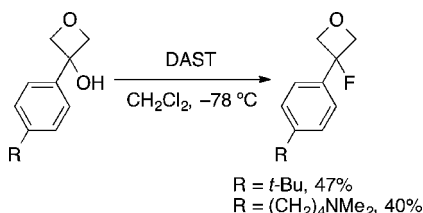
Oxetan-3-one was identified as a key intermediate and was synthesized in five steps from epichlorohydrin. A Strecker synthesis was then used to deliver the desired amino acid derivatives. Base hydrolysis of aminonitrileoxetane **204** at 95 °C for 2.5 h, followed by hydrogenolysis over $Pd(OH)_2$, delivered the amino acid **205** (Scheme 73). Alternatively, base hydrolysis at 50 °C for 30 min and then hydrogenolysis over $Pd(OH)_2$ resulted in the amino carboxamide.

Carreira and co-workers^{63,64} developed a general procedure for synthesis of 3-aryloxetan-3-ols from halogenated aromatic species, through a halogen–lithium exchange and then addition to oxetan-3-one (Scheme 74). This has been shown to be general for a large number of aromatic and heteroaromatic groups, including but not limited to pyridine, pyrimidine, pyrazole, and ortho-, meta-, and para-substituted phenyl-

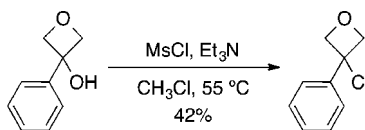
Scheme 74. Sample Synthesis of a 3-Aryloxetan-3-ol by Organometallic Addition

containing examples.^{289,294–309} Similarly, alkynyl^{289,310–312} and vinyl^{313,314} organometallics have been added directly.

The 3-hydroxy group has provided a useful handle for further reactions, making 3-aryloxetan-3-ols interesting reactive intermediates. The earliest demonstration of replacement of a tertiary alcohol at the 3-position of an oxetane with a suitable nucleophile was in 2006 by Carreira and co-workers.⁶³ Fluorination by stoichiometric DAST was achieved in yields between 40% and 47% (Scheme 75). Subsequently, this

Scheme 75. Fluorination of Oxetan-3-ol by Use of Diethylaminosulfur Trifluoride

methodology has been adopted and reported in numerous industrial medicinal chemistry patents for synthesis of 3-fluorooxetanes.^{315–339} Fluorinating agents such as Xtal-Fluor^{325,326} and Deoxo-Fluor^{327–329} have also been found to be applicable for this transformation. The reaction has been shown to be tolerant of various preinstalled aryl substituents, with good yields (>70%) being reported for *p*-cyano-,^{330–332} *m*-iodo-,³³³ and *p*-bromophenyl^{334,335} and pyridyl^{336–338} examples. Additionally, examples have been reported with pyrimidines,³²⁹ pyrazoles,^{339,326} and more complex diaryls.^{340–342} Chlorination of an oxetan-3-ol was also shown to be feasible; use of methanesulfonyl chloride and triethylamine at 55 °C formed the desired 3-chlorooxetane in 42% yield (Scheme 76).⁶⁴ This remains the only example of this transformation.

Scheme 76. Chlorination of 3-Phenyloxetan-3-ol by Use of Methanesulfonyl Chloride and Triethylamine

Acid-mediated dehydroxylation of 3-aryloxetan-3-ols has been successfully achieved by use of trifluoroacetic acid and triethylsilane as the hydride donor (Scheme 77a).⁶⁴ Although this reaction worked well for the *p*-anisyl derivative, neither the unsubstituted phenyl nor the 2,4-dimethylphenyl variants gave the desired product. A more general route was developed as a three-step, one-pot synthesis via the tosylate (Scheme 77b).⁶³ A low reaction temperature was required to prevent ring opening of the oxetane.⁶⁴

In 2013, scientists at Hoffman-La Roche³⁴³ reported in a patent an example of a four-step synthesis of dehydroxylated oxetane **208** from oxetan-3-ol **206** (Scheme 77c). Near-quantitative conversion to the xanthate **207** was realized, with subsequent conversion to 3-aryloxetane **208** achieved in 38% yield by a Barton–McCombie deoxygenation with azobisisobutyronitrile (AIBN) and tributylstannane.

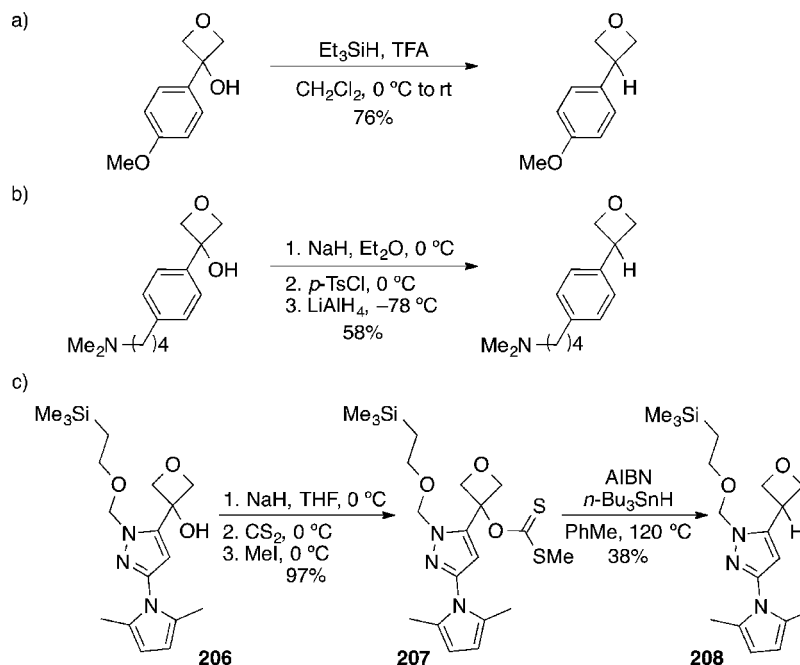
To generate 3-aminooxetanes, oxetan-3-one has been widely used in reductive amination sequences (also see section 5.3).^{344–349} Hamzik and Brubaker³⁵⁰ demonstrated the preparation of 3-aminooxetanes through condensation of oxetan-3-one and *tert*-butylsulfinimine (Bus), followed by addition of various organometallic reagents to imine **209** (Scheme 78a). Generation of an aziridine from the same imine with dimethyloxosulfonium methylide afforded aziridine **210** as an alternative electrophile. The activated aziridine opened preferentially, rather than the oxetane, generating 3-functionalized 3-aminooxetanes. The Bus group could be successfully removed with 4 N HCl in methanol in a short reaction time; longer reaction times gave ring opening with chloride. In a similar approach, Ellman and co-workers³⁵¹ described the Rh-catalyzed addition of aryl boroxines to the oxetane Bus-aldimines (Scheme 78b). The addition was tolerant of various functional groups on the aryl substituent, including phenol, ketone, and acetamide groups, though interestingly, omission of the phosphine ligand was required for a bromoaryl derivative to minimize side reactions.

Brady and Carreira³⁵² reported the synthesis of 3-amino-oxetanes by nucleophilic addition to N,O-acetals derived from oxetan-3-one. Alkynyl, vinyl, allyl, and allenyl trifluoroborates were added effectively by use of BF₃·OEt₂ to open the aminal, with tetrabutylammonium bromide included to solubilize the boron reagents (Scheme 79).

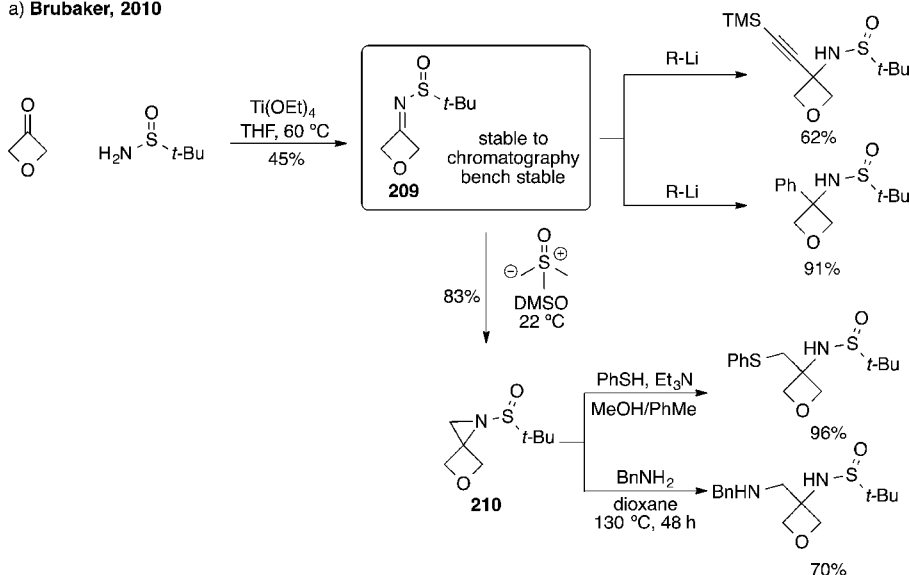
In the initial studies of Carreira and co-workers,⁶³ oxetan-3-one was used to prepare a series of oxetane Michael acceptors, which have proven to be valuable building blocks in their own right. The synthesis of α,β -unsaturated ester **211** and aldehyde **212** was achieved by a Wittig reaction with the corresponding stabilized ylide reagents (Scheme 80).⁶³ Additionally, nitroalkene **213** was synthesized by condensation with nitro-methane.

These unsaturated units **211–213** underwent conjugate addition with various nucleophiles including amines, organocuprates, arylboronic acids, and vinylboronic acids, allowing the preparation of various 3,3-disubstituted oxetanes (Scheme 81).⁶³ The physicochemical properties of oxetane-containing compounds **2–6** were compared to examine the influence of the oxetane motif (see section 2). Carreira and co-workers⁶⁵ also prepared the comparable α,β -unsaturated sulfonyl, nitrile, and phosphonate oxetane derivatives. Vinyl sulfone derivative **214** enabled the preparation of 3-functionalized 3-methyloxetane derivatives through reductive removal of the sulfonyl group, for example, by the conjugate addition of amines, followed by treatment with Mg/MeOH (Scheme 82). Furthermore, conjugate addition reactions into acceptors, such as **211**, followed by a small number of additional synthetic transformations, enabled the preparation of oxetane spirocycles (Scheme 83).^{69,2} In these examples, the oxetane was shown to be stable to a selection of organometallic reagents. An α -fluorinated derivative of **211** was prepared by Lequeux and co-workers³⁵³ through a Julia–Kocienski reaction between oxetan-3-one and fluoromethylsulfones, which was used to prepare fluorine-containing 3,3-disubstituted oxetanes.

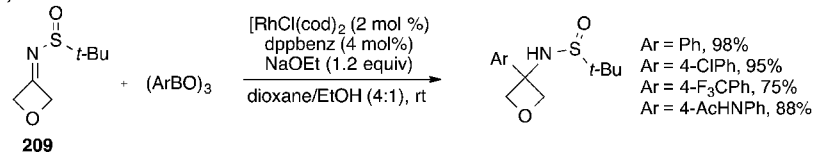
Scheme 77. Dehydroxylation of Oxetan-3-ols

Scheme 78. Preparation of 3-Aminooxetanes by Addition to an Imine^a

a) Brubaker, 2010



b) Ellman, 2011

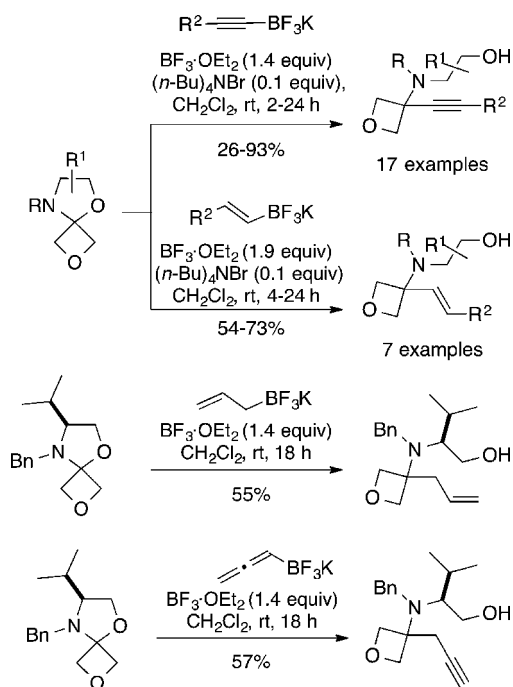
^a(a) Hamzik and Brubaker³⁵⁰; (b) Ellman and co-workers³⁵¹.

Diederich and co-workers³⁵⁴ showed that incorporation of a pendant oxetane improved the water solubility of **216**, an inhibitor of the enzyme IspE (4-diphosphocytidyl-2C-methyl-erythritol kinase, EC 2.7.1.148), targeting the treatment of diseases such as malaria and tuberculosis (Scheme 84). The key step in synthesis of **216** was conjugate addition of 5-iodocytosine **215** to Michael acceptor **211**, which gave 33% yield. Subsequent Sonogashira cross-coupling afforded **216** with

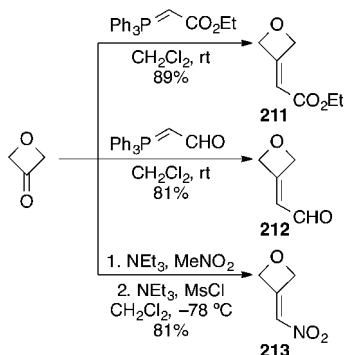
a yield of 71%. Similarly, the synthesis of oxetanylthaldomide by Carreira and co-workers⁸⁰ (Table 2, section 2) involved conjugate addition of an amine to a nitroolefin derived from oxetanone.

In 2014, Ellman and co-workers³⁵⁵ reported catalytic enantioselective addition of thioacids to an oxetane-containing nitroalkene using bifunctional organocatalyst **217** (Scheme 85a). Michael addition into the oxetane-containing nitroalkene

Scheme 79. Nucleophilic Addition of Carbon Nucleophiles onto Spirocyclic Oxetanes

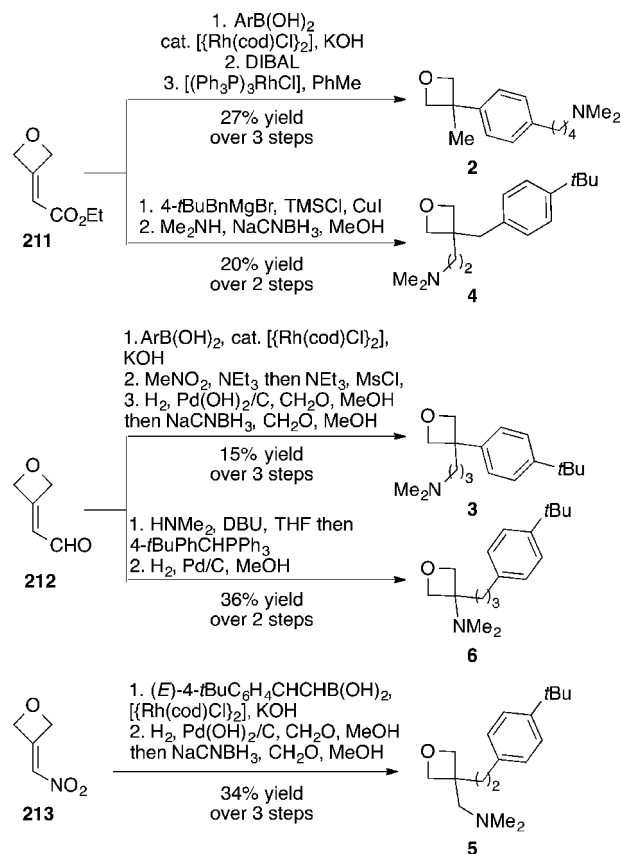
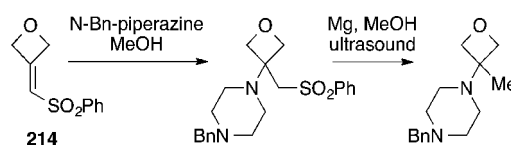
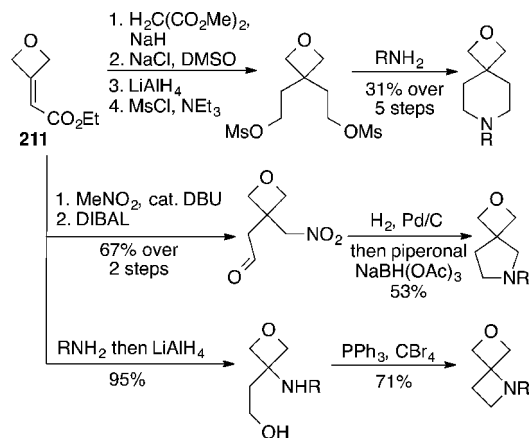


Scheme 80. Synthesis of Oxetane Michael Acceptors

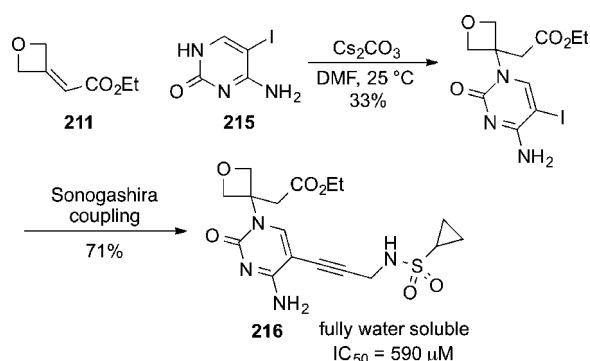
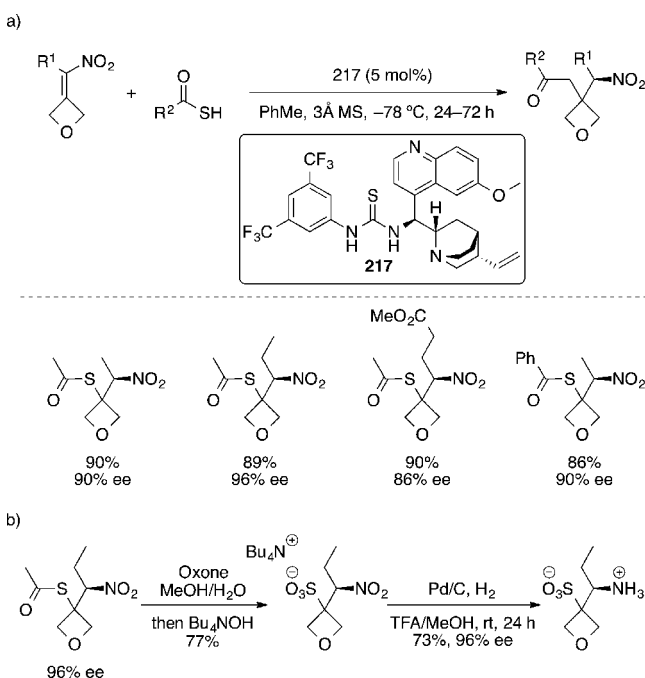


and subsequent enantioselective protonation led to the synthesis of 1,2-nitrothioacetate products in high yields and enantioselectivities for various substrates. Biomedically relevant 1,2-aminosulfonic acids were accessed via a high-yielding two-step route with complete retention of ee (Scheme 85b). Very recently, related work on conjugate addition, and subsequent enantioselective protonation, of pyrazol-5-ones to oxetane-containing trisubstituted nitroalkenes was reported.³⁵⁶

Carreira and co-workers³⁵⁷ and Shipman and co-workers³⁵⁸ simultaneously reported the use of oxetan-3-one to generate peptide mimics, with an aminooxetane providing a bioisostere for the amide linkage (Scheme 86). Peptides often confer poor properties as drug candidates because they are easily cleaved. Oxetanes may reduce the propensity for cleavage, providing an opportunity for new peptidomimetics with improved properties. In both cases, amine conjugate addition to nitroolefin **213** was used to introduce amino acid units. Shipman and co-workers³⁵⁹ recently reported an adaptation of this approach to generate oxetane-containing diketopiperazine derivatives. Very recently, Jørgensen and co-workers³⁶⁰ reported an organo-

Scheme 81. Synthesis of 3,3-Diaryloxetanes via Conjugate Addition to Oxetane-Derived α,β -Unsaturated Ester, Aldehyde, and NitroalkeneScheme 82. Conjugate Addition to Vinyl Sulfone **214** and Reductive RemovalScheme 83. Synthesis of Oxetane-Containing Spirocyclic Compounds Involving Conjugate Addition^a

^aR = piperonyl.

Scheme 84. Oxetane-Containing IspE Inhibitor with Improved Aqueous Solubility**Scheme 85. Catalytic Enantioselective Synthesis of (a) 1,2-Nitrothioacetates and (b) 1,2-Aminosulfonic Acids**

catalyzed cycloaddition to oxetanyl nitroolefins to generate spirocyclohexene-oxetane scaffolds.

Oxetan-3-one has been used in a number of complexity-generating reactions to incorporate oxetanes into interesting structural types. Shipman and co-workers³⁶¹ have used this unit in the Passerini reaction (Scheme 87a) and also in the Pictet–Spengler reaction³⁶² (Scheme 87b). Harrity and co-workers³⁶³ applied their sydnone cycloadditions to an oxetane-containing motif in both intermolecular and intramolecular cycloadditions to form oxetane-containing pyrazole derivatives (Scheme 88).

Bode and co-workers³⁶⁴ have developed a powerful one-step protocol for synthesis of saturated N-heterocycles, using stannyl amine reagents in combination with aldehydes (SnAP protocol). This approach has been expanded to spirocyclic saturated N-heterocyclic examples, using ketones.³⁶⁵ Significantly, oxetan-3-one was used in a key example to form an oxetane-containing spirocyclic piperazine (Scheme 89). Condensation of SnAP reagent 218 with oxetan-3-one generated an imine, which underwent Cu-catalyzed radical cyclization to form spirocyclic heterocycle 219.

In 2015, Soós and co-workers³⁶⁶ showed that oxetan-3-one (as well as other four-membered cyclic ketones) would undergo selective direct cross-aldol reactions with other ketones, such as cyclopentanone, promoted by pyrrolidine (Scheme 90). The selectivity was attributed to the inherent angle strain of oxetan-3-one and relief of this strain during the conversion of C(sp²) to C(sp³). When unsymmetrical acyclic ketone butan-2-one was employed, L-proline was used as the organocatalyst at 80 °C to overcome the formation of a stable enamine adduct, but a mixture of regioisomers was obtained (1.5:1).

5.2. Cross-Coupling of Oxetane Building Blocks

Synthesis of aryloxetanes has been greatly expanded by the use of 3-iodooxetane in transition-metal cross-coupling reactions. In 2008, Dunton et al.⁷⁹ (Evotec) demonstrated the use of 3-iodooxetane in cross-coupling reactions with a series of arylboronic acids (Scheme 91). Under conditions developed by González-Bobes and Fu³⁶⁷ for the cross-coupling of alkyl halides, a Ni-catalyzed Suzuki reaction achieved the coupling of 3-iodooxetane and also 3-iodoazetidines in moderate yields. The transformation was tolerant of various aryl groups but was unsuccessful with heterocyclic derivatives.

Zhang and Yang,³⁶⁸ in 2015, developed a milder Ni-catalyzed Suzuki cross-coupling reaction of alkyl halides and arylboronic acids, using K₂CO₃ as the base instead of the more standard Li/KOtBu or Na/KHMDS. In the substrate scope, 3-iodooxetane was found to be a viable substrate, forming the aryloxetane product in 68% yield (Scheme 92).

To incorporate an oxetan-3-yl group into heteroaromatic bases, Dunton et al.³⁶⁹ reported a Minisci reaction involving generation of the oxetane radical (Scheme 93). The reaction likely proceeded via addition of an oxetane radical to the protonated heterocycle, followed by rearomatization. Although the yields were generally low, the reaction proved tolerant of a number of different functional groups. Various N-heterocycles were successfully employed in the reaction, leading to synthetically useful yields, including quinoline, isoquinoline, pyridine, pyridazine, benzothiazole, benzimidazole, quinoxaline, quinazoline, and phthalazine examples. Of particular note, due to the existing functionality present, were the hydroquinine and gefitinib derivatives 220 and 221.

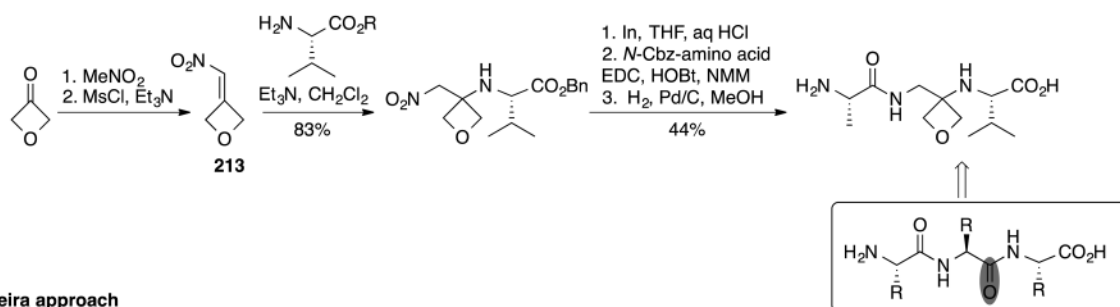
Molander and co-workers³⁷⁰ recently extended copper-catalyzed borylation methodology to prepare various heterocyclic trifluoroborates, several of which could be applied in a Minisci reaction with heteroaromatics. Several heterocyclic trifluoroborates were prepared from iodoheterocycles, including 3-iodooxetane (Scheme 94). The oxetane derivative was not demonstrated in the Minisci reaction; indeed, there are no reactions reported to date with oxetane boronates.

Molander et al.³⁷¹ established a Ni-catalyzed reductive coupling of saturated heterocyclic bromides with aryl and heteroaryl bromides. The reaction was developed by employing a high-throughput experimentation approach to screen Ni sources, ligands, additives, and solvents for the coupling of N-Boc-4-bromopiperidine with 4-bromoanisole. The scope of the saturated heterocycles included coupling of 3-bromooxetane with 4-bromoanisole in a yield of 43% (Scheme 95). Reaction conditions were reoptimized for heteroaromatic coupling partners, which had given poor yields under the previously developed conditions. Hence, the cross-coupling of N-Boc-5-bromoindole with 3-bromooxetane proceeded in 36% yield.

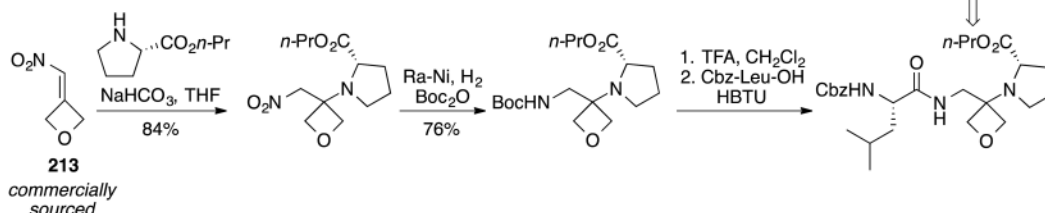
Very recently, Buchwald and co-workers³⁷² reported a system for Lipshutz–Negishi cross-coupling under aqueous conditions,

Scheme 86. Oxetane Peptidomimetics Formed via Conjugate Addition^a

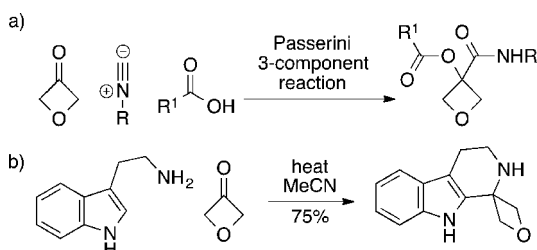
Shipman approach



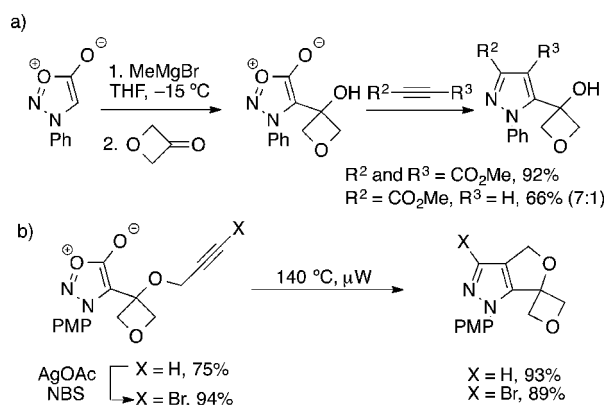
Carreira approach

^aShipman and co-workers³⁵⁸; Carreira and co-workers³⁵⁷.

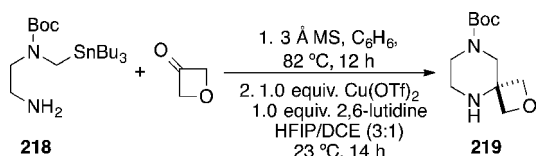
Scheme 87. (a) Passerini and (b) Pictet–Spengler Reactions Involving Oxetan-3-one



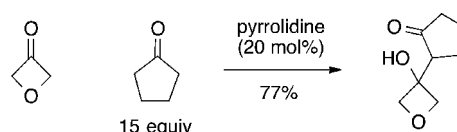
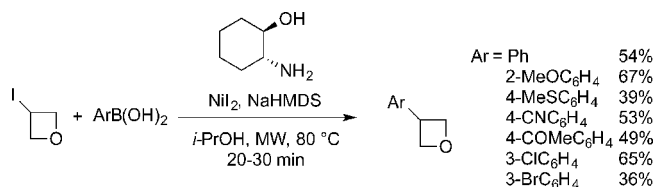
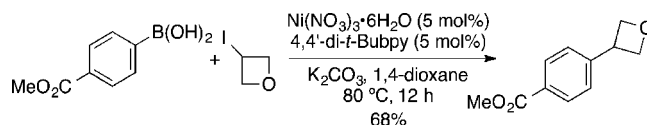
Scheme 88. Inter- and Intramolecular Sydnone Cycloadditions



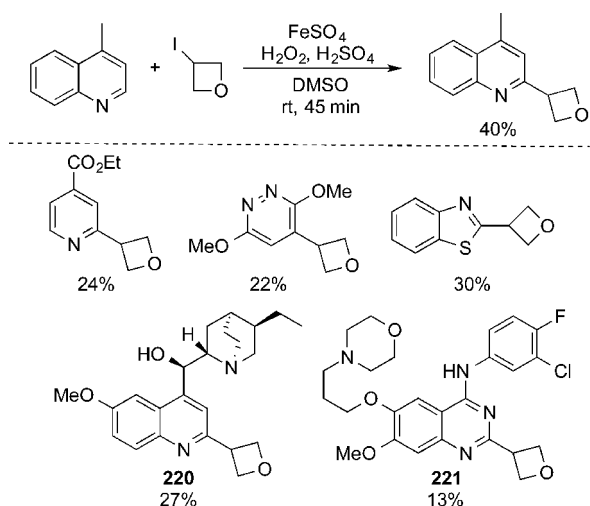
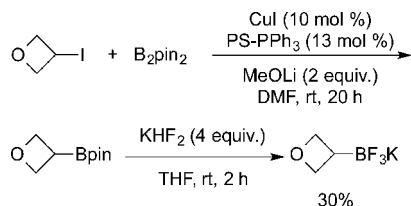
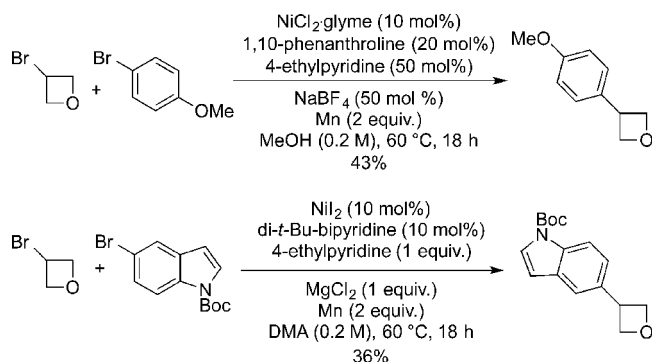
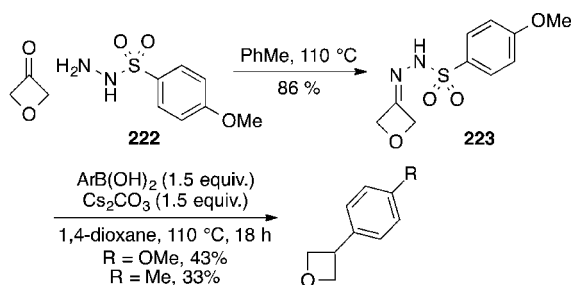
Scheme 89. Synthesis of Spirocyclic Piperazine–Oxetane by Use of SnAP Reagents



Scheme 90. Strain-Driven Direct Cross-Aldol Reaction with Oxetan-3-one

Scheme 91. Ni-Catalyzed Suzuki Coupling of 3-Iodooxetane^a^aDunton et al.⁷⁹Scheme 92. Ni-Catalyzed Suzuki Cross-Coupling Reaction of 3-Iodooxetane and Arylboronic Acids^a^aZhang and Yang.³⁶⁸

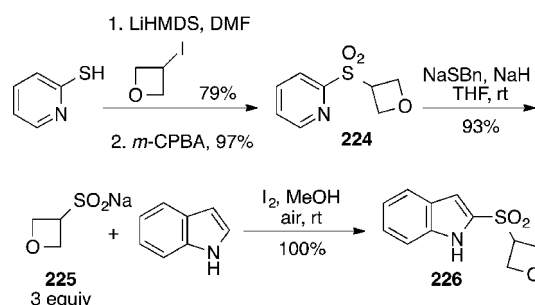
which included the coupling of 3-bromooxetane in high yields. A new ligand (VPhos) and Pd precatalyst were developed for coupling of alkyl bromides, particularly saturated heterocycles, and aromatic and heteroaromatic bromides and chlorides. Ley and co-workers³⁷³ published two examples of 3-aryloxetanes synthesized in two steps from oxetan-3-one via a sulfonyl hydrazone intermediate **223** and subsequent metal-free coupling with boronic acids (Scheme 96). The reaction was optimized on *N*-Boc-piperidinone-derived tosyl hydrazine with 4-chlorophenylboronic acid. Replacement of the tosyl group of

Scheme 93. Fe-Catalyzed Synthesis of Heteroaryloxetanes from 3-Iodooxetane**Scheme 94. Preparation of Oxetane Trifluoroborate****Scheme 95. Ni-Catalyzed Reductive Coupling of 3-Bromooxetane****Scheme 96. Metal-Free Coupling of Boronic Acids with Saturated Heterocycles by Use of Sulfonyl Hydrazones**

the hydrazone with a *p*-methoxyphenyl sulfonyl group, by use of **222**, improved the observed yields.

Harrity and co-workers³⁷⁴ prepared oxetane sulfinate salt **225** from 3-iodooxetane in a high-yielding three-step process

(Scheme 97). Interestingly the sulfonate salt could be displaced from the pyridylsulfone **224** with a thiolate nucleophile in

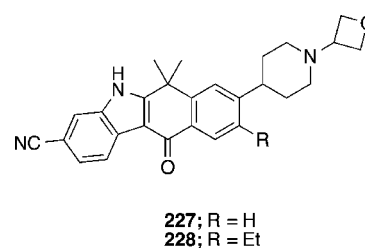
Scheme 97. Preparation and Indole Coupling Reactions of Oxetane Sulfinate Salts

preference to oxetane ring opening. The sulfinate salts could be coupled with electron-rich indoles to introduce a sulfonyl group at the indole 3-position (**226**) by use of I_2 in MeOH.

5.3. Applications in Medicinal Chemistry

The readily available oxetane units discussed above have recently found extensive use in medicinal chemistry. This section will cover the use of oxetanes in biologically active compounds prepared in drug discovery efforts. We will discuss examples where oxetanes have been used as part of an extensive screening and optimization approach. In most of these examples, the oxetane-containing example is the most bioactive compound and/or has the most desirable physicochemical properties as a potential therapeutic.

In 2011, Kinoshita et al.³⁴⁶ reported the development of a highly potent and selective anaplastic lymphoma kinase (ALK) inhibitor as a promising therapeutic for cancer. The incorporation of an oxetane group, via reductive amination of oxetan-3-one, led to a significant improvement in the *in vitro* clearance level in mouse and human liver microsomes when compared to an isopropyl group at the same position (**227**, Figure 16).

**Figure 16. Highly potent ALK inhibitors.**

good metabolic stability and strong antitumor efficacy against KARPAS-299, a NPM-ALK-positive ALCL cell line. In an extension of this study, the introduction of an ethyl substituent on the phenyl ring (**228**) led to an almost 2-fold increase in potency against KARPAS-299, proposed to be a result of improved ALK selectivity over off-target kinases.³⁴⁷

Stepan et al.^{82,83} explored arylsulfonamides as potential γ -secretase inhibitors toward treatment options for Alzheimer's disease. Lead compound **229** contained a cyclohexyl substituent and displayed good potency but suffered from poor metabolic stability and solubility (Figure 17; also see section 2). Incorporation of an oxetane resulted in the greatest improvement in metabolic stability and lipophilicity. Overall, 2,4,4-

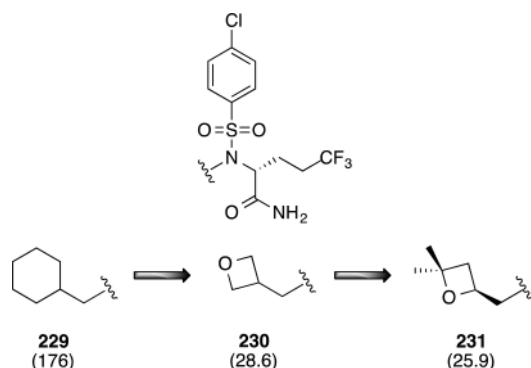


Figure 17. Comparison of metabolic stability of lead compound **229** compared to oxetane-containing analogues. $CL_{int,app}$ (milliliters per minute per kilogram), shown in parentheses, is total intrinsic clearance obtained from scaling in vitro HLM half-lives.

trisubstituted analogue **231** was the most stable γ -secretase inhibitor of the series.

Dowling et al.⁸¹ at AstraZeneca described a series of 5-anilinopyrazolo[1,5-*a*]pyrimidine inhibitors of CK2 kinase (Figure 9, section 2). An N-oxetanyl group was used in place of a N-cyclopropyl group to reduce lipophilicity without the introduction of a basic group. Although the oxetane examples were potent CK2 inhibitors, they were 10-fold less active than cyclopropyl counterparts.

Scott et al.³⁷⁵ at AstraZeneca developed a series of G-protein coupled receptor (GPCR) 119 agonists as a potential diabetes treatment. Initial development led to the discovery of a *tert*-butyl carbamate-containing compound that, although potent, suffered from nonideal aqueous solubility (24 μ M). In order to improve this, a number of carbamates were examined. Replacing the *tert*-butyl group with a 3-substituted oxetane resulted in a dramatic increase in aqueous solubility to >2200 μ M, over twice as soluble as the THF equivalent; however, these examples showed a reduction in potency. Addition of a methyl group to the oxetane increased the activity; ethyl and isopropyl groups did not further increase potency but led to an increase in metabolic instability. The alkyl substituent was revealed to be the site of metabolism, and to circumvent this, trifluoromethyloxetane-containing **233** was synthesized, which increased potency while maintaining a desirable solubility of 110 μ M (Scheme 98). This was incorporated via pentafluorophenyl carbonate **232**, developed specifically for this transformation after more standard approaches had failed.

Pei et al.³⁷⁶ at Genentech developed a potent and selective oxetane-containing mammalian target of rapamycin (mTOR) inhibitor as a potential future cancer treatment. An advanced tetrahydroquinazoline lead molecule was further optimized to reduce the unfavorable time-dependent inhibition of cytochrome P450 (CYP). This was achieved by replacing an N-substituted pyrimidine **234** with an N-substituted oxetane **235**, which prevented the interaction with CYPs via the pyrimidine unit (Figure 18). The oxetane unit, introduced by reductive amination of oxetan-3-one, reduced the basicity of the nitrogen atom compared to alkyl groups. It also led to lower hERG liability while maintaining the high potency of the initial advanced lead molecule. Following selection of the oxetane as the drug development candidate, further modification was carried out, replacing the tetrahydroquinazoline scaffold with a bicyclic pyrimidoaminotropane **236**.³⁴⁴ The oxetane unit was re-evaluated on this new backbone and compared to other

Scheme 98. Preparation of Trifluoromethyl-Substituted Oxetane GPCR119 Agonist

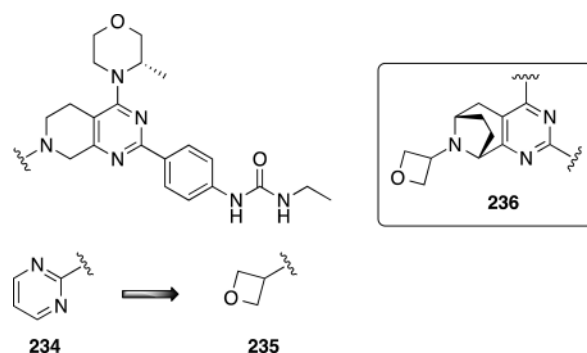
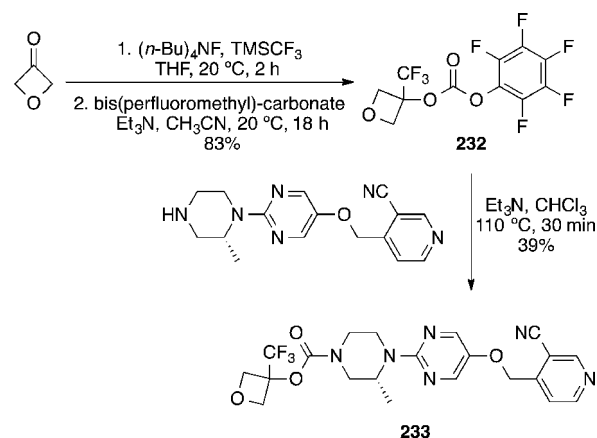


Figure 18. Potent and selective mTOR inhibitors.

substituents, and it was found to still possess the most desirable properties to be brought forward as a clinical candidate.

Leucine-rich repeat kinase 2 (LRRK2) is a gene related to Parkinson's disease that has stimulated significant interest within neuroscience research. Estrada et al.²⁸⁸ reported the development of highly potent, selective, and brain-penetrant small-molecule inhibitors of LRRK2 (Figure 19a). The lead compound was optimized to establish **237**, with a pendent oxetane motif, as one of the best inhibitors, with an IC_{50} value of 19 nM.

Jadhav et al.³⁷⁷ at Lilly discovered a series of noncovalent inhibitors of cathepsin S, useful as a potential treatment of abdominal aortic aneurysm. Following a medium-throughput screen, several hits were identified and one was selected for modification to improve its potency and physical properties. A key aspect of this modification process was replacing the N-methyl group on piperazine with an N-oxetanyl unit to modulate the basicity of the nitrogen atom and to lower the overall lipophilicity. This modification, along with others, led to the development of clinical candidate **238** (Figure 19b).

Zhang, Geng, and co-workers³⁴⁸ developed 2,4-diarylaminopyrimidine analogues with a flexible amino acid side chain that are potent inhibitors against wild-type and mutant ALK kinases as a potential treatment against crizotinib-resistant non-small-cell lung cancer. Variation of the substitution of the primary amino group was studied, and it was found that use of a substituted piperazine, one of which contained pendant oxetane (**239**, Scheme 99), generated highly potent and selective ALK inhibitors. A primary amino acetamide proved to be more

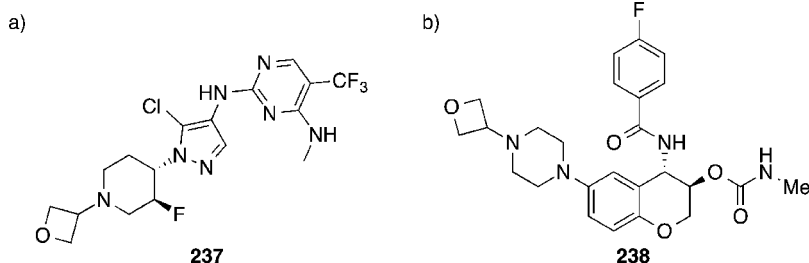
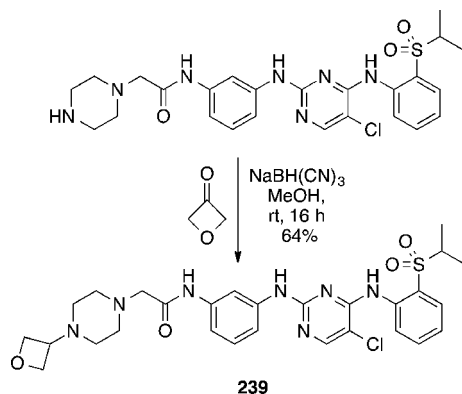


Figure 19. (a) Inhibitor of LRRK2. (b) Cathepsin S inhibitor.

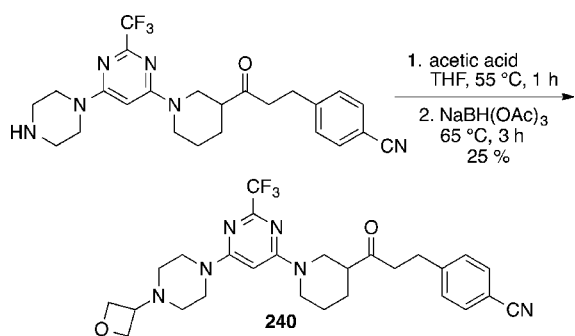
Scheme 99. 2,4-Diarylamino-pyrimidine Analogues as Potent Inhibitors against Wild-Type and Mutant ALK Kinases



active (ALK IC₅₀ = 2.7 nM vs 4.9 nM for the oxetane) and this was chosen for further evaluation.

Phillips et al.³⁴⁹ at Novartis developed GPCR TGR5 agonists, an attractive target for type 2 diabetes treatment and for chronic inflammation. An oxetane unit was used as part of a survey of alkyl substituents on a piperazine ring (240, Scheme 100). Although the oxetane unit successfully mitigated

Scheme 100. GPCR TGR5 Agonists for Potential Type 2 Diabetes Treatment



the issue of hERG risk and retained target potency, CYP3A4 inhibition and metabolic stability were not improved, so this example was not taken forward.

Schoenfeld et al.³⁷⁸ at Hoffmann-La Roche developed a series of hepatitis C virus inhibitors. An advanced lead structure was developed containing a *tert*-butyl group, which was susceptible to metabolic oxidation. An oxetane replacement showed similar activity. However, the increase in polarity led to reduced intrinsic permeability, so it was not advanced further (241, Figure 20a). The oxetane was synthesized via a C–O

bond-forming step from the corresponding diol under Mitsunobu conditions.

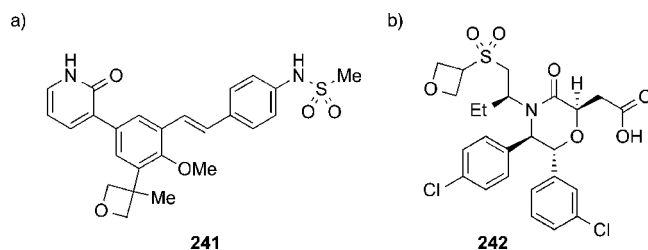


Figure 20. (a) Oxetane-containing hepatitis C virus inhibitor. (b) 3-Sulfonyl oxetane inhibitor of MDM2.

Gonzalez et al.³⁷⁹ (Amgen) utilized a 3-sulfonyl oxetane during variation of the N-alkyl substituent of a series of morpholinone inhibitors of the MDM2–p53 interaction. Disruption of MDM2 binding to p53 can reactivate the p53 pathway in tumor cells to allow cell cycle arrest and apoptosis. The 3-sulfonyl oxetane example 242 provided inhibitors with reduced cellular potency when compared to the more effective *tert*-butyl sulfone derivative (Figure 20b).

A novel class of γ -secretase modulators was developed by Austin et al.³⁸⁰ at Satori Pharmaceuticals as a potential treatment of Alzheimer's disease. An initial hit was identified from an extract of black cohosh root and developed to improve metabolic stability. A range of esters and carbamates was synthesized as bioisosteres to replace a glycoside moiety in order to improve chemical stability and decrease the topological polar surface area (tPSA) and HBD count. Oxetane examples were studied but did not prove to be potent inhibitors (243, Figure 21). Ultimately, increased activity correlated with increased basicity and hence nitrogen-containing groups, including azetidines, proved most potent. During an earlier structure–activity relationship study,³⁸¹ N-oxetanyl-substituted

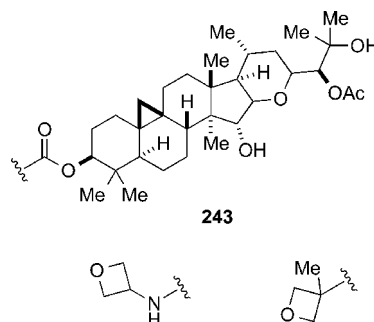


Figure 21. γ -Secretase modulators with improved metabolic stability.

morpholine derivatives were utilized to examine the effects of varying other key parts of the structure.

Procopiou et al.³⁸² at GlaxoSmithKline reported the development of a series of indazole arylsulfonamides as CC chemokine receptor 4 (CCR4) antagonists. A modified ligand lipophilicity index (LLE_{AT}), which combined lipophilicity, potency, and size and made comparisons to conventional ligand efficiency, was used as a metric to compare analogues. Oxetane amides **244** and **245** had inferior LLE_{AT} values compared to an acetamide group (Figure 22). The solubility increased for **244** and for THF and THP analogues but **245** was similar to the acetamide, attributed to the greater exposure of the oxygen in **244**.

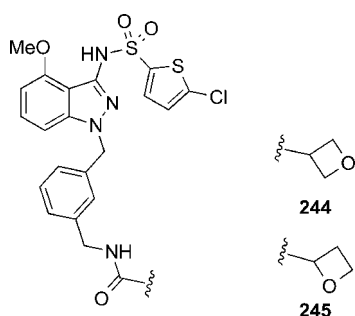


Figure 22. Oxetane-containing indazole CCR4 antagonists.

Dineen et al.³⁸³ (Amgen) identified a potent inhibitor of β -site amyloid precursor protein cleaving enzyme (BACE1). Previously reported aminooxazoline xanthene scaffold **246** was modified to improve BACE1 potency and prevent off-target hERG channel activity. Principally this was achieved by incorporating a N atom in the 4-position of the xanthene core and by replacing the 5-pyrimidyl group with a 2-fluoro-3-pyridyl analogue (Figure 23). To further reduce hERG activity,

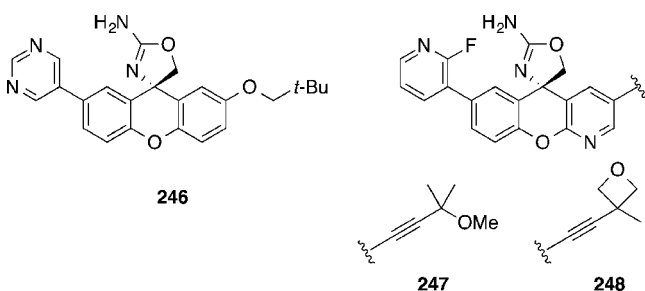


Figure 23. 4-Azaxanthene BACE1 inhibitors containing a pendent oxetane.

the side chain at the 4-position was modified. An alkynyl side chain with a pendant methoxy group proved effective, maintaining BACE1 potency while reducing hERG binding affinity (**247**, Figure 23). However, oxidative demethylation of the methoxy group resulted in poor metabolic stability. An oxetane group was successfully incorporated to reduce this oxidative dealkylation, resulting in a compound with good stability in human and rat liver microsomes (**248**, Figure 23). Additionally, the oxetane unit was found to be stable in the presence of glutathione.

Plancher and co-workers³⁸⁴ at Hoffmann-La Roche developed a series of 5-hydroxyindole-based histamine 3 receptor inverse agonists as a potential treatment for obesity. A 3-

oxetanyl unit was assessed during modification of the basic piperidine side chain (**249**, Figure 24a). The oxetane led to the largest reduction in basicity with a pK_a of 6.4, compared with 9.7 for isopropyl, 9.1 for cyclobutyl, and 7.7 for cyclopropyl. The oxetane-containing example retained potent hH₃R binding (K_i = 23 nM), although it suffered from poor microsomal clearance.

Samuelsson and co-workers³⁸⁵ described a series of HIV-1 protease inhibitors with a number of different substituents containing hydrogen-bond acceptors. The isopropyl group from the L-Val methyl side chain, reported previously,³⁸⁶ was replaced with a 3-oxetane (**250**), an ethoxymethyl, and a 1-methyl-substituted ethoxymethyl in order to “extend” a H-bond acceptor from the original position of the isopropyl (Figure 24b). This was designed to promote a positive interaction with the nitrogen of the Asp-30 residue of the HIV-1 protease backbone. Although the oxetane increased the tPSA and led to a significant lowering of logP, there was a considerable loss of potency compared to the original isopropyl group. The structural rigidity of the oxetane was proposed to be the cause of the loss in potency, forcing the oxygen atom to point away from the N–H of Asp-30 residue.

Heffron et al.³⁸⁷ at Genentech undertook an in silico design approach in the development of inhibitors of phosphatidylinositol 3-kinase (PI3K), a target for potential cancer treatment, in particular, glioblastoma multiforme (GBM) brain tumors. Previous PI3K inhibitors discovered by Genentech suffered from poor penetration of the blood–brain barrier (BBB) due to high efflux. In order to improve the physicochemical properties of these inhibitors to increase BBB penetration, a central nervous system multiparameter optimization (CNS MPO) was utilized. In silico correlation of the CNS MPO score with desirable efflux ratios, and subsequently with the probability of metabolic stability, resulted in a very narrow range of physicochemical properties. Thus, a small number of molecules were selected for synthesis, including a number of oxetane-containing examples. One of the two key candidates discovered, a 3-methoxy-substituted oxetane (**251**, Figure 24c), was subjected to testing in mice; it successfully inhibited tumor growth beyond the BBB and was taken forward for further study toward clinical application.

Lewcock, Siu, and co-workers³⁸⁸ have recently developed a series of inhibitors of dual leucine zipper kinase (DLK, MAP3K12), prominent in the regulation of neuronal degradation. Following the discovery of an initial hit through high-throughput screening, optimization led to oxetane **252** as a potent and selective DLK inhibitor (Figure 24d). A key aspect of the optimization was to reduce the lipophilicity and basicity of the analogues. An oxetane was successfully used to reduce the basicity of a key piperidine to limit efflux, important for a brain penetrant, while maintaining good metabolic stability. The bioactivity of this compound was shown in a number of animal models of neurodegenerative diseases.

5.4. Survey of Oxetanes in Drug Discovery Patents

The use of oxetanes disclosed in the patent literature has increased dramatically in the last 5 years. In this section, we examine the synthesis of oxetane-containing compounds that appeared in international or U.S. patents for use in medicinal chemistry or drug discovery programs. Here, oxetane-containing molecules from these patents are collated to include structure, source of the oxetane building block used, and bioactivity including any available data, along with the patent

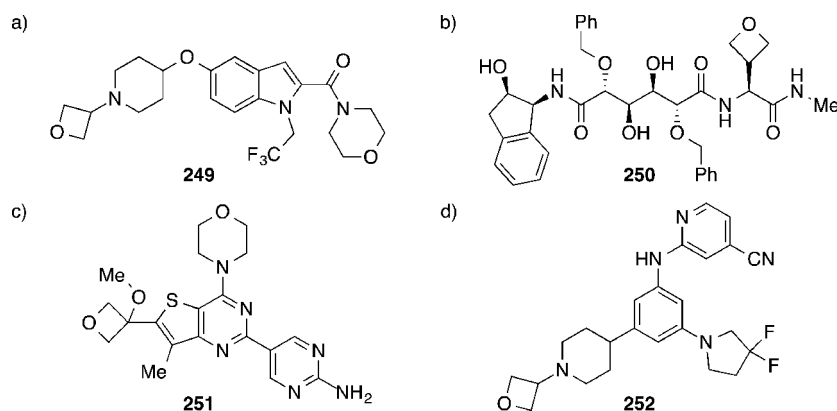
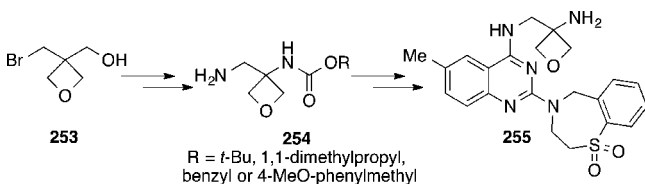


Figure 24. (a) Oxetane modulating the basicity of H₃R agonists. (b) HIV-1 protease inhibitor. (c) Brain-penetrant 3-methoxy-substituted oxetane PI3K inhibitor. (d) Potent and selective DLK kinase inhibitor.

number and company (Table 18). In the cases where there are multiple examples of oxetanes in a given patent, an example has been selected, usually the most bioactive compound in the target screen if the data were available.

One particular patent warrants further discussion. The original patent, filed by Hoffmann-La Roche, described the preparation of benzothiazepines and analogues for the treatment of respiratory syncytial viral (RSV) infection.³⁸⁹ In this patent, the authors describe the synthesis of a large number of oxetane-containing compounds, several of which are reported to have very low IC₅₀ values in comparison to other non-oxetane-containing examples. This new class of RSV inhibitors displayed EC₅₀ values as low as 0.2 nM. Compound 255 (Scheme 101) was shown to have a less potent EC₅₀ value

Scheme 101. Large-Scale Preparation of Benzothiazepine RSV Inhibitors

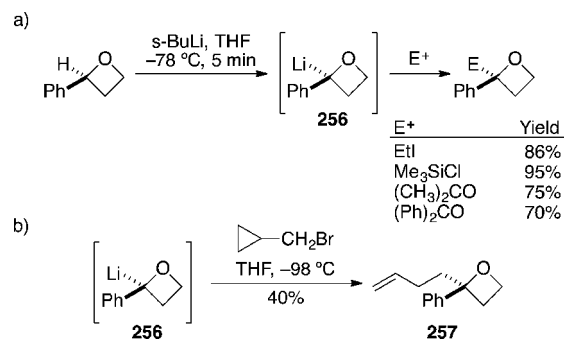


of 5 nM. Despite this, a recently disclosed patent describes the scale-up process for the synthesis of >5 kg of this compound.³⁹⁰ The scale-up route begins with oxidation of [3-(bromomethyl)-oxetan-3-yl]methanol 253 to the corresponding carboxylic acid, followed by carbamate formation and amination to form 254. A double amination with 2,4-dichloroquinazoline was then carried out, first with the primary aminooxetane fragment at the 4-position, followed by the benzothiazepine. Deprotection of the carbamate under acid conditions furnished 5.82 kg of 255 (Scheme 101).

6. FUNCTIONALIZATION OF INTACT OXETANE DERIVATIVES THROUGH METALATED AND RADICAL INTERMEDIATES

Recently a small number of examples of the functionalization of intact oxetane rings at the 2-position have emerged, involving deprotonation of oxetane derivatives. Capriati and co-workers⁴⁴² reported the synthesis of 2-substituted phenyloxetanes by formation of 2-lithio-2-phenyloxetane 256, which was chemically stable at −78 °C for up to 30 min (Scheme 102a). 2-Phenyloxetane was regioselectively deprotonated by use of

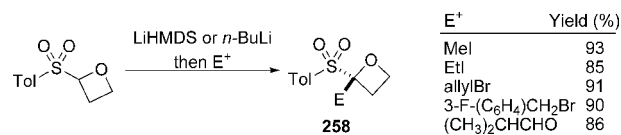
Scheme 102. Formation and Reactivity of 2-Lithio-2-phenyloxetane



s-BuLi at −78 °C in THF and then trapped with reactive electrophiles, including alkyl halides as well as aromatic and aliphatic aldehydes and ketones, in good to excellent yields. Employing enantiomerically enriched 2-phenyloxetane resulted in racemic 2-substituted 2-phenyloxetanes in both polar (THF) and nonpolar (hexane/TMEDA) solvents, the lithiated intermediate being configurationally unstable. Reaction of the lithiated intermediate with cyclopropylmethyl bromide gave the butenyl-coupled product 257, which was cited as support for a single-electron transfer mechanism, also being the cause of racemization (Scheme 102b).

Bull and co-workers²⁴⁶ reported the regioselective lithiation of 2-tolylsulfonyl oxetane, followed by reaction with electrophiles to generate 2-substituted 2-sulfonyl oxetanes 258 (Scheme 103). Depending on the nature of the electrophile,

Scheme 103. Functionalization of 2-Arylsulfonyl Oxetanes via Lithiation of the Oxetane Ring



*n*BuLi or LiHMDS could be employed as the base, in THF at −78 °C. These reaction conditions were developed to minimize a concurrent ortho-lithiation of the aromatic ring, directed by the sulfone moiety, that was particularly prominent when *s*BuLi was employed.

Shipman and co-workers⁴⁴³ reported the enantioselective synthesis of 2-substituted oxetan-3-ones by α -lithiation and

Table 18. Oxetanes Prepared in Patents during Drug Discovery Research

Oxetane	Oxetane Source	Potential Therapeutic Use/ Biological Data	Patent No.	Ref
	Cyclization; C-O bond via OTs displacement	Human renal renin, IC ₅₀ = 0.19 nM	WO9222313A1 <i>Abbott Laboratories, USA.</i>	391
	n.d.	Hematopoietic synergistic activity in stromal cells	WO9717964A1 <i>Smithkline Beecham Corporation, USA.</i>	392
	 From 2-methyleneoxetane ³⁹³	Nucleoside analog related disorders	WO2005051944A1 <i>University of Connecticut, USA.</i>	394
	 C-O bond cyclization from chlorohydrin	β -secretase inhibitors	US20050282826A1 <i>Wyeth, John, and Brother Ltd., USA.</i>	395
	 From corresponding diol by Mitsunobu	Antagonists, agonists of serotonin 1 (5-HT ₁) receptors, specifically the 5-HT _{1B}	WO2006106416A1 <i>Pfizer Inc., USA.</i>	396
		Glucokinase activators	US20080021032A1 <i>Hoffmann-La Roche Inc., USA.</i>	397
		Phosphodiesterase inhibitors (PDE4) IC ₅₀ = 52 nM	WO2008104175A2 <i>Leo Pharma A/S, Den.</i>	398
		Raf kinase inhibitor	WO2009111279A1 <i>Array BioPharma Inc., USA; Genentech, Inc.</i>	399
		Anti-hepatitis C viral activity (NS5B polymerase) IC ₅₀ = 0.013 μ M (R = H) IC ₅₀ = 0.134 μ M (R = Me)	WO2009101022A1 <i>F. Hoffmann-La Roche AG, Switz.</i>	400
		Human CRTH2 IC ₅₀ = 0.0018 μ M	WO2010055004A1 <i>F. Hoffmann-La Roche AG, Switz.</i>	401

Table 18. continued

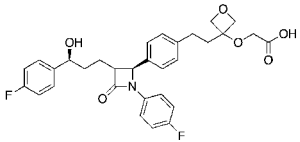

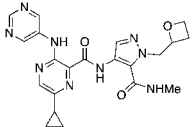

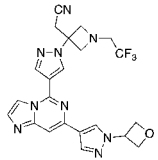

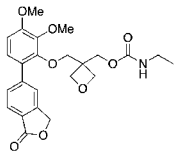

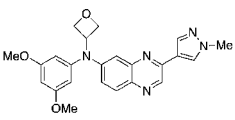

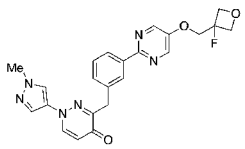

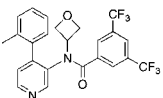

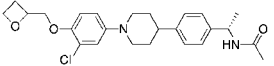

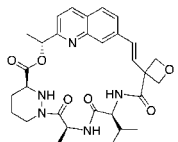

Oxetane	Oxetane Source	Potential Therapeutic Use/ Biological Data	Patent No.	Ref
		Hypocholesterolemic activity, 87% inhibition of cholesterol absorption in mice at 1 mg/kg	WO2010100255A1 <i>Lipideon Biotechnology AG, Switz.</i>	402
		phosphodiesterase (PDE10A) inhibitor	WO2011154327A1 <i>F. Hoffmann-La Roche AG, Switz.</i>	403
	 via mesylate	JAK kinase inhibitor (Tyk2) $IC_{50} < 10$ nM	WO2011130146A1 <i>Array BioPharma Inc., USA.</i>	404
		phosphodiesterase (PDE4) inhibitor $IC_{50} < 10$ nM	WO2011134468A1 <i>LEO Pharma A/S, Den.</i>	405
		FGFR1 kinase inhibitors $pIC_{50} = 7.97$	WO2011135376A1 <i>Astex Therapeutics Limited, UK.</i>	406
	 Cyclization: C-O bond from bromohydrin	Tyrosine kinase MET inhibitor $IC_{50} < 100$ nM	WO2011084402A1 <i>Merck Sharp & Dohme Corp., USA.</i>	407
		GPBAR1 agonist $EC_{50} = 1.20$ μ M	WO2012117000A1 <i>F. Hoffmann-La Roche AG, Switz.</i>	408
		Acetyl-CoA carboxylase inhibitor (ACC2) $IC_{50} = 1.1$ nM	WO2012001107A1 <i>Boehringer Ingelheim International GmbH, Germany.</i>	409
		Viral replication inhibitor	WO2013185103A1 <i>Gilead Sciences, Inc., USA; Selcia Limited.</i>	410

Table 18. continued

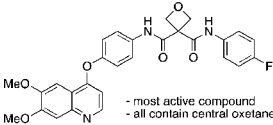

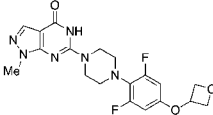

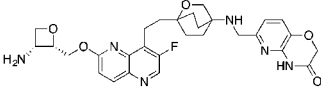

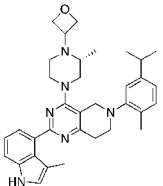

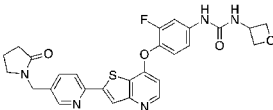

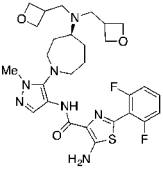

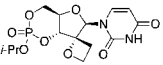
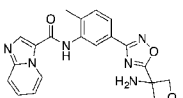

Oxetane	Oxetane Source	Potential Therapeutic Use/ Biological Data	Patent No.	Ref
 <p>- most active compound - all contain central oxetane</p>		Protein kinase activity modulator Human c-Met kinase assay $IC_{50} < 0.1 \mu M$	WO2013032797A2 <i>New Hope R & D Bioscience, Inc., USA.</i>	411
		Tankyrase inhibitor (TNKS1) $IC_{50} = 0.017 \mu M$	WO2013182546A1 <i>F. Hoffmann-La Roche AG, Switz.; Hoffmann-La Roche Inc.</i>	412
	 <p>Cyclization: C-O bond from OTs</p>	Antibacterial activity (<i>S. aureus</i> Smith) $MIC = 0.25 \mu g/mL$	WO2013003383A1 <i>Kyorin Pharmaceutical Co., Ltd., Japan; Merck Sharp & Dohme Corp., USA.</i>	413
		C5A Receptor modulators $IC_{50} = 16 nM$	WO2013016197A1 <i>Novartis AG, Switz.</i>	414
		PTK inhibitor (VEGFR/KDR) $IC_{50} = 0.035 \mu M$	WO2013044360A1 <i>MethylGene Inc., Can.</i>	415
		Pim kinase inhibitor PIM1 LC3K $K_i = 0.962 nM$	US20130079321A1 <i>Genentech, Inc., USA.</i>	416
	Mesylation and cyclization of corresponding diol	HCV antiviral agent $EC_{50} = 0.13 \mu M$	WO2013174962A1 <i>Janssen R&D Ireland, Ire.</i>	417
		C-kit kinase inhibitor	WO2013033116A1 <i>IRM LLC, Bermuda.</i>	418

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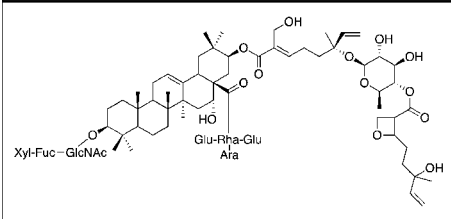
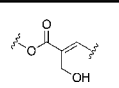
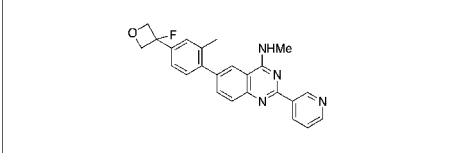

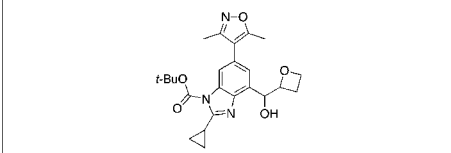

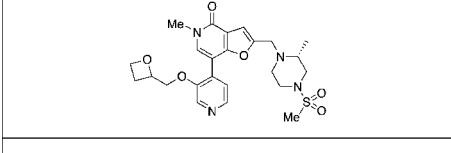

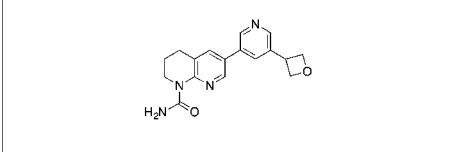

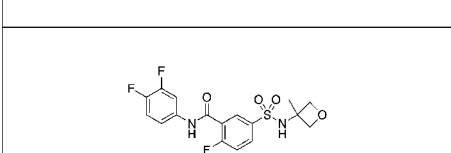

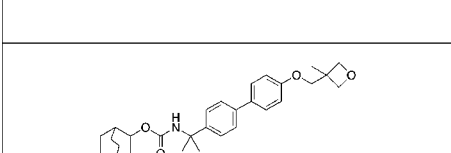

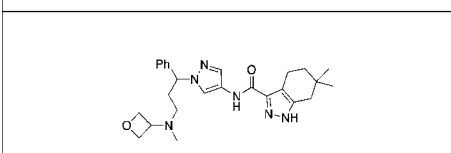

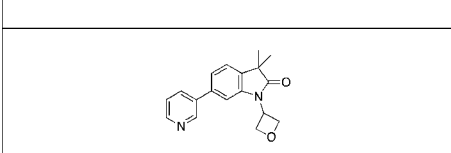

Oxetane	Oxetane Source	Potential Therapeutic Use/ Biological Data	Patent No.	Ref
	 via avicin D (above) using phosphate buffer	Oxetane analog of avicin D, antitumor agents, increased potency compared to natural product	WO2013126730A1 <i>Research Development Foundation, USA.</i>	419
		Striatal-enriched tyrosine phosphatase inhibitor	WO2013003586A1 <i>Otsuka Pharmaceutical Co., Ltd., Japan.</i>	420
		Bromodomain inhibitors (BRD4)	WO2014182929A1 <i>Gilead Sciences, Inc., USA.</i>	421
		Bromodomain inhibitors BRD4 BD1 assay $pIC_{50} \geq 6.0$	WO2014140077A1 <i>Glaxosmithkline</i>	422
		Aldosterone synthase inhibitor $IC_{50} = 14.3 \text{ nM}$	US20140323468A1 <i>Boehringer Ingelheim International GmbH, Germany.</i>	423
		HBV antiviral agent	WO2014106019A2 <i>Philadelphia Health & Ed. Corp., D/B/A Drexel and 2 others.</i>	424
		Glucosylceramide synthase inhibitors $IC_{50} = 7.2 \text{ nM}$	WO2014043068A1 <i>Genzyme Corporation, USA.</i>	425
		ITK Kinase inhibitors $K_i = 0.6 \text{ nM}$	WO2014023258A1 <i>F.Hoffmann-La Roche AG, Switz.; Genentech, Inc.</i>	426
		L-687,414-Induced hyperlocomotion inhibitor (CNS diseases)	WO2014202493A1 <i>F. Hoffmann-La Roche AG, Switz.</i>	427

Table 18. continued

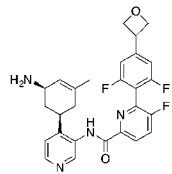

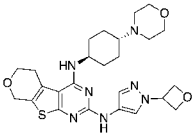

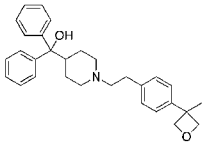

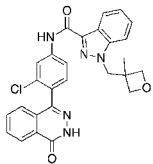

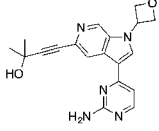

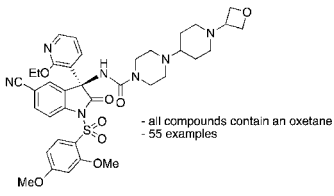

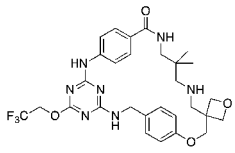

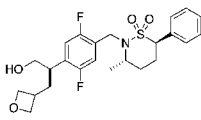

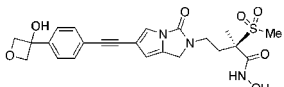

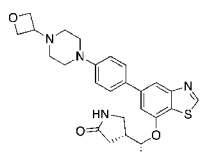

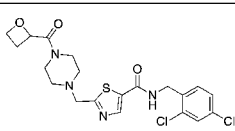
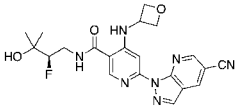

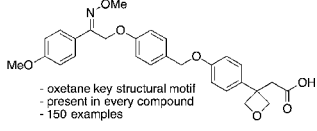

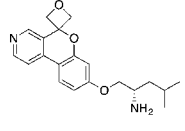

Oxetane	Oxetane Source	Potential Therapeutic Use/ Biological Data	Patent No.	Ref
		Pim kinase inhibitor (Pim 1) $IC_{50} = 0.02 \text{ nM}$	WO2014033631A1 <i>Novartis AG, Switz.</i>	428
		Fms-like tyrosine kinase 3 inhibitor (FLT-3) $IC_{50} \leq 1 \text{ }\mu\text{M}$	WO2014194242A2 <i>Nimbus Iris, Inc., USA.</i>	429
		Anti-infective activity $MIC = >256 \text{ }\mu\text{g/mL}$	WO2014052836A2 <i>University of Rochester, University of Kansas, USA.</i>	430
		Rho-kinase inhibitor (ROCK1) $IC_{50} = 0.1\text{--}100 \text{ nM}$	WO2014113620A2 <i>Bristol-Myers Squibb Company, USA.</i>	431
		NIK inhibitor (MSD MBP) $IC_{50} = 15 \text{ nM}$	WO2014174021A1 <i>Janssen Pharmaceutica NV, Belg.</i>	432
		Vasopressin-related diseases (V1b receptor) $K_i = < 1 \text{ nM}$	WO2014140186A1 <i>Abbvie Deutschland GmbH & Co. KG, Germany.</i>	433
		HCV entry inhibitor (H77C) $EC_{50} = 0.796 \text{ nM}$	WO2014123894A1 <i>Bristol-Myers Squibb Company, USA.</i>	434
		RORc modulator $IC_{50} = 0.004 \text{ }\mu\text{M}$	WO2015104356A1 <i>F. Hoffmann-La Roche AG, Switz.; Genentech, Inc.</i>	435

Table 18. continued

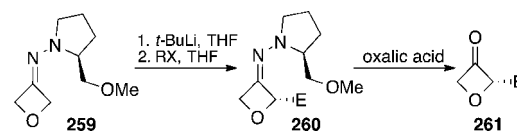
Oxetane	Oxetane Source	Potential Therapeutic Use/ Biological Data	Patent No.	Ref
		Antibacterial activity MIC <i>E. Coli</i> = 0.5 mg/L MIC <i>P. aeruginosa</i> = 1 mg/L MIC <i>K. Pneumoniae</i> = 1 mg/L	WO2015132228A1 <i>Actelion Pharmaceuticals Ltd., Switz.</i>	436
		Spleen tyrosine kinase (Syk) inhibitor IC ₅₀ = 0.6086 nM	WO2015017610A1 <i>Gilead Sciences, Inc., USA</i>	437
	n.d.	Soluble epoxide hydrolase (sEH) IC ₅₀ = 9.67 nM	WO2015082474A1 <i>Sanofi, Fr.</i>	438
		Interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitor IC ₅₀ = 3.7 nM	WO2015103453A1 <i>Bristol-Myers Squibb Company, USA</i>	439
 - oxetane key structural motif - present in every compound - 150 examples		G-protein coupled receptor (GPR40) EC ₅₀ = >5 but <200 nM	WO2015028960A1 <i>Piramal Enterprises Limited, India.</i>	440
		AAK1 kinase inhibitor	WO2015038112A1 <i>Bristol-Myers Squibb Company, USA.</i>	441

^aSee refs 391, 392, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, and 441.

alkylation of the (*S/R*)-1-amino-2-methoxymethylpyrrolidine (SAMP/RAMP) hydrazones **259** derived from oxetan-3-one⁴⁴⁴ (Table 19). Deprotonation of hydrazone **259** with *t*BuLi to form the azaenolate, followed by electrophilic trapping, accessed 2-alkylated oxetanes **260** in good yields and diastereoselectivities. By use of ozone or oxalic acid, the alkylated hydrazones **260** were converted to the corresponding enantioenriched oxetan-3-ones **261** with ee values of up to 84%. Synthesis of a 2,2-disubstituted oxetan-3-one was achieved in 90% ee by a one-pot sequential metalation/alkylation protocol. Furthermore, 2,4-disubstituted examples could be accessed by thermal isomerization of the hydrazone configuration. Notably, there are no examples of the direct deprotonation of oxetane itself to form 2-metalated oxetane.

Oxetanes have recently been shown to be powerful directing groups for ortho-lithiation on aromatic rings. Capriati and co-workers⁴⁴⁵ first developed this feature of the oxetane ring in 2012, using 2-methyl-2-phenyloxetane **262**, without a benzylic

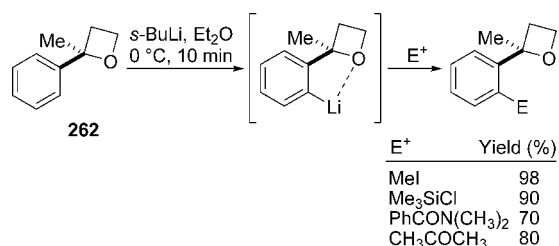
Table 19. Enantioselective Synthesis of 2-Substituted Oxetan-3-ones

				
entry	electrophile (RX)	yield 260 (%)	yield 261 (%)	ee (%)
1	BnBr	73	79	74
2	BrCH ₂ CH=CHPh	57	77	84
3	CH ₃ (CH ₂) ₇ I	60	85	83
4	ICH ₂ CH ₂ CH ₂ OTBS	68	60	84
5	PhCHO	62	92 ^a	54, 2 ^b

^a1:1 dr. ^b(*S,R*) = 54; (*S,S*) = 2.

proton, for regioselective synthesis of functionalized 2-aryloxetanes (Scheme 104). Treatment of oxetane **262** with

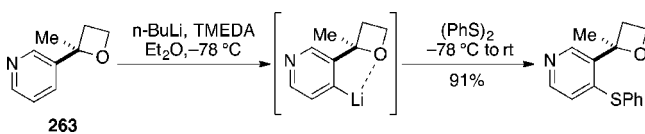
Scheme 104. Exploiting Ortho-Directing Ability of the Oxetane Ring To Access Functionalized 2-Aryloxetanes



s-BuLi in Et₂O resulted in lithiation of the ortho position of the aryl ring, which was reacted with a variety of electrophiles including aldehydes, ketones, Me₃SiCl, and Bu₃SnCl in good yields. Alternatively, biaryl compounds could be accessed in one pot with a Li–B exchange followed by Suzuki cross-coupling with aryl and heteroaryl bromides. The oxetane substituent was shown to be as powerful a directing group as the dimethylaminomethyl group but not as effective as a sulfonyl group.⁴⁴⁵ This allowed functional groups known to be weak directing groups to be present on the aromatic ring without affecting the regioselectivity of the metalation.

Rouquet et al.⁴⁴⁶ reported the regioselective ortho-functionalization of 3-oxetanylpiperidines. Treating 3-(2-methyloxetan-2-yl)pyridine **263** with 1.4 equiv of *n*BuLi in the presence of TMEDA at –78 °C in Et₂O resulted in lithiation at the pyridine C4 position (Scheme 105). A wide range of electrophiles was

Scheme 105. Ortho-Metalation on Pyridine Directed by an Oxetane



employed to generate the 4-functionalized pyridines, including, for example, diphenyl disulfide. The reaction was carried out on a gram scale, with methyl *tert*-butyl ether as the solvent and I₂ as the electrophile, to afford the 4-iodopyridine derivative in 67%.

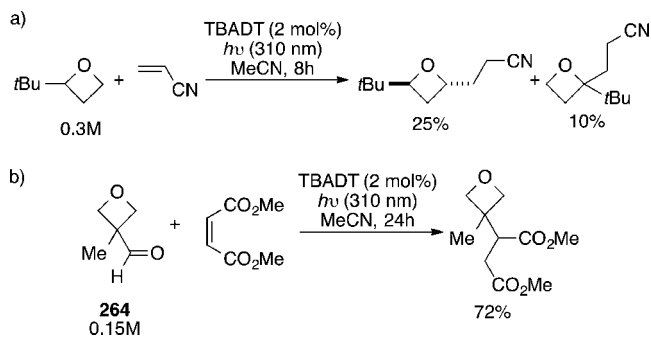
There have been two recent reports of radical functionalization at the 2-position of oxetane itself, maintaining the ring intact.^{447–449} Ravelli et al.⁴⁴⁷ reported the functionalization of oxetane through C–H activation by decatungstate photocatalyst TBADT, [(*n*-Bu)₄N]₄[W₁₀O₃₂], and addition to an electron-poor olefin (Table 20). Oxetane (3 equiv relative to the olefin) was irradiated in the presence of TBADT (2 mol %) in acetonitrile to generate the oxetane α -oxy radical. Substituted oxetanes were generated by use of terminal olefins and those with β -substituents. Employing olefins with two electron-withdrawing substituents resulted in good yields despite the increased steric hindrance. 3,3-Dimethyloxetane was also successfully employed in the reaction to form 2,3,3-trisubstituted derivatives.⁴⁴⁷

When a 2-substituted oxetane was used, in the presence of a nonhindered olefin, a mixture of 2,2- and 2,4-disubstituted regioisomers was formed. When a bulky substituent (e.g., *t*Bu) was present at C2 of the oxetane, reaction at the secondary radical was preferred (Scheme 106a). This was suggested to be due to a decreased reaction rate allowing back-hydrogen transfer to occur. Functionalization at the 3-position could be

Table 20. Photocatalytic Synthesis of Oxetane Derivatives

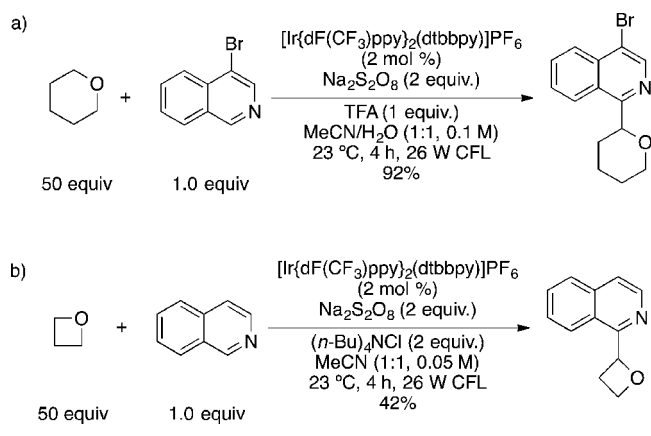
$\text{Oxetane (0.3 M)} + \text{Olefin (0.1 M)} \xrightarrow[\text{MeCN, 8–24 h}]{\text{TBADT (2 mol \%), } h\nu (310 \text{ nm})}$ Product TBADT = [(<i>n</i> -Bu) ₄ N] ₄ [W ₁₀ O ₃₂]			
Entry	Olefin	Product	Yield (%)
1			70
2			51
3			62
4			60
5			75
6			88

Scheme 106. Regioselectivity of Alkylation of Oxetane by Use of Decatungstate Photocatalyst



achieved by employing oxetanecarbaldehyde **264** (Scheme 106b).⁴⁴⁷

Jin and MacMillan⁴⁴⁸ recently developed a visible-light-promoted photoredox catalytic method for direct α -arylation of dialkyl ethers with electron-deficient heteroarenes. Use of a highly tuned Ir-based photocatalyst in the presence of a persulfate salt generated an α -oxyalkyl radical, which underwent Minisci-type coupling with heteroarenes in excellent yields (Scheme 107a). The scope of the dialkyl ether component included a number of THFs, 1,4-dioxane, and 1,3-dioxolane as well as acyclic dialkyl ethers, which were all coupled with isoquinoline (77–93% yields). Most significant, however, was the use of oxetane as a substrate. Under the standard reaction conditions, an oxetanyl radical was generated; however, it underwent a ring-opening polymerization reaction. Modification of the reaction conditions by using MeCN as the sole solvent under more dilute conditions (0.05 vs 0.1 M), along with addition of (*n*Bu)₄NCl to solubilize the persulfate anion,

Scheme 107. Direct α -Arylation of Ethers by Photoredox Catalysis—Minisci Reaction Sequence

led to successful coupling of oxetane and isoquinoline, albeit in a yield of 42% (Scheme 107b).

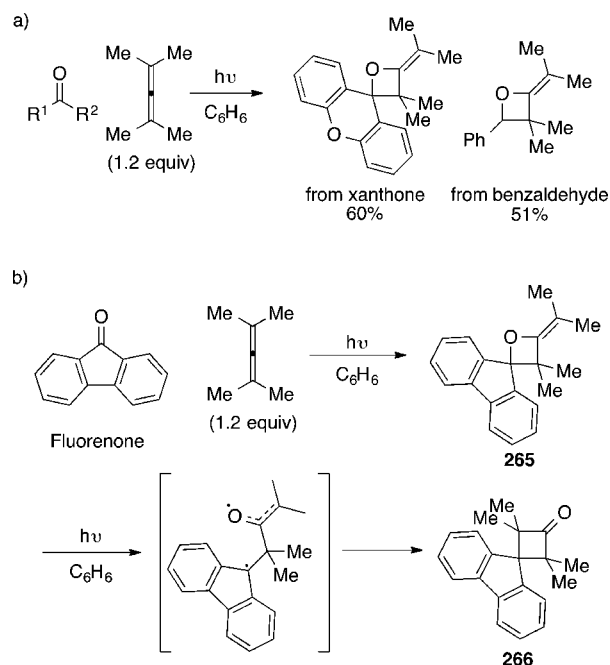
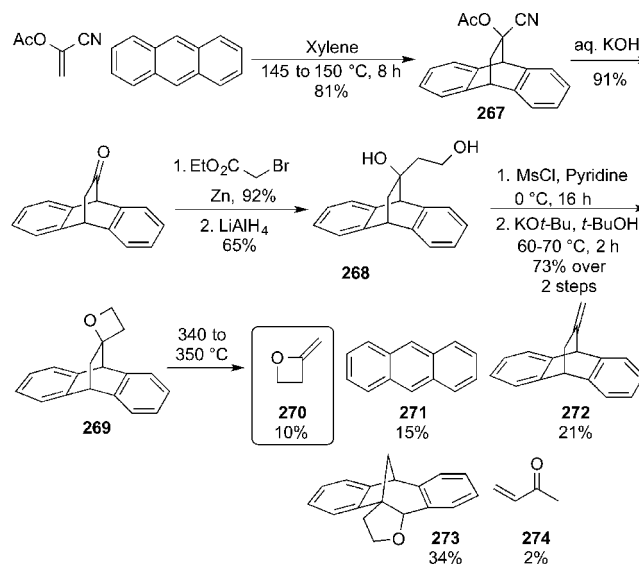
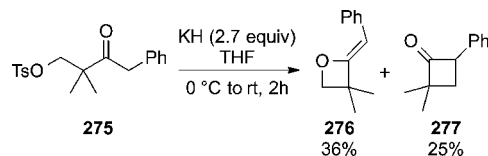
7. SYNTHESIS AND REACTIVITY OF 2-METHYLENEOXETANES

7.1. Synthesis of 2-Methyleneoxetanes

2-Methyleneoxetanes, oxetanes that bear an exocyclic C=C double bond at the 2-position, have been known since the late 1960s. The first examples of 2-methyleneoxetanes were synthesized by the Paternò–Büchi reaction. In 1966, Arnold and Glick⁴⁵⁰ showed that excited-state carbonyl derivatives could be added to allenes under a high-pressure mercury arc lamp. Low yields were obtained and the major product of these reactions tended to be the bis-spirocyclic oxetanes (1,6-dioxaspiro[3.3]heptanes). Around the same time, Hammond and co-workers^{451,452} extended the Paternò–Büchi reaction with allenes and carbonyl compounds to include xanthone and benzaldehyde (Scheme 108a). The yields of the product oxetanes were higher, presumably due to the oxetane derivatives being more stable, but bis-spirocyclic oxetanes were also isolated. The use of fluorenone also afforded 2-methyleneoxetane **265**; however, this was always isolated with the isomeric ketone **266** formed as a result of a rearrangement aided by the similar excitation energy of fluorenone and 2-methyleneoxetane **265** (Scheme 108b).

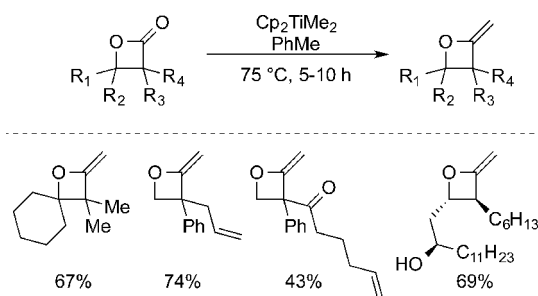
In the 1970s, Hudrlík et al.^{453,454} prepared the parent 2-methyleneoxetane **270** through a retro-Diels–Alder reaction (Scheme 109). A lengthy synthesis commenced with a Diels–Alder reaction between anthracene and α -acetoxyacrylonitrile to afford **267**, followed by several transformations to afford diol **268**. The primary alcohol was activated with MsCl and the crude reaction material was cyclized under Williamson etherification conditions (KOtBu/tBuOH), affording spirocyclic oxetane **269**. Pyrolysis of oxetane–anthracene adduct by heating at 330–350 °C gave a mixture of products including 2-methyleneoxetane **270** (10%) along with other products (**271**–**274**) and remaining starting material.⁴⁵⁴

Hudrlík and Mohtady⁴⁵⁵ also demonstrated that 2-methyleneoxetanes could be synthesized through intramolecular O-alkylation of enolates (Scheme 110). Treatment of ketone **275** with KH afforded 2-benzylideneoxetane **276** through O-alkylation, along with cyclobutanone **277** from C-alkylation. Each of the compounds in this synthetic route was taken

Scheme 108. 2-Methyleneoxetanes from Xanthone, Benzaldehyde, and Fluorenone**Scheme 109.** First Synthesis of 2-Methyleneoxetane **270****Scheme 110.** Synthesis of 2-Methyleneoxetanes via Intramolecular O-Alkylation of Enolates

through crude, so the yields for final products are estimated. The *gem*-dimethyl group was essential to facilitate cyclization.

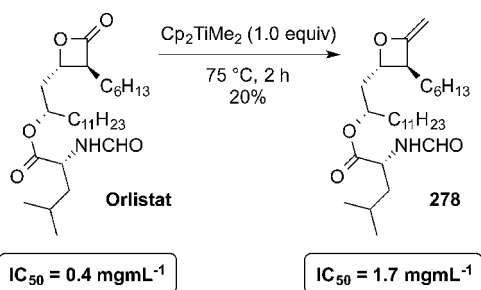
With no further investigations reported for over 20 years, in 1996 Dollinger and Howell⁴⁵⁶ reported a new approach to 2-methyleneoxetanes through methylenation of β -lactones (Scheme 111). Good yields were achieved with the Petasis

Scheme 111. Synthesis of 2-Methyleneoxetanes via Methylenation of β -Lactones

reagent to generate varied substituted methyleneoxetanes, whereas with the more Lewis acidic Tebbe reagent the product could not be isolated. Howell has used this method extensively for preparation of 2-methyleneoxetanes and in numerous studies on their reactivity (see section 7.2).

A 2-methyleneoxetane analogue of Orlistat (**278**), a pancreatic lipase inhibitor, was prepared in 20% yield by use of the Petasis reagent to react at the β -lactone (Scheme 112).^{457–459} This analogue was then directly compared against

Scheme 112. Synthesis of 2-Methyleneoxetane Analogue of Orlistat

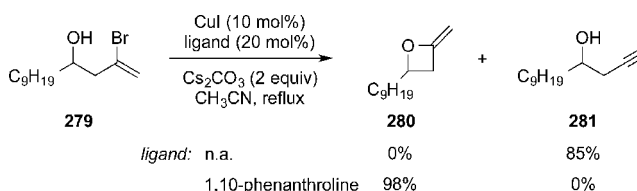


Orlistat in an assay against porcine pancreatic lipase (PPL) with tributyrin as the substrate.^{459,460} Comparative IC_{50} values showed that analogue **278** displayed activity against PPL, albeit lower than Orlistat ($IC_{50} = 1.7 \text{ mg mL}^{-1}$ vs $IC_{50} = 0.4 \text{ mg mL}^{-1}$), and preliminary kinetic studies suggested irreversible inhibition. Despite the lower activity of the methyleneoxetane analogue, this was a significant result, as the carbonyl group of Orlistat was believed to be integral to both interaction and reaction with pancreatic lipase.

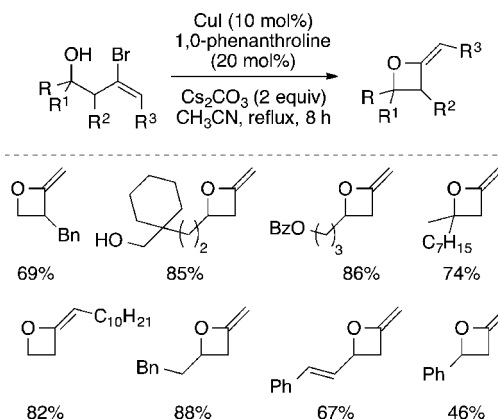
In an alternative approach, Fang and Li⁴⁶¹ reported the synthesis of 2-methyleneoxetanes by Cu-catalyzed intramolecular O-vinylation. γ -Bromohomoallylic alcohols such as **279** were prepared through a Sn-mediated Barbier reaction. When 1,10-phenanthroline ligands were used with CuI for the Ullmann cyclization, good yields of the desired 2-methyleneoxetane **280** were observed (Scheme 113). Only alkyne **281** was observed in the absence of a ligand, formed by direct elimination of HBr.

Primary, secondary, and tertiary alcohols were all good substrates under these cyclization conditions (Scheme 114), with the order of reactivity of secondary alcohols being aliphatic > allylic > benzylic. The configuration of a substituted C=C double bond was retained in the cyclization, but the presence of the additional substituent required higher temperatures. γ -Chlorohomoallylic alcohol analogues were unreactive under the reaction conditions. The reaction was successful for other ring

Scheme 113. Synthesis of 2-Methyleneoxetanes through Cu-Catalyzed O-Vinylation



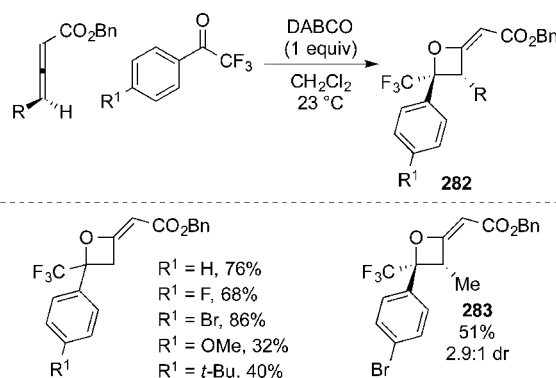
Scheme 114. Sample Scope of Cu-Catalyzed Intramolecular Ullman Coupling



sizes, and interestingly, competition experiments established that the 4-*exo* ring closure was preferred over ring closure to form five- or six-membered rings. This was proposed to be due to precoordination of the Cu catalyst to the alkoxide prior to oxidative addition, leading to the formation of a favorable five-membered ring structure containing Cu, following oxidative addition. Interestingly, the equivalent Pd-catalyzed reactions favor the 5-*exo*-ring closure.⁴⁶¹

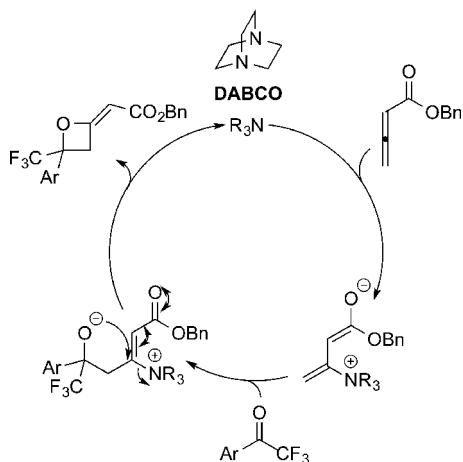
In 2011, Saunders and Miller⁴⁶² showed that formal cycloadditions of allenates and 2,2,2-trifluoroacetophenones could be achieved to form either dihydrofurans or 2-alkylideneoxetanes when Lewis basic catalysts were used. While phosphines catalyzed the [3+2] cycloaddition to give the dihydrofurans, 1,4-diazobicyclo[2.2.2]octane (DABCO) catalyzed the formal [2+2] cycloaddition to form 2-alkylideneoxetanes **282** (Scheme 115).

Scheme 115. Synthesis of 4-Trifluoromethyl-2-methyleneoxetanes via Lewis Base-Catalyzed Formal [2+2] Cycloaddition



The reaction was successful with various aryl substituents: 4-halo-substituted aromatics were well tolerated, but low yields were obtained with electron-rich aryl substituents. Ketones that did not possess a trifluoromethyl group were unreactive. Substitution at the γ -position of the allenic esters was also viable, with oxetane **283** formed in 51% yield (2.9:1 dr). The proposed mechanism involved addition of DABCO to the allenolate, followed by γ -addition to the ketone (Scheme 116).

Scheme 116. Proposed Mechanism for Lewis Base-Catalyzed Formal [2+2] Cycloaddition of Allenates and 2,2,2-Trifluoroacetophenones



The subsequent oxyanion could undergo conjugate addition onto the β -carbon, re-forming the enolate, which then eliminated DABCO. Though the reaction progressed when catalytic amounts of DABCO were used, the optimized conditions used stoichiometric amounts to obtain higher yields.

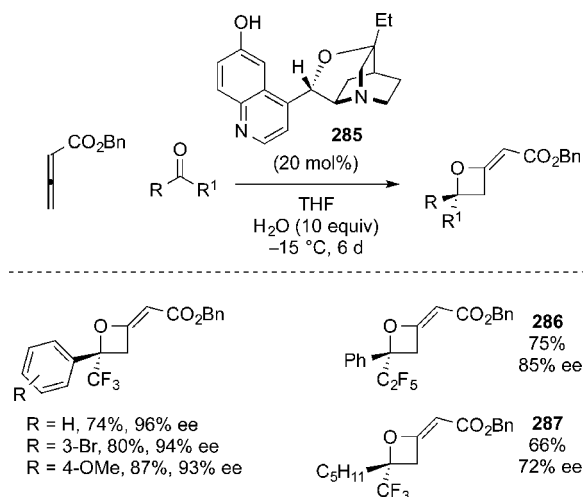
At around the same time, Ye and co-workers⁴⁶³ reported a similar reaction that used catalytic quantities of DABCO (20 mol %) in THF at 0 °C to form 2-alkylideneoxetanes **284** (Table 21). Again, electron-rich ketones gave lower yields, and some sterically bulky ester groups (Cy and *t*-Bu) were tolerated on the allenolate.

Table 21. Selected Examples of 2-Alkylideneoxetanes Synthesized by Use of Catalytic Amounts of DABCO

entry	R	Ar	yield (%)
1	Et	3-MeC ₆ H ₄	73
2	Et	2-thienyl	47
3	Cy	Ph	79
4	<i>t</i> Bu	Ph	60

In 2012, an asymmetric version of this Lewis base-catalyzed formal [2+2] cycloaddition was reported (Scheme 117).⁴⁶⁴ The optimized conditions used 20 mol % β -isocupreidine **285** as catalyst and 10 equiv of water as an additive in THF at -15 °C for 6 days. High yields and good to excellent ee were obtained with a variety of substrates including both electron-rich and electron-deficient aromatics. As well as trifluoromethylaryl ketones, the reaction worked similarly with a pentafluoroethyl

Scheme 117. Asymmetric Formal [2+2] Cycloaddition with β -Isocupreidine **285 as Catalyst**



ketone (**286**) and with a pentafluoromethyl ketone (**287**). The proposed role of water was to stabilize the transition state for γ -addition of the extended enolate to the ketone through formation of a six-membered hydrogen-bonded ring with the hydroxy group of the catalyst.

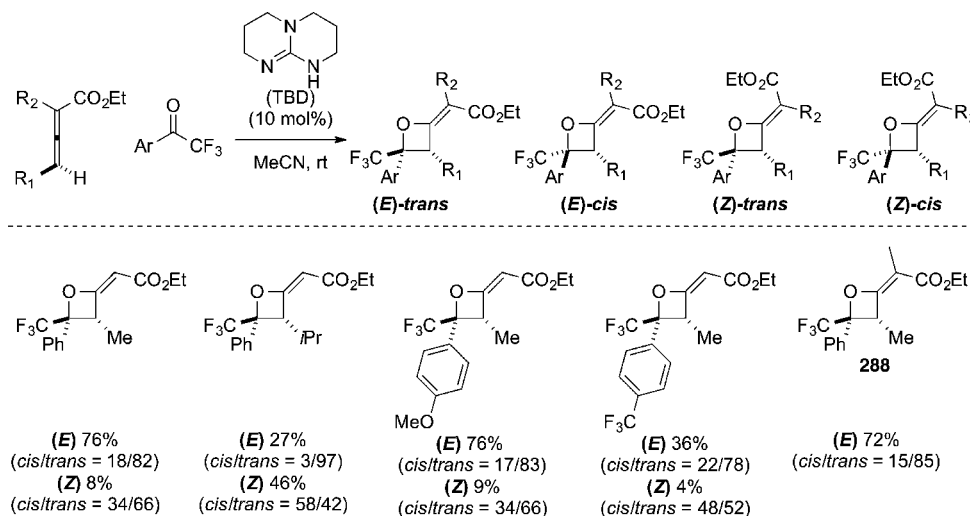
A formal [2+2] cycloaddition was developed by Selig et al.⁴⁶⁵ to form more substituted 2-alkylideneoxetanes through the incorporation of additional substituents on the allenolate. By use of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), a highly active nitrogen Lewis base,⁴⁶⁶ for allenolate activation, a variety of γ -substituted allenates were transformed into highly substituted 2-alkylideneoxetanes (Scheme 118). All four possible isomers were formed during the reaction, but increasing the steric bulk of the γ -substituent led to increased formation of the *Z* isomer. Electron-rich ketone substrates gave higher yields than electron-deficient ketones, due to the electron-deficient ketones undergoing addition reactions with TBD itself, poisoning the catalyst. An α,γ -disubstituted allenolate was also a viable substrate, forming a highly substituted oxetane in good yield and diastereoselectivity with a slightly higher catalyst loading (30 mol %) and a longer reaction time (**288**).

7.2. Reactivity of 2-Methyleneoxetanes

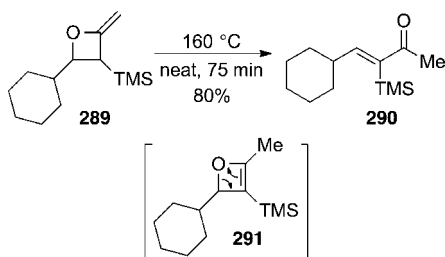
The reactivity of 2-methyleneoxetanes can be separated into two types: (i) ring opening of the oxetane and (ii) functionalization of the C=C double bond. Ring-opening reactions include conversion to homopropargylic alcohols through elimination,⁴⁶⁷ nucleophilic attack with carbon or heteroatom nucleophiles at C4 to generate ketones,^{468,469} and reductive ring opening of 4-aryl derivatives by use of Li/4,4'-di-*tert*-butylbiphenyl (DTBB) to generate ketones.^{470,471} Certain 2-methyleneoxetanes have also been reported to undergo a conversion to α,β -unsaturated methyl ketones at high temperatures (Scheme 119).⁴⁷² The incorporation of a silyl group at the 3-position of the ring in **289** enhanced the reaction, which was proposed to occur by alkene isomerization through oxetene **291**, followed by a 4π -electron electrocyclic ring opening to give ketone **290**.

The first example of functionalization of the exocyclic C=C double bond of a 2-methyleneoxetane, such as **292**, was reported in 1998 through epoxidation to form 1,5-dioxaspiro[3.2]hexanes (e.g., **293**, Scheme 120).³⁹³ By use of anhydrous, acetone-free dimethyldioxirane (DMDO) to

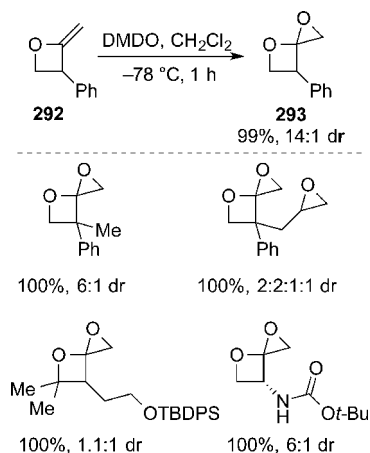
Scheme 118. Use of TBD as Lewis Base Catalyst for Synthesis of Highly Substituted 2-Alkylideneoxetanes



Scheme 119. Tandem Alkene Isomerization/Electrocyclic Ring Opening of 2-Methyleneoxetanes



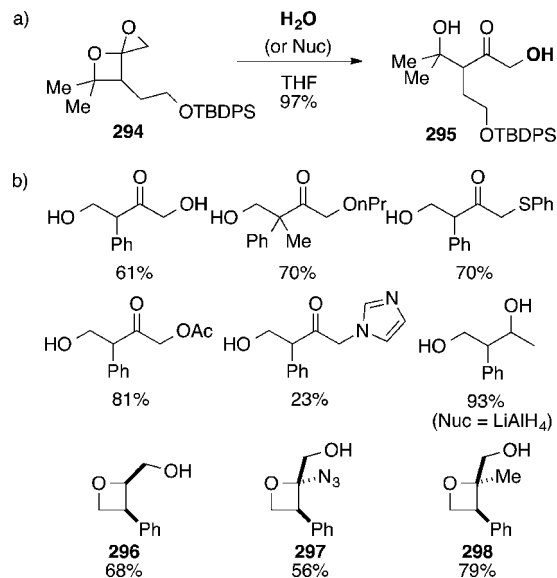
Scheme 120. Epoxidation of 2-Methyleneoxetanes: Synthesis of 1,5-Dioxaspiro[3.2]hexanes



provide neutral conditions,⁴⁷³ quantitative yields of the sensitive spirocycles were obtained from a variety of substituted 2-methyleneoxetane derivatives. Moderate diastereoselectivity was observed with one substituent at the C3 position, but an additional substituent at C3 or any substitution at the C4 position lowered the dr.

The internal acetal of these spirocycles, such as **294**, underwent hydrolysis in the absence of acid to afford ketones such as **295** in very high yields (Scheme 121a).³⁹³ This reactivity was then reported for a variety of nucleophiles: oxygen nucleophiles gave good yields of hydroxy ketones,

Scheme 121. Nucleophilic Ring Opening of 1,5-Dioxaspiro[3.2]hexanes

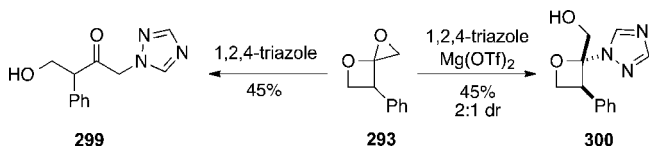


thiophenol was slow to react but the sodium thiolate gave a good yield, imidazole gave low yields, and ring opening followed by reduction to a 1,3-diol occurred with LiAlH₄ (Scheme 121b).⁴⁷⁴ Unexpectedly, the use of DIBAL gave nucleophilic attack at the internal position of the epoxide to leave the oxetane ring intact (**296**). Coordination of the Lewis acid to the epoxide oxygen was proposed with participation of an oxetane oxonium ion. Ring opening of the epoxide, leaving the oxetane ring intact, also occurred with nucleophiles such as TMSN₃ (**297**) and AlMe₃ (**298**).

A detailed study of heteroaromatic nucleophiles was undertaken with the epoxide of 3-phenyl-2-methyleneoxetane **293** which related pK_a of the nucleophile to the reaction product.⁴⁷⁵ Both imidazole and TMS-imidazole gave oxetane ring opening, pyrrole and indole did not react, and 1,2,4-triazole and its TMS-linked analogue also caused oxetane ring opening. However, 1,2,3-triazole gave the 2,2-disubstituted oxetane, as did benzotriazole, TMS-benzotriazole, and tetrazole. This study concluded that more acidic nucleophiles formed the 2,2-disubstituted oxetanes, potentially due to activation of the

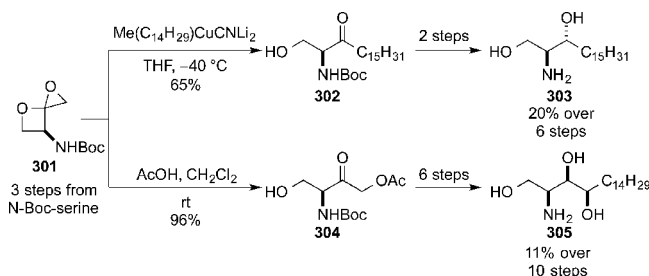
epoxide so that intramolecular oxonium formation could occur more easily. Howell and co-workers⁴⁷⁵ therefore investigated other Lewis acids, and the addition of $\text{Mg}(\text{OTf})_2$ with 1,2,4-triazole, which originally gave oxetane ring opening (299), gave 2,2-disubstituted oxetane formation (300, Scheme 122).

Scheme 122. Synthesis of 2,2-Disubstituted Oxetane 300 by Use of $\text{Mg}(\text{OTf})_2$ and 1,2,4-Triazole



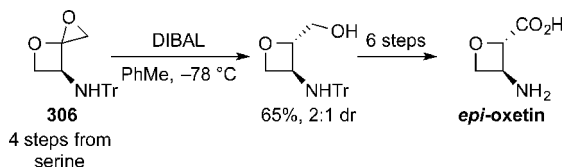
The tandem ring opening of 1,5-dioxaspiro[3.2]hexanes was utilized in synthesis of the challenging sphingoid base of glycosphingolipids.⁴⁷⁶ 1,5-Dioxaspiro[3.2]hexane 301 was prepared in three steps from N-Boc-protected L-serine (Scheme 123). Addition of a higher-order cuprate led to formation of

Scheme 123. Synthesis of D-erythro-Dihydrosphingosine and D-xylo-Phytosphingosine by Tandem Ring Opening of 1,5-Dioxaspiro[3.2]hexane



ketone 302 through nucleophilic attack at the least hindered epoxide carbon, which was converted to D-erythro-dihydrosphingosine 303 in two steps. 1,5-Dioxaspiro[3.2]hexane 301 also underwent facile epoxide ring opening with acetic acid, and subsequent functionalization converted ketone 304 to D-xylo-phytosphingosine 305 in six steps. A similar strategy was used in the synthesis of *epi*-oxetin, involving a DIBAL opening of epoxide 306 (Scheme 124).⁴⁷⁷

Scheme 124. Synthesis of *epi*-Oxetin through DIBAL Opening of 1,5-Dioxaspiro[3.2]hexane^a

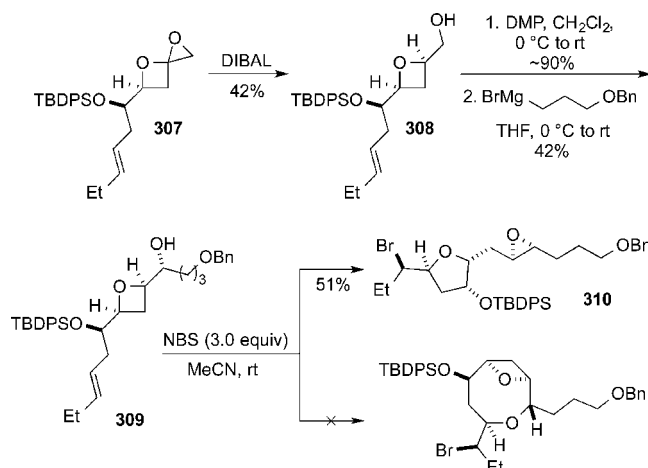


^aBlauvelt and Howell.⁴⁷⁷

In 2012, ring opening of spirocyclic epoxide 307 was used to generate hydroxymethyloxetane 308 as a possible intermediate in the synthesis of Laureatin.⁴⁷⁸ However, treatment of derivative 309 with NBS instead mediated a rearrangement, forming epoxytetrahydrofuran 310 in a 51% yield (Scheme 125).

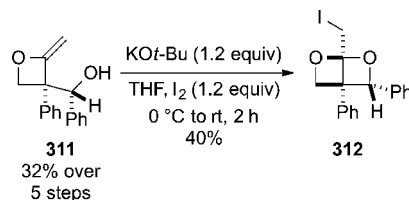
Howell and co-workers⁴⁷⁹ also examined the reactivity of the enol ether of 2-methyleneoxetanes with haloelectrophiles,

Scheme 125. Unexpected Rearrangement of Oxetane 309 Affording Epoxytetrahydrofuran



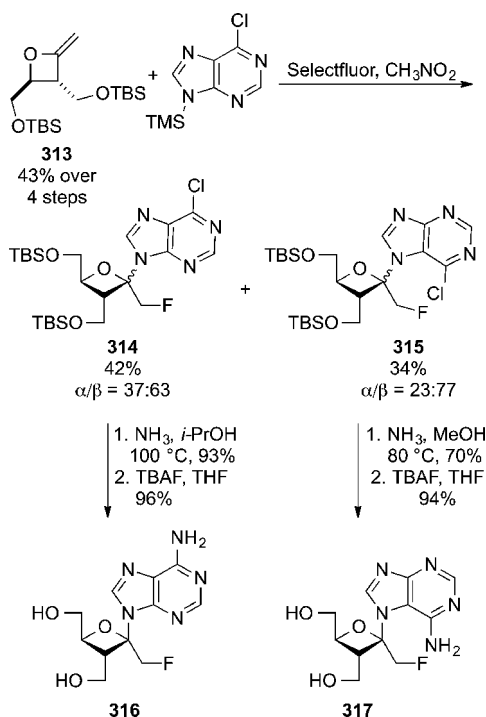
intending to trap the intermediate oxonium ion. Treatment of oxetane 311 with KOtBu , followed by the addition of I_2 , gave the first example of a [2.2.0] fused ketal, 312, in 40% yield (Scheme 126).

Scheme 126. Synthesis of [2.2.0]-Fused Ketal

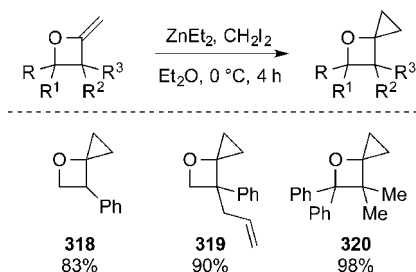
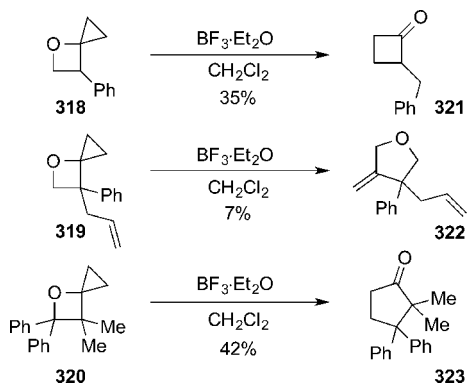


A similar strategy was used to access oxetane-containing *psico*-nucleosides, that is, with a hydroxymethyl group adjacent to the base, related to the natural product oxetanocin A. This was achieved through electrophilic addition of F^+ followed by nucleophilic attack of the nucleobase (Scheme 127).⁴⁸⁰ From 2-methyleneoxetane 313, selectfluor gave a good yield for nucleobase incorporation, but both N7 (314) and competing N9 alkylation (315) occurred. After multiple purifications, 314 was obtained as a 37:63 mixture (α : β epimers, 42% yield) and 315 as a 23:77 mixture (α : β epimers, 34% yield), with both favoring the desired β -isomers. Oxetane-containing *psico*-nucleosides 316 and 317 were then prepared through a substitution reaction with ammonia, followed by deprotection of the silyl ethers.⁴⁸⁰

Cyclopropanation of the exocyclic $\text{C}=\text{C}$ double bond of 2-methyleneoxetanes was achieved to form 4-oxaspiro[2.3]-hexanes (Scheme 128).⁴⁸¹ Using ZnEt_2 and CH_2Cl_2 in the modification by Furukawa et al.⁴⁸² of the Simmons–Smith reaction gave a good yield of spirocyclic cyclopropanes, providing the reaction temperature was not raised above 0 °C, across a variety of substituted oxetanes. Bekolo and Howell⁴⁸¹ showed that 4-oxaspiro[2.3]hexanes underwent rearrangement when treated with $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 129). For example, treatment of oxetanes 318–320 with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ led to three different products being formed: cyclobutanone 321, THF 322, and cyclopentanone 323. The reaction was proposed to proceed via ring opening to form carbocationic intermediates, which could rearrange through cyclopropane

Scheme 127. Synthesis of Oxetane-Containing *psico*-Nucleosides

Scheme 128. Cyclopropanation of 2-Methyleneoxetanes To Form 2-Oxaspiro[2.3]hexanes

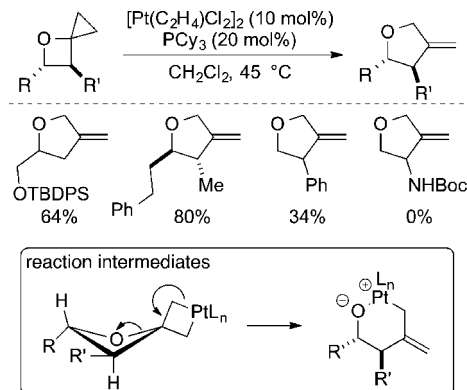
Scheme 129. Rearrangement of 4-Oxaspirohexanes Catalyzed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ 

opening and hydride shifts, with the pathway influenced by the substitution on the oxetane ring.

Oxaspirohexanes that were synthesized from 2-methyleneoxetanes also underwent rearrangement catalyzed by Zeise's $\text{Pt}(\text{II})$ dimer.⁴⁸³ Monosubstituted as well as 5,6-trans-disubstituted oxaspirohexanes rearranged in good yields via a

platinacyclobutane intermediate (Scheme 130). 5,6-cis-disubstituted oxaspirohexanes ring-opened to afford allyl chlorides as the major product.

Scheme 130. Rearrangement of Oxaspirohexanes to 3-Methylenetetrahydrofurans via Platinacyclobutane Intermediate



8. RING-OPENING AND RING-EXPANSION REACTIONS OF OXETANES

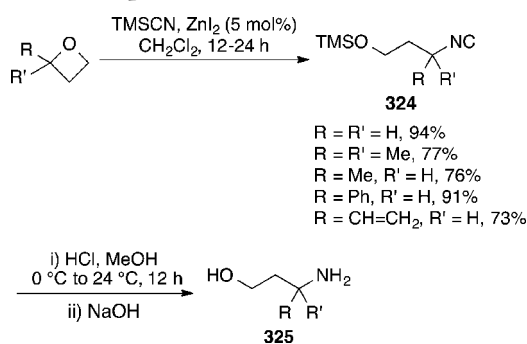
In an apparent contradiction with the stability required of the oxetane ring in many medicinal chemistry applications, the strain present in the ring ($106 \text{ kJ} \cdot \text{mol}^{-1}$) renders oxetanes useful synthetic intermediates.^{31,32} This section considers reactions that result in ring opening of oxetanes, through attack at the 2-position releasing the ring strain, and also ring-expansion reactions that form larger heterocyclic systems. Here, ring expansion is defined as when the oxygen atom from the oxetane ring remains in the new ring structure formed in the relevant reaction; ring opening is the term used when the oxetane O-atom is not in the new ring, even if a ring is formed. Readers are also directed to recent reviews by Malapit and Howell,⁷ on aspects of using oxetanes in the preparation of other heterocycles, and by Sun and co-workers,⁸ on enantioselective oxetane ring-opening desymmetrization reactions. Ring-opening reactions of oxetanones are not covered specifically,⁵ and for ring-opening reactions of 2-methyleneoxetanes, see section 7.

8.1. Ring-Opening Reactions of Oxetanes

Under acidic conditions, the oxetane ring can be opened with simple nucleophiles, including hydrolysis to give 1,3-glycols.^{484,485} Various nucleophiles have been employed, including amines,^{486–489} KPPH_2 ,⁴⁹⁰ lithiated alkynes,^{491–493} TMSCN ,^{494,495} allyl silanes,⁴⁹⁶ LiAlH_4 ,⁴⁹⁷ and azaenolates.⁴⁹⁸ Lithium enolates have been used to open mono- or disubstituted oxetanes in the presence of $\text{BF}_3 \cdot \text{OEt}_2$.⁴⁹⁹ Gassman and Haberman⁴⁹⁵ reported the treatment of 2-substituted and 2,2-disubstituted oxetanes with TMSCN in the presence of zinc iodide to afford γ -hydroxyisocyanides **324** in yields of 73–94%, by ring opening at the more substituted position (Scheme 131). The isocyanides were converted into the corresponding γ -amino alcohols **325** in 65–81%, following deprotection and hydrolysis.

Organometallic reagents alone can open oxetane at higher temperatures. In 1916, oxetane was treated with *n*-propylmagnesium bromide under reflux in ether/benzene, which resulted in the formation of *n*-hexanol in 49% yield.⁵⁰⁰ This prompted

Scheme 131. Ring Opening of Oxetanes by Attack of an Isonitrile Nucleophile



the seminal work by Searles⁵⁰¹ on reaction of oxetane with organometallic compounds. Oxetane, with a variety of aromatic and aliphatic organometallic reagents, such as PhMgBr, BnMgCl, and PhLi, was heated under reflux in benzene for 4 h to afford the corresponding open-chain alcohols in moderate to good yields (Table 22). It is notable that ring opening occurred, whereas in the more strained epoxide, these organometallic reagents would be likely to result in deprotonation on the ring.^{502,503}

Table 22. Ring Opening of Oxetane with Organometallic Reagents

entry	Grignard reagent	yield (%)
1	PhMgBr	84
2	CyMgBr	28
3	1-naphthyl-MgBr	80
4	<i>i</i> -PrMgCl	28
5	BnMgCl	83
6	PhLi	85
7	<i>n</i> -BuLi	28

Huynh et al.⁵⁰⁴ reported milder, room-temperature reaction conditions for the opening of oxetane by Grignard reagents in the presence of CuI (10 mol %) for 20 h. Grignard reagents,

including *n*BuMgCl, PhMgBr, and allyl-MgBr, successfully reacted with oxetane with yields of 50–75%. High-temperature reactions have also been reported.⁵⁰⁵

In 2008, Pineschi and co-workers⁵⁰⁶ developed a regioselective ring opening of 2-aryloxetanes with aryl borates under mild, neutral conditions. The use of enantiomerically pure 2-phenyloxetane led to the formation of enantioenriched β -aryloxy alcohols such as **327** or **328** with little reduction in ee. This was proposed to occur via intramolecular delivery of the aryloxy group in a six-membered transition state (**329**, Scheme 132), resulting in retention of configuration at the reacting center. When electron-rich aryl borates were used, the C-alkylation product dominated, formed via a Friedel–Crafts process, in low ee (**326**). A range of aryl borates could be used, including a number of ortho-halo-substituted examples and a catechol borate, in yields up to 86% and up to 86% ee (e.g., **328**, Scheme 132).

In 2002, Dussault et al.¹¹³ reported the regioselective Lewis acid-catalyzed ring opening of oxetanes to afford enantiomerically enriched 1,3-hydroperoxy alcohols and 1,3-peroxy alcohols which could be converted into enantiomerically enriched 1,2,4-trioxepanes. Enantioenriched oxetanes were treated with ethereal H₂O₂ in the presence of Lewis acids to form hydroperoxy alcohols. No reaction was observed when MgCl₂, ZnCl₂, or BF₃·OEt₂ was employed, and the use of TFA, CSA, BF₃·OEt₂, or H₂SO₄ resulted in significant amounts of 1,3-diol being formed. However, treating the oxetanes with ethereal H₂O₂ in the presence of TMSOTf, Yb(OTf)₃, or Sc(OTf)₃ resulted in the desired products **330** being formed in good yields (Table 23). The reaction was extended to tertiary oxetanes with alkyl hydroperoxides, such as *t*-BuOOH, cumyl-OOH, and THP-OOH, to produce 3-peroxy alkanols in yields of 39–51%.

Dai and Dussault⁵⁰⁷ reported the corresponding intramolecular reaction in 2005. Oxetanes **331** were treated with O₃ in methanol to give intermediate **332**, which underwent a 5-exo cyclization to afford 1,2-dioxolanes **333** as a 1:1 mixture of cis and trans isomers (Table 24). Interestingly, cyclization onto a monosubstituted oxetane gave the desired product despite the corresponding intermolecular reaction being unsuccessful. Alkyl hydroperoxides were also generated by cobalt-mediated reductive dioxygenation, such as from **334**, which afforded triethylsilyl peroxide **335** in 80% yield (Scheme 133).

Scheme 132. Ring Opening of 2-Aryloxetanes with Aryl Borates

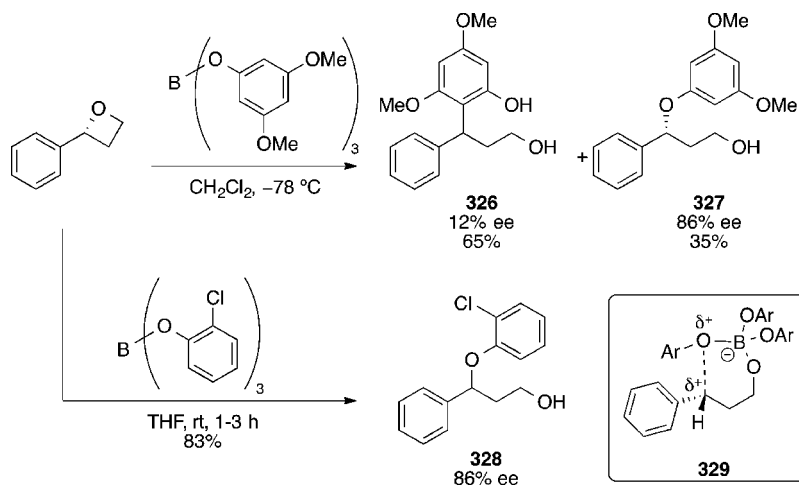


Table 23. Opening of Substituted Oxetanes with Hydrogen Peroxide To Access Hydroperoxy Alcohols

330

Entry	Oxetane	Lewis Acid (equiv)	Conditions	Product	Yield (%)
1		TMSOTf (0.4)	−25 to 0 °C, 0.5 h		48
		Yb(OTf) ₃ (0.1)	−25 to 0 °C, 2 h		60
		Sc(OTf) ₃ (0.1)	−25 to 0 °C, 3 h		50
2		TMSOTf (0.1)	0 °C to rt, 1.5 h		31
		Yb(OTf) ₃ (0.1)	0 °C to rt, 2 h		40
3		TMSOTf (0.1)	0 °C to rt, 1.5 h		45
		Yb(OTf) ₃ (0.1)	0 °C to rt, 2.5 h		29

Table 24. Intramolecular Opening of Substituted Oxetanes

333

entry	R	R ¹	R ²	yield (%)
1	Me	Me	H	57
2	C ₆ H ₁₃	Me	H	73
3	C ₆ H ₁₃	H	H	77
4	C ₆ H ₁₃	Me	Me	72

Deprotection with HF followed by 5-exo cyclization afforded 1,2-dioxolane **336**.⁵⁰⁷

Han and Wu⁵⁰⁸ reported the perhydrolysis of tertiary and secondary oxetanes in the presence of a molybdenum species, Na₂MoO₄·Gly, in H₂O₂/t-BuOMe. In addition to the desired product **337**, alcohol **338** (often not isolated) and elimination product **339** were formed (Table 25). Different diastereoisomers showed differences in the stereoselectivity of the reaction (Table 25, entries 3 and 4). Secondary oxetanes were less reactive than tertiary oxetanes under the reaction conditions; therefore a more acidic catalyst, PMA (phosphomolybdic acid), was required.⁵⁰⁸

In 2014, Okamoto and co-workers⁵⁰⁹ reported the ring opening of 2-substituted oxetanes by Fe-catalyzed reductive magnesiation at the 2-position to afford substituted 3-oxidopropylmagnesium compounds such as **340** in excellent yields. 2-Phenyloxetane was treated with a Grignard reagent in THF in the presence of FeCl₃ to form the ring-opened product **341** in 54% yield after workup, and this yield was increased to 99% by addition of a phosphine ligand (Scheme 134). Ring opening occurred in high yields under modified conditions

when 2-alkyl, 2,2-diphenyloxetane, and 2,2-phenylmethyloxetane substrates were used, but no reaction occurred when a 3,3-disubstituted oxetane was investigated.

The 3-oxidopropylmagnesium intermediates **342** were also successfully quenched with electrophiles (Table 26). Okamoto and co-workers⁵⁰⁹ proposed that the reaction proceeded via a radical mechanism, involving a low-valent Fe species. This proposal was supported by the loss of stereochemical information when diastereomeric pairs of oxetanes were used.

In 2013, Okamoto and co-workers⁵¹⁰ reported the reductive ring-opening reaction of oxetanes catalyzed by a low-valent titanium species, formed from a titanatrane complex (Scheme 135). Complex **344** was treated with Me₃SiCl and Mg powder to form a low-valent titanium alkoxide that, in the presence of 1,4-cyclohexadiene, reduced oxetanes to alcohols in good yields. 3,3-Disubstituted oxetanes, 2-monoaryl and 2-monoalkyl oxetanes, 2,2-disubstituted oxetanes, and spiro compounds were all successfully reduced to the corresponding alcohols (Table 27). Okamoto and co-workers⁵¹⁰ proposed that the oxetane coordinated to an intermediate Ti complex and then underwent a single-electron transfer to generate a titanoxyl radical. This resulting radical could then abstract hydrogen from 1,4-cyclohexadiene. The stability of this radical intermediate affected the regioselectivity of the reaction, generally resulting in formation of the less-substituted alcohols as the major products.

Murakami and co-workers,⁵¹¹ in 2013, showed that cyclobutanols underwent ring opening and addition to isocyanates with a Rh catalyst. Conventionally, carbamates would be formed when cyclobutanols are reacted with isocyanates, but this combination of Rh catalyst and 1,1'-bis-(diphenylphosphino)ferrocene (DPPF) ligand directed isocyanate addition through the C-atom, generating amide

Scheme 133. Intramolecular Opening of Substituted Oxetanes with Alkyl Hydroperoxides

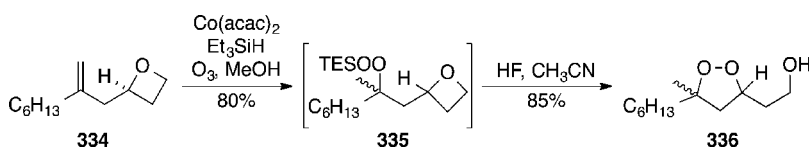


Table 25. Perhydrolysis of Oxetanes in the Presence of Molybdenum Species

$\text{R}-\text{oxetane} \xrightarrow[\text{H}_2\text{O}_2/\text{t-BuOMe, rt}]{\text{Na}_2\text{MoO}_4\cdot\text{gly}} \text{Product 337} + \text{Product 338} + \text{Product 339}$					
Entry	Oxetane	Product 337	Yield (%)	Product 339	Yield (%)
1			48		13
2			54		13
3			33 (cis) 23 (trans)		14
4			8 (cis) 34 (trans)		12

Scheme 134. Fe-Catalyzed Reductive Magnesiation of 2-Phenylloxetane

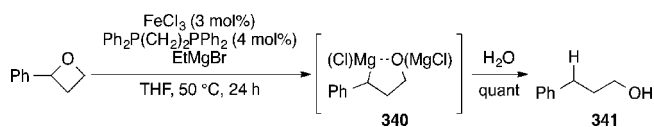
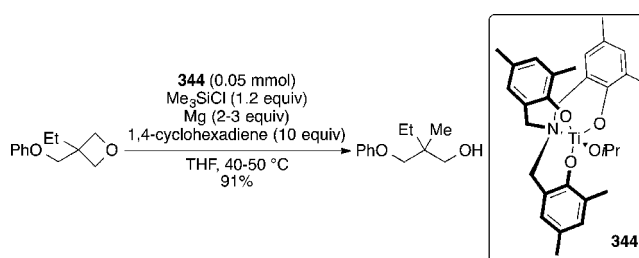


Table 26. Electrophilic Trapping of Oxidopropylmagnesium Compounds

$\text{Ph-oxetane} \xrightarrow[\text{THF, 50 °C, <12h}]{\text{FeCl}_3 (3 \text{ mol\%}), \text{Ph}_2\text{P}(\text{CH}_2)_2\text{PPh}_2 (4 \text{ mol\%}), n\text{-PrMgCl}} \text{Intermediate 342} \xrightarrow{\text{E}^+} \text{Product 343}$		
Entry	E ⁺	Yield 343 (%)
1		91
2	<i>n</i> -BuBr (CuCN 10 mol%)	81
3	Me ₃ SiCl	98
4	PhCHO + Ti(O <i>i</i> Pr) ₄	91
5	CO ₂	 61
6	Et ₂ SiCl ₂	 94

derivatives. As part of the substrate scope, it was shown that oxetanols were compatible with this Rh-catalyzed C-carbamoylation (Scheme 136). The Rh-catalyzed C-carbamoylation of oxetanols occurred in very good yields, and the stereochemical

Scheme 135. Formation of Primary Alcohols by Ring Opening of Oxetanes



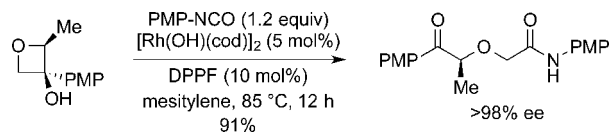
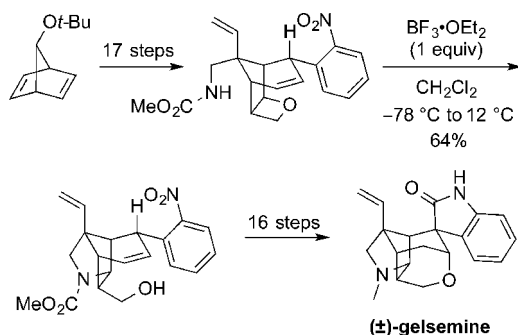
integrity of an enantioenriched oxetanol (>98% ee; >20:1 dr) was retained in ring-opened amide (>98% ee).

8.1.1. Intramolecular Ring Opening. The use of intramolecular nucleophiles can be effective in generating new ring systems. In the total synthesis of (±)-gelsemine, Danishefsky and co-workers^{512,513} utilized a Lewis acid-mediated intramolecular oxetane ring-opening strategy with a nitrogen nucleophile (Scheme 137).

In 1996, Bach and Kather⁵¹⁴ reported intramolecular ring-opening reactions of oxetanes **345** to give diastereomerically pure sulfur, nitrogen, and oxygen heterocycles **346** (Table 28). A Paternò–Büchi reaction of silyl enol ethers followed by a Mitsunobu reaction generated oxygen-, sulfur-, or nitrogen-containing precursors.^{514,515} Cyclization to six- and seven-membered heterocycles was achieved by treatment with organometallic reagents and heating. A tetrahydropyran was synthesized in 54% yield by removing a pivaloyl protecting group with MeLi in DME and then heating at reflux to promote cyclization (Table 28, entry 1). However, the seven-membered oxepane derivative could not be generated under the same conditions, with only deprotection being observed (entry 2). Replacing dimethoxyethane (DME) with high-boiling (162 °C)

Table 27. Radical Ring Opening of Oxetanes by Treatment with Low-Valent Titanium Complex 344

Entry	Oxetane	Product	Yield of Alcohol (%)
1			76
2			58
3			74
4			99
5			80
6			98
7			89

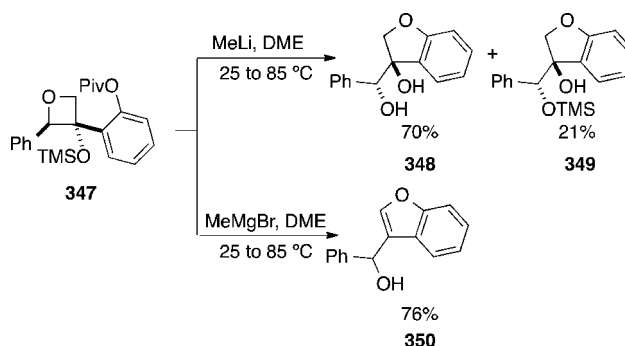
Scheme 136. Rh-Catalyzed C-Carbamylation of Oxetanols and Isocyanates**Scheme 137. Oxetane Ring Opening in Total Synthesis of (±)-Gelsemine^a**^aDanishefsky and co-workers.^{512,513}**Table 28. Scope of Ring-Opening Reaction^a**

entry	<i>n</i>	X	PG	reagent	time (h)	yield (%)
1	1	O	Piv	MeLi	6	54
2	2	O	Piv	MeLi	5	0
3	1	S	Ac	MeLi	4	91
4	2	S	Ac	MeMgBr	5	54
5	1	NTs	H	MeMgBr	5	52

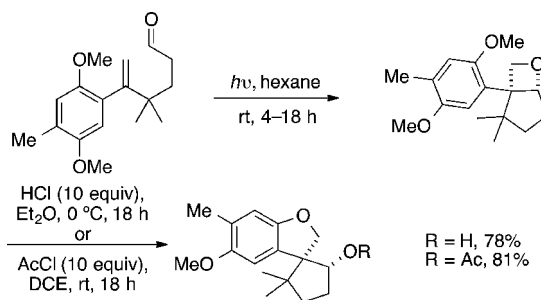
^aBach and Kather.⁵¹⁴

diglyme allowed the oxepane derivative to be synthesized in a 32% yield as a mixture of diastereomers.⁵¹⁵ Thiotetrahydropyran and thioxepane derivatives could be delivered as single diastereoisomers by use of MeLi and MeMgBr, respectively (entries 3 and 4). Similarly, use of MeMgBr yielded the piperidine derivative in a synthetically useful 52% yield (entry 5). The Mg cation was thought to coordinate to the oxetane oxygen, encouraging nucleophilic substitution.

Similarly, oxetane **347**, prepared in three steps from 2-hydroxyacetophenone by Paternò–Büchi reaction, could be cyclized by use of MeLi to give a mixture of dihydrobenzofuran derivatives **348** and **349**, with the diol as the major product and the monosilylated derivative as the minor product (Scheme 138).^{514,515} Treatment with MeMgBr gave the benzofuran derivative **350**, where the silyl ether was eliminated.

Scheme 138. Intramolecular Cyclization to Dihydrobenzofuran or Benzofuran Derivatives

Grainger and co-workers⁵¹⁶ examined the ring opening of oxetanes to yield dihydrobenzofurans. A Paternò–Büchi reaction formed the oxetane moiety, and then acid-promoted intramolecular cyclization occurred with a proximal arylmethoxy group acting as the nucleophile (Scheme 139). The use

Scheme 139. Synthesis of Bis-Spirocycles through Paternò–Büchi Reaction and Acid-Promoted Intramolecular Cyclization

of 10 equiv of HCl gave the bis-spirocyclic hydroxy products in yields between 34% and 78%. Acetyl chloride could also be used as a promoter to give acetate derivatives.

In 2012, Sun and co-workers⁵¹⁷ reported the synthesis of eight-membered lactones via a [6 + 2] cyclization process between oxetane-containing benzaldehydes and ynol silyl ethers. When oxetane **351** was treated with siloxy alkynes **352** in the presence of trifluoromethanesulfonimide as a Lewis acid, eight-membered lactones **353** were formed (Table 29). Nucleophilic attack on the aldehyde moiety of oxetane **351** resulted in an intramolecular oxetane ring-opening process.

Table 29. Intramolecular Ring Opening of Oxetane Resulting in Formation of Eight-Membered Lactones

Entry	Ar	R	Yield 353 (%)
1		<i>n</i> Bu	71
2		cyclopropyl	62
3		Ph	47
4		<i>n</i> Bu	47
5		<i>t</i> Bu	53

Oxetanes with aryl linkers substituted with an electron-withdrawing or electron-donating group could be employed in the reaction. Interestingly, when the oxetane ring was substituted by an epoxide, a similar intermolecular reaction was not observed. Instead an intermolecular homocyclization between the oxirane and the aldehyde moiety occurred.

Yadav et al.⁵¹⁸ utilized an acid-catalyzed oxetane ring-opening approach to form a key substituted tetrahydropyran (THP) skeleton in synthesis of the C1–C17 fragment of the polyether natural product salinomycin. By use of a model substrate, the desired regioselective ring opening was achieved with both Lewis and Brønsted acids with MeOH as the solvent; however, the methyl ether product was favored over THP. Switching to an aprotic solvent (CH₂Cl₂) led to selective formation of the THP, and the use of a 15:1 ratio of CH₂Cl₂:*i*PrOH resulted in significantly faster reaction times with either camphorsulfonic acid or *p*-toluenesulfonic acid (entry 1, Table 30). The reaction was viable for formation of a number of more complex THPs, particularly those with multiple substituents (entries 2 and 3). Formation of the key THP ring for the C1–C17 fragment of salinomycin proceeded cleanly in 92% yield (entry 4). The C1–C11 fragment of (+)-zincophorin was formed from the corresponding oxetane in 83% yield in a similar manner (entry 5). Subsequent protecting-group manipulation allowed access to the desired fragment.⁵¹⁹

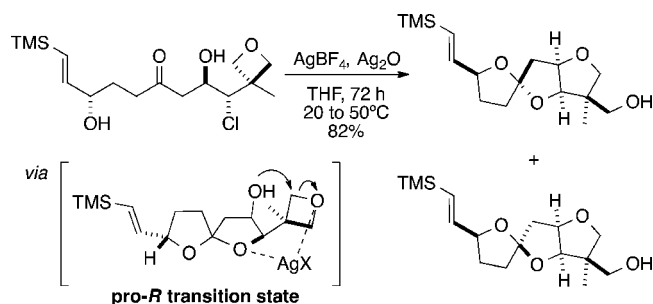
In 2015, Britton and co-workers^{520,521} reported a total synthesis of the marine fungus-derived natural product ascospiroketal, targeted due to potential biological activity. An Ag(I)-promoted oxetane ring opening was used to install the desired tricyclic structure. A brief screen of Ag(I) salts found a combination of AgBF₄ and Ag₂O gave the best yield of 82% with complete diastereoselectivity (Scheme 140). The complete diastereoselectivity was attributed to the ability of the pro-*R*

Table 30. Acid-Catalyzed Tetrahydropyran Formation by Intramolecular Oxetane Ring Opening: Natural Product Fragments^a

Entry ^a	Substrate	Product ^a	Yield (%)
1			94
2 ^b			70
3			80
4			92
5 ^c			83

^aConditions: CSA (1 equiv), CH₂Cl₂/*i*PrOH (15:1), 0 °C to rt, 2–2.5 h. ^bReaction was run for 48 h. ^cReaction was run overnight.

Scheme 140. Oxetane Ring-Opening Step in Total Synthesis of Ascospiroketal

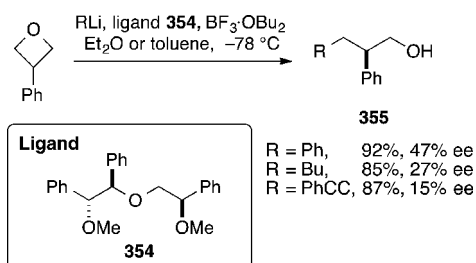


oxetane transition structure to form bidentate chelation between the oxygen of the oxetane ring and the oxygen of the central ring to the Ag(I) salt (Scheme 140). This stabilization is not available to the pro-*S* transition structure.⁵²⁰ The undesired spiroketal was readily epimerized by use of ZnCl₂ and MgO.

8.1.2. Enantioselective Ring Opening. Tomioka and co-workers⁵²² reported the first example of enantioselective desymmetrization of 3-substituted oxetanes, in 1997, by treatment with organolithium reagents. 3-Phenyloxetane was treated with PhLi, stoichiometric BF₃·OEt₂, and an external chiral tridentate ligand **354** at –78 °C to afford chiral alcohol **355** in a yield of 92% and ee of 47% (Scheme 141). *n*-Butyllithium and lithium phenylacetylide also successfully gave the corresponding alcohols in good yields but with low ee values of 27% and 15%, respectively.

Catalytic enantioselective ring opening of 3-substituted oxetanes, by use of 2-mercaptobenzothiazoles **356** as nucleophiles with chiral phosphoric acid catalyst **358**, was reported in 2013 by Sun and co-workers^{8,289} (Scheme 142). Substituted and unsubstituted mercaptobenzothiazoles were

Scheme 141. Enantioselective Ring Opening of 3-Substituted Oxetanes with Stoichiometric Chiral Ligand

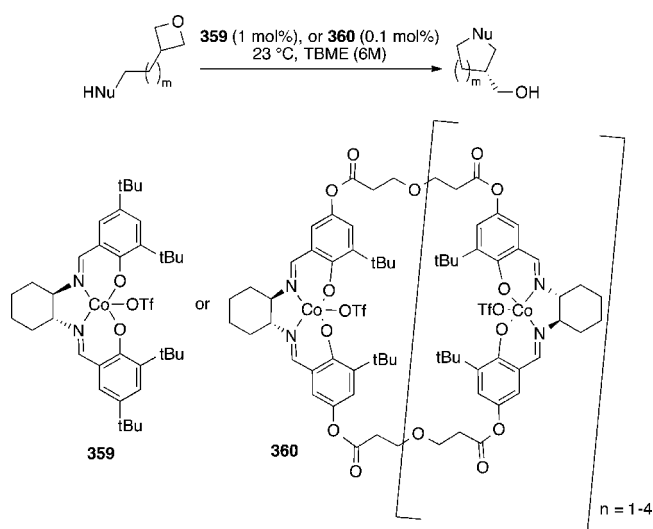


used and could generate tertiary or quaternary chiral centers in the products **357**. Low catalyst loadings of 2.5 mol % were employed, and broadly excellent enantioselectivities of 71–99% ee were obtained.

In 2009, Loy and Jacobsen⁵²³ reported the intramolecular enantioselective ring opening of 3-substituted and 3,3-disubstituted oxetanes catalyzed by Co–salen complex **359** or **360** (Scheme 143). Bimetallic catalyst **360** ($n = 1$) showed enhanced reactivity compared to monomeric catalyst **359**, likely due to cooperative interaction between (salen)Co motifs. Tetrahydrofurans were formed in high yields of 89–93% and excellent ee values (96–99%) when oligomeric catalyst **360** was employed (Table 31). Alkyl and phenyl substitution at the 3-position of oxetane was tolerated under the reaction conditions, affording THFs with quaternary stereocenters. Phenolic substrates were also tolerated; however, a higher catalyst loading was required to attain good enantioselectivity.

Sun and co-workers⁸ have recently reported several examples of intramolecular enantioselective oxetane ring opening. In 2013, the intramolecular ring opening of oxetanes to access chiral 1,2,3,4-tetrahydroisoquinolines was described (Scheme 144).⁵²⁴ Reaction of aldehydes **361** with anilines in the presence of a Hantzsch ester (**364**) and enantiopure chiral phosphoric acid **363** afforded tetrahydroisoquinolines **362** in excellent yields and high enantioselectivities. This reaction was successful with a range of electron-donating and electron-withdrawing aryl aldehydes. With 3,3-disubstituted oxetanes, the product with a quaternary center (**365**) was formed with an

Scheme 143. Co-Catalyzed Intramolecular Ring Opening of 3-Substituted Oxetanes



excellent yield of 94% but moderate enantioselectivity (56% ee).

By a similar principle, Sun and co-workers⁵²⁵ reported the asymmetric three-component aza-Diels–Alder reaction of indoles using a chiral phosphoric acid catalyst and an oxetane ring as the directing group. Oxetane-tethered aldehydes **366** were combined with indoles **367** and arylamines **368** in the presence of catalyst **363** to afford a variety of polycyclic alkaloid-like products **369** (Table 32).

Yang and Sun⁵²⁶ described the enantioselective synthesis of 1,4-dioxanes via intramolecular desymmetrization of oxetanes in 2016. 3,3-Disubstituted oxetanes **370** were treated with a chiral phosphoric acid catalyst **372** of the same type to access chiral 1,4-dioxanes **371** bearing a quaternary stereocenter (Table 33). Alkyl and aryl substituents were tolerated as substituents at the 3-position of the oxetane ring; however, the presence of a trifluoromethyl substituent retarded the reaction, and an increase in temperature was required to obtain conversion. Increased steric hindrance in close proximity to the alcohol functional group did not affect the reaction

Scheme 142. Enantioselective Ring Opening of 3-Substituted Oxetanes with Mercaptobenzothiazoles

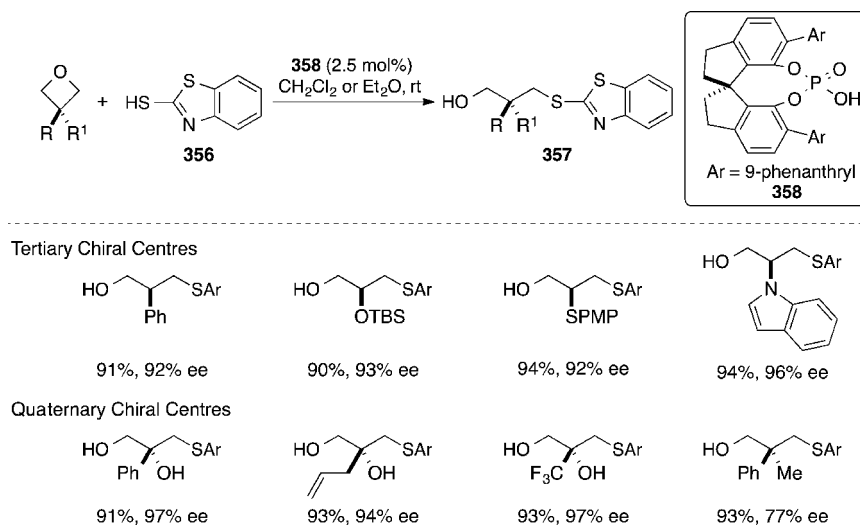
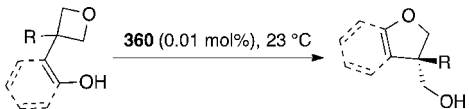


Table 31. Scope of Enantioselective Intramolecular Ring-Opening Reaction of 3-Substituted and 3,3-Disubstituted Oxetanes



Entry	Substrate	Product	Yield (%)	ee (%)
1			93	96
2			88	96
3			98	99
4			89	98
5			94	88
6			98	99

efficiency or enantioselectivity. When the oxygen atom in the side chain was replaced with a carbon atom (373), other oxaheterocycles 374 were synthesized in yields of 89–94% and ee values of 68–91% (Scheme 145). Very recently, the same group reported an enantioselective opening of 3-substituted oxetanes, with chloride as a nucleophile, to generate functionalized γ -chlorohydrins.⁵²⁷ Trimethoxychlorosilane was used as the chloride source in the presence of wet molecular sieves for a controlled release of HCl.

8.1.3. Ring Opening of Oxetan-3-one Derivatives. The last five years has seen reports of the conversion of oxetan-3-one to a variety of heterocycles. Carreira and co-workers⁵²⁸ developed a formation of isoxazoles via a base-mediated rearrangement of 3-(nitromethylene)oxetanes. The use of *i*Pr₂EtN in THF resulted in clean conversion to the isoxazole. This was proposed to occur by deprotonation of the oxetane to form a strained oxetene intermediate, which could undergo ring opening by the nitronate anion followed by dehydration to furnish the isoxazole-4-carboxaldehyde 375. A one-pot cascade reaction was then successfully developed, starting with a Henry reaction between (2-nitroethyl)benzene and oxetan-3-one (Scheme 146). Subsequent mesylation and elimination of the corresponding oxetan-3-ol, and then rearrangement, furnished the 3-benzylisoxazole-4-carboxaldehyde. The scope of the isoxazole-4-carboxaldehyde products at the 3-position was quite varied. The phenyl group could be replaced with electron-rich and electron-deficient aromatic and heteroaromatic groups, aliphatic groups, remote esters, and terminal alkenes, as well as protected alcohols and amines. Aryl substitution at the 3-position was also viable starting from aryl nitromethanes.

Carreira and co-workers⁵²⁹ generated a series of morpholines, thiomorpholines, and piperazines from oxetan-3-one via N,O-, N,S-, and N,N-acetals derived from oxetan-3-one.⁵²⁹ The acetals were treated with TMSCN in the presence of catalytic indium triflate to form saturated nitrogen-containing heterocycles (Table 34). This involved a Strecker reaction with TMSCN to introduce the nitrile and then activation of the oxetane by the Lewis acid to promote intramolecular cyclization, which proceeded in excellent yields and dr.⁵²⁹

Reaction of trifluoroborate nucleophiles with similar N,O-acetals, promoted by BF₃·OEt₂, generated aminooxetanes (see Scheme 79, section 5).³⁵² These products were shown to undergo ring opening to produce substituted morpholine rings. This two-step process could also be performed in one pot; for example, animal 376 were converted to benzomorpholines 377 by employing an excess of BF₃·OEt₂ with substituted alkynyl potassium trifluoroborates (Table 35).

Orr and co-workers⁵³⁰ reported the microwave-mediated condensation of oxetan-3-one with primary amides or thioamides to afford (hydroxymethyl)oxazoles 378 and (hydroxymethyl)thiazoles 379 (Table 36). A range of aromatic substituents as well as tertiary and secondary alkyl groups were

Scheme 144. Asymmetric Ring Opening of 3-Substituted Oxetanes by Use of Aromatic Amines and Chiral Phosphoric Acid Catalyst

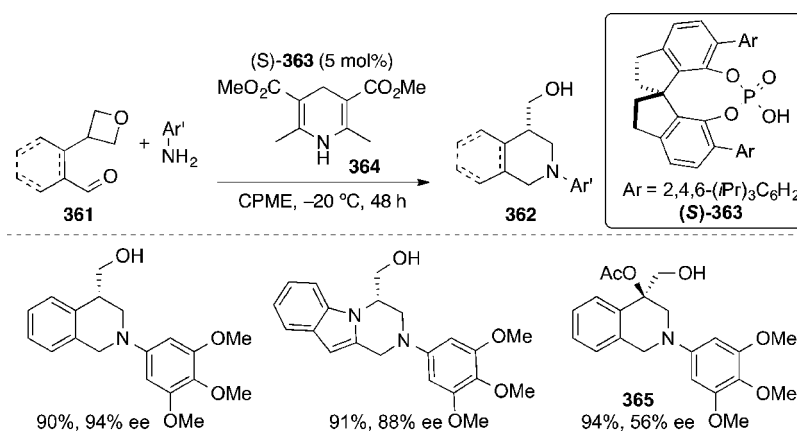
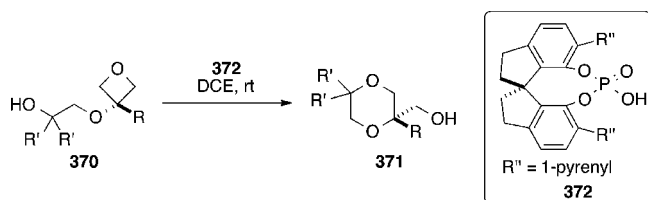


Table 32. Catalytic Asymmetric Multicomponent Aza-Diels–Alder Reaction

Entry	Ar	R	R ¹	R ²	R ³	R ⁴	Yield 369 (%)	ee (%)	dr
1		H	Br	OMe	H	OMe	68	92	80/20
2		H	Br	OMe	H	OMe	93	78	>95/5
3		H	Br	OMe	H	OMe	67	88	>95/5
4		H	H	OMe	OMe	OMe	45	65	>95/5
5		OAc	H	OMe	H	OMe	67	63	>90/10

Table 33. Enantioselective Synthesis of 1,4-Dioxanes via Oxetane Desymmetrization

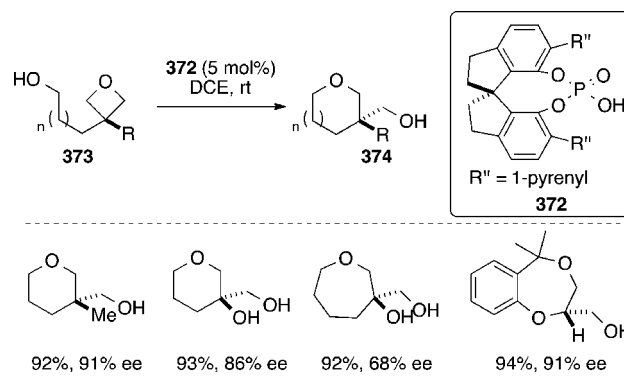


entry	R	R'	cat loading (mol %)	time (h)	yield 371 (%)	ee (%)
1	Me	H	2	12	93	98
2	iPr	H	3	36	95	92
3 ^a	CF ₃	H	10	60	92	98
4	HO(CH ₂) ₄	H	5	12	99	97
5	vinyl	H	5	8	93	96
6	allyl	H	3	12	89	98
7	Ph	H	5	30	98	92
8	Me	Me	5	12	92	94

^aReaction was run at 60 °C.

tolerated under the reaction conditions. The mechanism was proposed to involve first the opening of oxetan-3-one, followed by condensation.

Scheme 145. Enantioselective Synthesis of Alternative Oxaheterocycles



8.2. Ring-Expansion Reactions of Oxetanes

There have been investigations over many years into the ring expansion of oxetanes to generate larger oxygen heterocycles. In particular, oxetanes react with diazo compounds, which can afford mixtures of products resulting from ring expansion and ylide formation with protonation or rearrangement.^{531,532} In the 1960s, Nozaki et al.^{533,534} found that, when treated with a diazo compound in the presence of a chiral copper chelate, 2-

Scheme 146. Cascade Formation of Isoxazoles by Rearrangement of Oxetanes

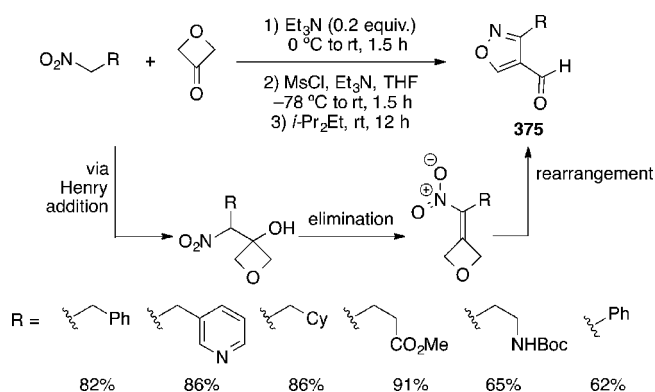


Table 34. Conversion of Oxetan-3-one into Saturated Nitrogen Heterocycles via Formation of Intermediate Spirocycles

entry	X	R	R ¹	yield (%)	dr
1	O	H	<i>i</i> Pr	92	>20:1
2	O	H	Me	80	>20:1
3	O	H	Ph	97	>16:1
4	O	Et	H	80	
5	O	Ph	H	79	
6	NTs	H	Et	67	
7	S	H	H	41	
8	S	Bn	Bn	89	2:1

Table 35. One-Pot Ring Expansion of Spirocyclic Oxetanes

entry	R	yield 377 (%)
1	<i>p</i> -Cl-C ₆ H ₄	85
2	Ph	69
3	H	81
4	TMS	75
5	Cy	64
6	(CH ₂) ₃ Cl	82

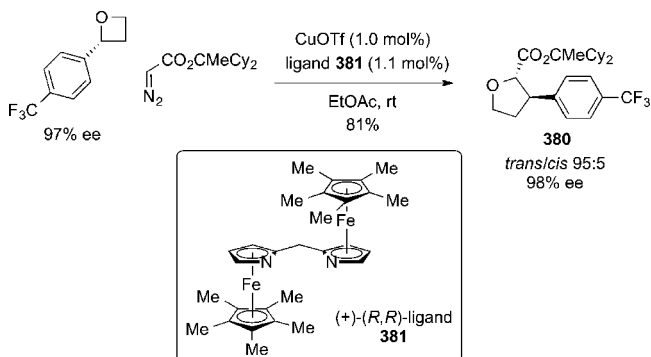
phenyloxetane would undergo ring expansion to give a mixture of *cis/trans* THF derivatives. In 1994, Ito and Katsuki⁵³⁵ reported asymmetric ring expansion of oxetanes to THFs. Aryl oxetanes were treated with *t*-butyl diazoacetate in the presence of a chiral bipyridyl Cu complex to afford the THFs in yields of 31–40%. Interestingly, whereas racemic 2-(phenyl)oxetane afforded a 1:1 mixture of *trans*- and *cis*-*t*-butyltetrahydrofuran-2-carboxylates, (*R*)-2-phenyloxetane preferentially afforded the *trans* isomer while reaction with (*S*)-2-phenyloxetane afforded the *cis* isomer preferentially.^{536–539}

Table 36. Microwave-Mediated Synthesis of Oxazoles and Thiazoles

entry	R	yield (%)	
		378, X = O	379, X = S
1	Ph	36	64
2	cyclohexyl	17	63
3	<i>t</i> Bu	14	40
4	3-F ₃ C-Ph	24	36
5	4-MeO-Ph	15	50

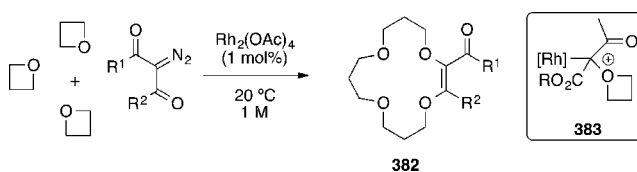
In 2001, Lo and Fu¹¹¹ published conditions for asymmetric ring expansion of oxetanes to THFs using diazo esters in the presence of a Cu(I)/bis(azaferrocene) catalyst, giving excellent diastereo- and enantiocontrol over the newly generated stereocenter (Scheme 147). Both the *cis* and *trans* diastereoisomers could be synthesized simply by swapping the enantiomer of the bis(azaferrocene) ligand [(*R,R*)-**381** gave *trans*-**380** in 98% ee, while (*S,S*)-**381** gave *cis*-**380** in 95% ee].

Scheme 147. Asymmetric Ring Expansion of 2-Aryloxetanes by Use of Cu(I)/Bis(azaferrocene) Catalyst



isomers could be synthesized simply by swapping the enantiomer of the bis(azaferrocene) ligand [(*R,R*)-**381** gave *trans*-**380** in 98% ee, while (*S,S*)-**381** gave *cis*-**380** in 95% ee].

Lacour and co-workers⁵⁴⁰ described the formation of a number of interesting functionalized 15-membered macrocycles via Rh-catalyzed condensation of a single α -diazo- β -keto ester with three oxetane molecules (Scheme 148). The reaction

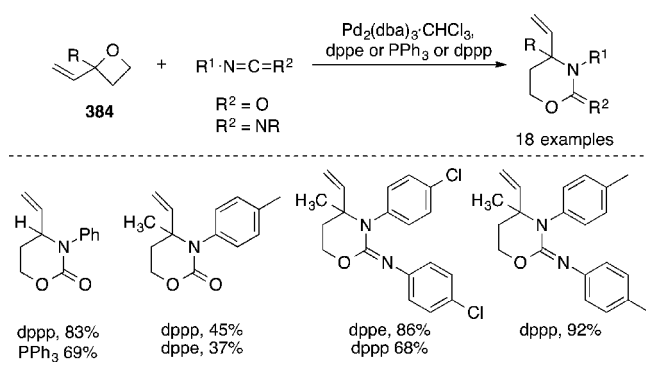
Scheme 148. Macrocyclization of Oxetanes with α -Diazo- β -keto Esters

proceeded under mild conditions at 20 °C, with catalyst loading of just 1 mol % Rh₂(OAc)₄ and oxetane as the solvent, forming the macrocycle in yields up to 84%. Different ester substituents were well-tolerated (R¹ = Me, Et, *t*Bu, allyl; R² = Me), as were different ketone substituents (R² = Et, Pr, Ph, *i*Pr; R¹ = Et), giving excellent yields (55–84%) of the macrocyclic products (**382**). Substituted oxetanes such as 3,3'-dimethyl- and 3,3'-

diethyloxetanes could be used to form the corresponding substituted macrocycles in 65% and 51% yield, respectively. The reaction was proposed to proceed via initial addition of oxetane oxygen to the Rh-carbenoid, generated from the α -diazo- β -keto ester, to form an oxetane ylide (**383**, Scheme 148). This oxetane unit then propagates the reaction through the electrophilic carbon at the oxetane 2-position, with two further oxetane units adding before trapping with the keto carbonyl becomes favored to furnish the macrocycle.

In 1999, Larksarp and Alper⁵⁴¹ reported the cycloaddition of vinyloxetanes with heterocumulenes as a method to access 1,3-oxazines. 2-Vinyloxetane **384** was reacted with an isocyanate or a carbodiimide in the presence of palladium(0) catalyst and a phosphine ligand (Scheme 149). Alper proposed that the

Scheme 149. Synthesis of 1,3-Oxazines via Cycloaddition of Vinyloxetanes with Isocyanates or Carbodiimides



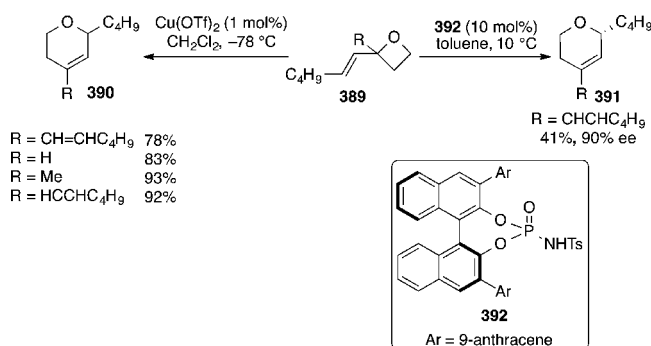
reaction proceeded via a π -allyl palladium intermediate, formed by addition of the vinyloxetane to the palladium complex, followed by reaction with the isocyanate or carbodiimide. The reaction yields were lower when isocyanates were used, possibly due to a faster rate of dimerization of the isocyanate than the rate of dimerization of carbodiimide, relative to the rate of cyclization. Bicyclic oxazines could be accessed from the cycloaddition of bicyclic vinyl oxetanes with isocyanates or carbodiimides but required a pressurized reactor.

Njardarson and co-workers⁵⁴² have reported the ring expansion of vinyl-substituted oxetanes **385** in the presence of diazo compounds **386** and catalytic $\text{Cu}(\text{tfacac})_2$. Both the [2,3] ring-expansion product **387** and the [1,2] insertion product **388** were observed in good combined yields, with the product ratio dependent on which diazo substrate was used (Scheme 150). The formation of an oxonium ylide intermediate was crucial for formation of both products.

In subsequent studies, Njardarson and co-workers^{543–546} reported the ring expansion of vinyloxetanes **389** to 3,6-dihydro-2H-pyrans **390** in the presence of 1 mol % $\text{Cu}(\text{OTf})_2$ or 10 mol % triflic acid. Njardarson proposed that $\text{Cu}(\text{OTf})_2$ coordinated to the oxetane oxygen atom, prompting ring

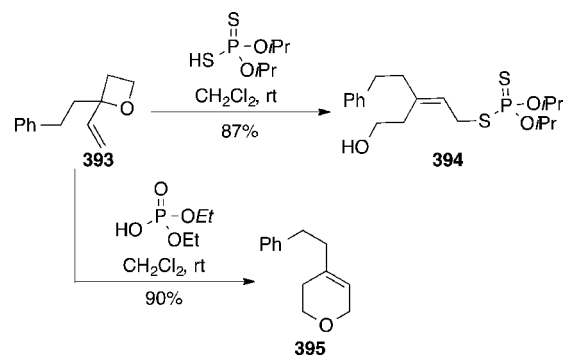
opening, and the resulting allylic cation was then captured by the oxygen atom in a 6-endo-trig cyclization. When a chiral phosphoric acid catalyst **392** was employed, a chiral dihydropyran **391** was synthesized with 90% ee but in reduced yield (Scheme 151).

Scheme 151. Ring Expansion of Vinyloxetanes to 3,6-Dihydro-2H-pyrans



Treating vinyl oxetane **393** with diisopropyl dithiophosphate resulted in nucleophilic ring opening to form **394** with Z-selectivity, while a less nucleophilic reagent, diethyl phosphoric acid, resulted in ring expansion to form the six-membered ring **395** (Scheme 152).⁵⁴⁷ Sterics played an important role in this

Scheme 152. Z-Selective Ring Opening and Ring Expansion of Vinyloxetanes



reaction, with substituents at the olefin terminus inhibiting the nucleophilic ring opening and enhancing the acid-catalyzed pathway to form the ring-expanded product. No reaction was observed when alkynyloxetanes were exposed to the reaction conditions.

Alkynyloxetanes have been used in metal-catalyzed oxidative cyclization reactions. Gagosz and co-workers⁵⁴⁸ showed that when alkynyloxetane **396** was treated with a Cu(I) catalyst in the presence of an oxidant, ring expansion occurred to form both dihydrofuran **397** and lactone **398** (Table 37). Careful

Scheme 150. Ring Expansion of Vinyloxetanes to Medium-Sized Oxacycles

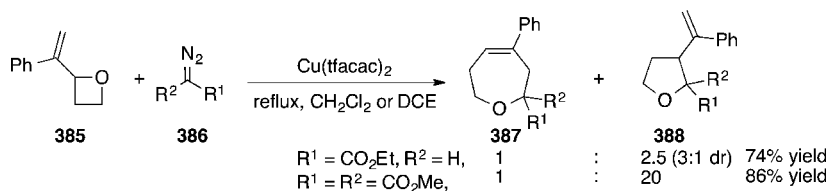


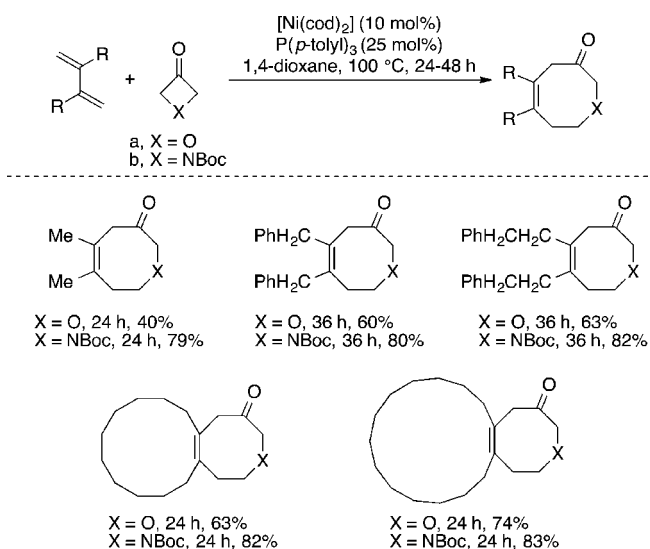
Table 37. Cu(I)-Catalyzed Ring Opening of Alkynyloxetane 396 to Lactone and Dihydrofuran

entry	R	ratio (397:398)	yield (%)
1	H	1.9:1	84
2	3-Br	1:0	85
3	4-OMe	0:1	74

tuning of the substituents on the pyridine *N*-oxide promoted selective formation of either product. The use of a more electron-deficient 3-bromopyridine *N*-oxide favored dihydrofuran formation, being a better leaving group for 5-exo-trig cyclization (entry 2). The more electron-rich 4-methoxypyridine *N*-oxide favored lactone formation (entry 3). This ring expansion was successful with a variety of alkynyloxetanes, including both aryl and alkyl substitution at the 2-position as well as methyl and phenyl groups at the 3-position of the oxetane ring.

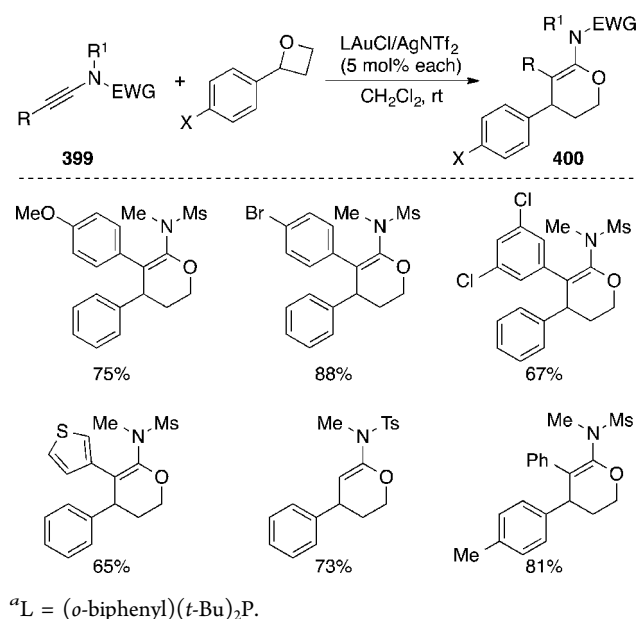
Formation of eight-membered heterocycles via Ni-catalyzed reaction of oxetan-3-ones with 1,3-dienes was reported by Louie and co-workers in 2013.⁵⁴⁹ Oxetan-3-one was treated with 1,3-dienes in the presence of Ni(cod)₂ and P(*p*-tolyl)₃ to afford medium-sized rings (Scheme 153). The methodology

Scheme 153. Nickel-Catalyzed Cycloaddition of 1,3-Dienes with Oxetan-3-ones and Azetidin-3-ones



was also successful in reaction of azetidin-3-ones with 1,3-dienes to form eight-membered N-heterocycles. Dienes with benzyl and homobenzyl substituents were well-tolerated under the reaction conditions, as were macrocyclic dienes.

In 2014, Liu and co-workers⁵⁵⁰ reported the [4 + 2] cycloaddition of ynamides 399 with 2-aryloxetanes in the presence of an Ag/Au complex to afford six-membered 6-amino-3,4-dihydro-2*H*-pyrans 400 (Scheme 154). Excellent

Scheme 154. Au- and Ag-Catalyzed [4 + 2] Cycloaddition of Ynamides with Oxetanes⁵⁵⁰

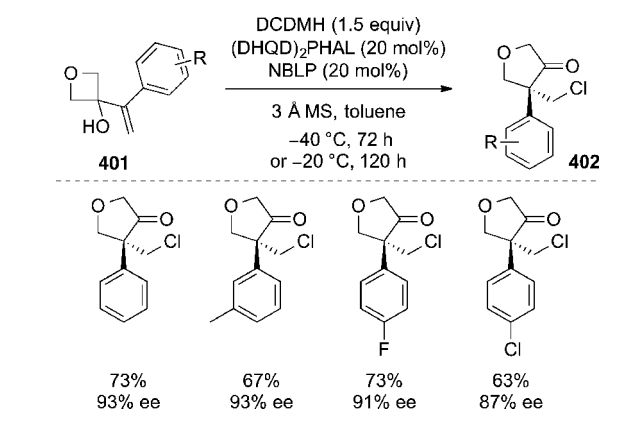
regioselectivity was observed due to the electrophilicity of the Au- π -ynamides, which react with the oxetane nucleophiles.⁵⁵⁰ A variety of aryloxetanes and arylynamides were successfully employed in the cycloaddition reaction.

In 2014, Yin and You⁵⁵¹ reported an enantioselective chlorination/ring-expansion cascade of cyclobutanols, accessing chiral 2-alkyl-2-aryl cycloalkanones with excellent ee values by use of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), (DHQD)₂PHAL as a catalyst, and *N*-Boc-L-phenylglycine (NBLP) as a ligand. Yin and You also showed that oxetanols 401 were also compatible with this methodology, accessing enantioenriched dihydrofuran-3(2*H*)-ones 402 in good yields and excellent enantioselectivities (Scheme 155). Substrates bearing halogenated aryl rings showed decreased reactivity compared with more electron-donating substituted aromatics.

9. CONCLUSION

This review aims to provide an overview of the extensive recent works involving oxetanes in synthesis and medicinal chemistry and to highlight the continuing challenges. This interest has been facilitated, and partly driven, by the emergence of oxetanes for applications in medicinal chemistry. Oxetanes

Scheme 155. Asymmetric Chlorination/Ring Expansion of Oxetanols



present important opportunities to tune physicochemical properties and increase the stability of a molecule, as well as providing intellectual property novelty within a compact motif. Thanks to the increasing commercial availability of oxetane-containing building blocks, along with improved methods for synthesis, oxetanes are likely to be increasingly used in medicinal chemistry programs. However, to date it remains challenging to target specific oxetane derivatives and to position substituents and functional groups around the ring at prescribed locations, especially for chiral nonracemic oxetanes. These synthetic challenges continue to limit the full exploitation of this ring system.

Williamson etherification remains the most common approach for oxetane synthesis, with cyclization from 1,4-functionalized precursors providing a reliable strategy. However, the functionality that can be installed on the ring by this approach is sometimes limited, and the synthesis of (enantioenriched) cyclization precursors presents its own challenge. An epoxide-opening and ring-closure sequence with sulfoxonium ylides can take advantage of chiral epoxide precursors to generate enantioenriched oxetanes. Sugars are also valuable precursors to oxetanes but can require lengthy sequences to unveil the heterocycle, with the stereochemical outcome determined by the starting sugar. Alternative C–C bond-forming cyclization methods are emerging that offer the potential to access new and valuable derivatives in relatively short sequences and to provide oxetanes bearing more varied functional groups. Increasing the options for cyclization through alternative strategies that are applicable to a wide array of substrates would be a valuable addition to the current methodology.

The Paternò–Büchi reaction continues to present a conceptually attractive approach to bring together readily available reactive partners to form oxetane rings. The substituent requirements for photochemical activation have perhaps limited the application of this methodology in medicinal chemistry to date. However, this reaction presents considerable scope for further development, likely to exploit technological developments and engineering solutions to facilitate the photochemistry. At the same time, small-molecule-catalyzed formal [2+2] methods offer a compelling alternative, especially where chiral catalysts can be exploited to generate enantioenriched products. The scope of recent developments has been limited to highly electrophilic ketones, such as trifluoromethyl ketones and closely related derivatives,

but offers considerable potential upon extension to wider classes of reagents.

One approach to access oxetane derivatives likely to see extensive development in coming years is the functionalization of intact oxetane rings, taking advantage of preformed oxetane derivatives as building blocks and also allowing divergent synthesis. To date this is not well-developed, with few bond-forming reactions available, although S_N2 reactions have been demonstrated by use of good nucleophiles on oxetanes bearing leaving groups. There is considerable potential for the application of more (stereocontrolled) methods to attach oxetane derivatives to target structures. Carreira's oxetanone has been widely embraced by synthetic and medicinal chemistry communities, with simple reactions such as reductive amination being very popular, as well as having applications in more complex ketone chemistry and multicomponent reactions. Simple cross-couplings of other oxetane units, such as halide and boronic acid derivatives, are not well-developed, but some important examples of cross-coupling at the oxetane 3-position include Negishi cross-couplings and reductive coupling of an oxetane halide with an aryl halide component. Furthermore, only monosubstituted oxetane derivatives have been demonstrated in these cross-coupling reactions.

Attempts to deprotonate oxetanes and form oxetanyl anions have been limited to date, presumably due to the reactive carbenoid nature of the deprotonated intermediate, and stabilizing groups have been required in these limited examples. Complementary radical methods have emerged recently by use of oxetane itself. While these approaches have often used a large excess of oxetane reagent, there is considerable potential for method development and application to a wider range of oxetane structures.

2-*exo*-Methyleneoxetanes present interesting precursors for further reaction and another strategy to introduce groups onto the oxetane ring, through activation of the olefin and addition of nucleophiles. Subtle reactivity differences between nucleophiles can lead to different outcomes, potentially with ring opening as a competing reaction pathway. Enantioselective syntheses of alkylideneoxetanes have recently emerged through formal [2+2] methods from allenes and ketones, with the reaction scope to date limited to activated ketones.

The wide variety and number of oxetane compounds appearing in the medicinal chemistry and patent literature highlights the breadth of occurrence and the advantages perceived from incorporation of this motif. Most commonly, 3-substituted oxetane derivatives are observed in these potential medicinal compounds, being derived from simple building blocks; 3-amino and 3-mono- or 3,3-disubstituted oxetane derivatives (alkyl–alkyl or aryl–alkyl) are most prevalent. Occasionally 2-substituted derivatives have been made, though there are fewer available building blocks, and these derivatives can introduce chirality and hence complexity. Nucleoside analogues, containing fused and spirocyclic oxetanes, have also shown interesting activity and profiles. However, it is apparent that the oxetane structures are most commonly present as pendant motifs. Further growth in the numbers of simple, small oxetane building blocks that are readily available and can be readily incorporated through simple linkages would certainly be welcomed by medicinal chemists. Such small motifs, without additional functionality to utilize in synthesis, are not trivial to prepare in large quantities through current methods.

There continue to be important questions on the stability of the oxetane motif in biological settings, which is crucial

information in the context of medicinal chemistry. In many cases, high stability has been observed; however, this is likely to be dependent on specific cases and surrounding molecular structure and functional groups, and more studies are required. For acid stability and stability to nucleophiles, a greater understanding of structure–stability relationships, including the effect of different substituents and substitution patterns on the oxetane ring, as well as the effects of other groups in the molecule that may have stabilizing or destabilizing effects, would be very valuable. Such precompetitive information could facilitate the more targeted installation of appropriate oxetane derivatives, and the design of new derivatives that may offer improved properties. On the other hand, the small ring, being unusual and not well recognized by the body, is unlikely to present specific metabolic liabilities. Indeed, the beneficial increase in polarity upon incorporation of an oxetane provides a general reduction of lipophilicity, often associated with an increase in metabolic stability.

Oxetanes present considerable potential as isosteres. To date, the majority of studies from Carreira concerned the replacement of *gem*-dimethyl groups or carbonyl groups; replacement of the carbonyl of thalidomide with an oxetane to prevent racemization provides an elegant example. Peptide mimics have recently appeared in the literature, in the form of aminooxetanes, which show stability to enzymatic cleavage. Other specific isosteres can be envisaged that could offer attractive properties, for example, specific ester or ketone derivatives, which could be examined through direct pairwise comparison. Furthermore, novel substituted oxetane derivatives can readily provide access to new chemical space. More data will inevitably emerge as usage in medicinal chemistry continues and as new attractive building blocks and methods facilitate further use, contributing to the body of knowledge on the appropriateness of the oxetane ring in different circumstances.

Powerful examples of the use of oxetanes as intermediates in the synthesis of complex molecules and natural products have been reported in the last five years. Exploitation of oxetanes as reactive intermediates in this way provides a valuable disconnection that is likely to be exploited more widely. However, there remains space for fundamental studies on methods for the ring opening of oxetanes. As a synthon, oxetane is not yet close to being afforded a similar profile in ring-opening reactions as the analogous epoxide, but it offers similar potential. The opening of enantioenriched oxetanes provides valuable chiral building blocks, but nucleophilic opening remains underexplored.

On the other hand, enantioselective opening of prochiral oxetanes has taken great strides, through the desymmetrization of prochiral 3-substituted and 3,3-disubstituted oxetanes. Very high ee values have been obtained, and there are clear opportunities for further development to extend the range of nucleophiles and substrates, as well as to applying these strategies to additional transformations that generate complexity. Furthermore, the development of enantioselective kinetic resolutions of racemic chiral derivatives would present alternative approaches to enantioenriched building blocks.

It is feasible that improved understanding of oxetane ring opening could lead to applications in medicinal chemistry, for example, as covalent irreversible inhibitors with an oxetane “warhead”. Alternatively, as a labeling tool in chemical biology, subtle changes in oxetane structure may be able to promote selective reactions, for example, with protein side chains.

Throughout this review, we have considered applications toward biologically active compounds and medicinal chemistry. Undoubtedly, improved access to oxetane derivatives and understanding of ring opening will have impact in other fields, such as polymer and materials science, through bespoke oxetane monomers. The development of shorter and stereo-controlled routes to oxetane derivatives, bearing a greater variety of functionality around the ring, as well as novel readily accessible oxetane building blocks, are required to develop the applicability of the four-membered ring in these and other fields. Numerous challenges remain in synthesis, reactivity, and understanding of oxetane properties, but we expect further exciting developments in coming years.

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Notes

The authors declare no competing financial interest.

Biographies

James A. Bull is a University Research Fellow in the Department of Chemistry at Imperial College London. He obtained his M.Sci. degree from University of Cambridge, then spent a year at GlaxoSmithKline. He returned to University of Cambridge to obtain his Ph.D. in organic chemistry under the supervision of Professor Steven V. Ley (2006). He then spent two years undertaking postdoctoral research with Professor André B. Charette at Université de Montréal. In 2009 he joined Imperial College London as a Ramsay Memorial Research Fellow. In 2011 he was awarded an EPSRC Career Acceleration Fellowship on strategies to access novel heterocycles of interest in drug discovery. In 2016 he was awarded a University Research Fellowship from The Royal Society.

Rosemary A. Croft received her M.Sci. degree in 2014 from the University of Bristol, having completed her final-year research project working on carbonylative ring-expansion methodology. She was awarded an Imperial College Scholarship and moved to Imperial College London in October 2014 to commence a Ph.D. under the supervision of Dr James Bull. Her project is focused on the synthesis and derivatization of novel oxetane scaffolds of particular interest to the pharmaceutical industry.

Owen A. Davis received his first-class honours M.Sci. degree in chemistry from Imperial College London in 2012. He then continued his Ph.D. studies at Imperial College, where he was awarded an EPSRC DTG scholarship with Dr. James Bull. His Ph.D. studies focused on the synthesis and functionalization of highly substituted oxetanes and other small-ring heterocycles. In 2016, he joined the Institute of Cancer Research in a postdoctoral position in the group of Dr. Swen Hoelder.

Robert Doran, from County Wicklow, Ireland, graduated from University College Dublin (UCD) in 2010 with a first-class honours B.Sc. degree in chemistry. He was awarded an Embark postgraduate scholarship from the Irish Research Council in 2010 to undertake Ph.D. studies with Professor Patrick J. Guiry at UCD on the total synthesis of lactone-containing natural products and catalytic asymmetric synthesis of α -aryl ketones. He received his Ph.D. in 2014, after which he moved to the group of Dr James A. Bull at Imperial College London for postdoctoral studies on the synthesis and functionalization of oxetanes and sulfoximines.

Kate F. Morgan graduated from St. Andrews University in 2010 with a first-class M.Chem. degree in chemistry with an industrial placement.

Her final-year project was based on synthesis of glucosinolates, under the supervision of Dr. Nigel Botting. In 2011 she moved to London to undertake Ph.D. studies, sponsored by AstraZeneca, in organic chemistry under the supervision of Dr. James Bull. She was awarded a Ph.D. in 2015 for her work on the synthesis and functionalisation of oxetanes. In 2015 she moved to the Royal Society as a grants scheme manager.

ACKNOWLEDGMENTS

We are grateful for funding to EPSRC (CAF, EP/J001538/1; Impact Acceleration Account, EP/KS03733/1), The Royal Society (University Research Fellowship to J.A.B.), and Imperial College London.

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