Oxetanes: Recent Advances in Synthesis, Reactivity and Medicinal Chemistry

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TITLE RUNNING HEAD: Oxetanes: synthesis and reactivity

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ABSTRACT: The 4-membered oxetane ring has been increasingly exploited for its contrasting behaviors, i.e. influence on physicochemical properties as a stable motif in medicinal chemistry, and 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 5 years up to the end of 2015. These methods are clustered by strategy for preparation of the ring (Sections 3 and 4), and further derivatisation of preformed oxetane-containing building blocks (Sections 5-7). 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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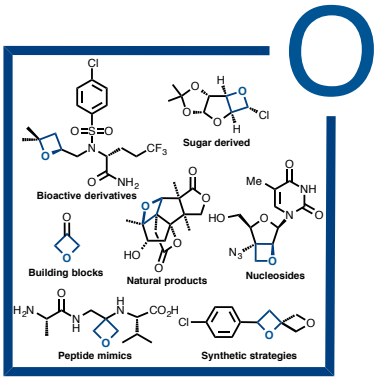

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1. INTRODUCTION

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 replacements groups for *gem*-dimethyl and carbonyl groups with improved physicochemical properties. The small, polar nature of the heterocycle has led to its incorporation as a pendant motif to improve 'drug-like' properties, in particular solubility, and also to offer intellectual property (IP) advantages. As a result, these units have been widely adopted in medicinal chemistry programs in recent years. These recent studies have relied both on established synthetic methods and the 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 comment 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 the structural features of the oxetane ring and the 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 the C–O or the C–C bond (Section 3), and (formal) [2+2] cycloadditions forming both C–C and C–O bonds (Section 4). Selected transformations of the 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 which 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 as well the patent literature. Section 6 continues the functionalisation of intact oxetane derivatives through metalation. Section 7 focuses specifically on 2-*exo*-methyleneoxetanes, their synthesis and functionalisation, both in ring opening reactions and methods that maintain the ring structure leading to functionalized oxetane derivatives. The final part reviews ring opening and ring expansion reactions of oxetanes, where the 4-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,[1,2] Abe,[3] D'Auria,[4] De Kimpe,[5] Mahal,[6] Howell,[7] Sun[8] and others.[9,10,11] The extensive use of oxetane motifs in other fields including polymer chemistry as a monomer,[12,13,14,15,16,17,18] and a cross linker[19,20] and for example in catalytic reaction with CO_2 to generate cyclic carbonates,[21,22,23,24,25,26,27] is outside the scope of this review and will not be considered.[28,29,30]

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

Physical Properties of Oxetanes Oxetane itself is a 4-membered ring containing an oxygen atom with an inherent ring strain of 106 kJ mol^{-1} (epoxides 112 kJ mol^{-1}; THFs 25 kJ mol^{-1}).[31,32] The ring adopts an essentially planar structure with a puckering angle of only 8.7 º at 140 K (10.7 º 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 (c.f. 30 º puckering for cyclobutane).[35]

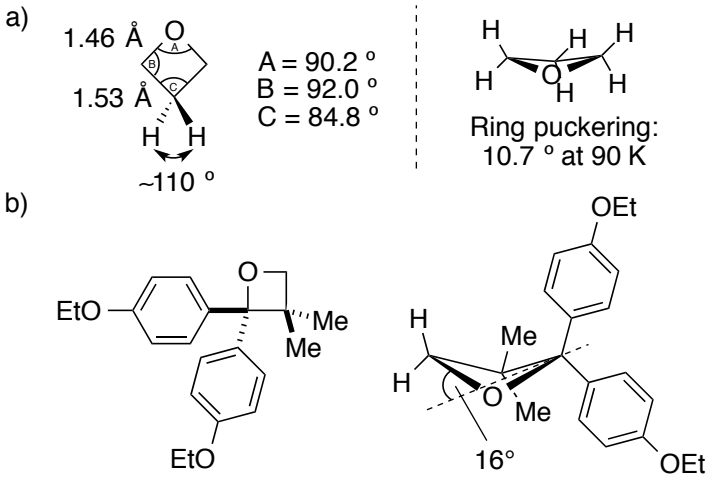


Figure 1. Structural Properties of Oxetane and Puckering of the Substituted Oxetane Ring in EDO.

The introduction of substituents onto the oxetane ring can increase the unfavorable eclipsing interactions, resulting in a more puckered conformation. For example, X-ray crystallography investigations showed that the puckering angle of the biodegradable insecticide EDO was 16 º (Figure 1b).[36] The carbon-oxygen bond length in unsubstituted oxetane is 1.46 Å whilst the carbon-carbon bond length is 1.53 Å, which results in bond angles of 90.2 º (C–O–C), 92.0 º (C–C–O) and 84.8 º (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 the hybridisation in small rings, there is increased p-character to the bonds in the ring and *exo*-cyclic substituents have increased bond angles. The increasing s-character of the oxygen lone pairs as the ring size of the cyclic ethers decreases does not have a significant influence on the H-bonding ability until 3-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.

Oxetanes in Natural Products The oxetane ring appears in relatively few natural product structures, but when present, there is important biological activity which is often reliant on the ring (Figure 2). Perhaps the most well known is paclitaxel, 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 stabilising 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 is 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, the cyclization occurs via an enzyme mediated epoxy ester/oxetane ester rearrangement mechanism. Three separate mechanisms for this transformation have been proposed by a neutral-concerted pathway (Figure 3a),[50] an acid catalyzed route (Figure 3b),[51] or a dissociative pathway (Figure 3c).[52] Computation studies by Tantillo and Willenbring were unable to find evidence to conclusively distinguish among the three mechanisms.[53]

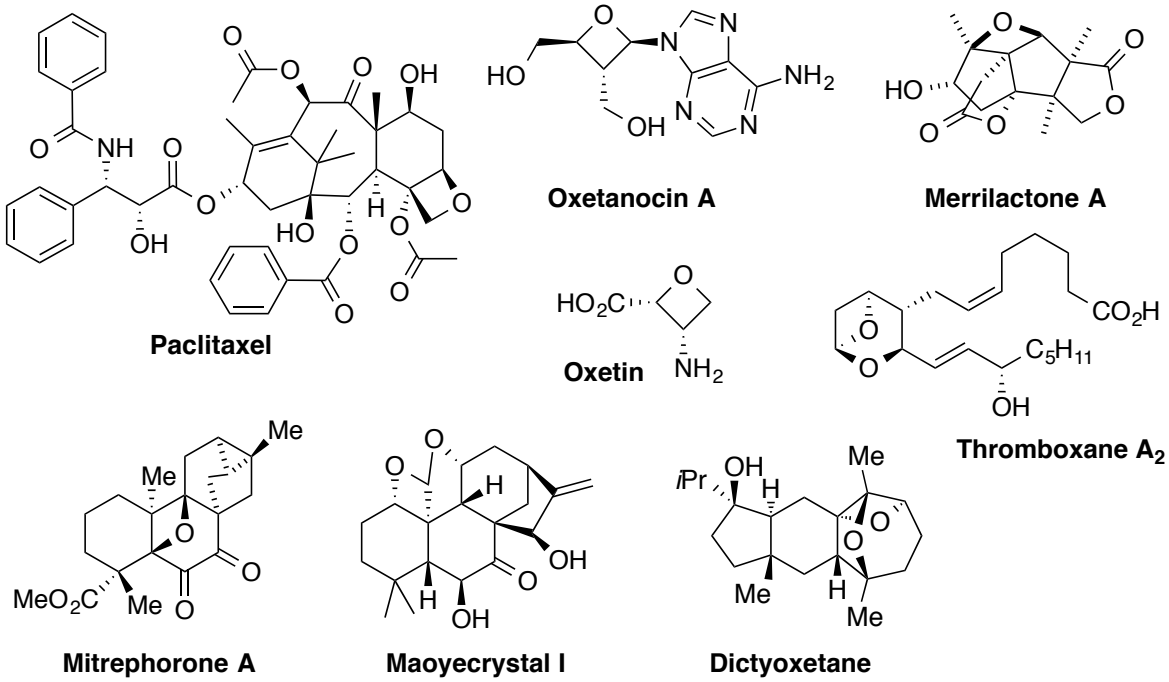


Figure 2. Oxetane-Containing Natural Products.

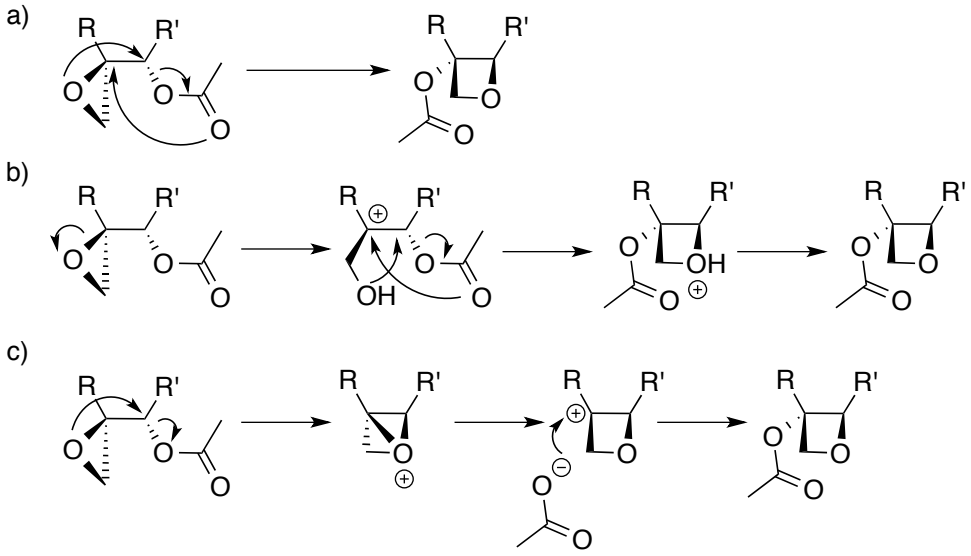


Figure 3. Three Proposed Pathways for the Biosynthesis of the Oxetane Ring of Taxol.

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 the HIV virus.[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 A_2 has prothrombotic properties, and the oxetane is very short lived in the body due to the acetal structure.[58] Merrilactone 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 algae *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 bacteria *Bradyrhizobium japonicum*, has two pendent oxetane rings.[62]

Oxetanes as replacement groups. In 2006, Carreira, Rogers-Evans (Hofmann La Roche), and co-workers 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).[63,64,65] *gem*-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.

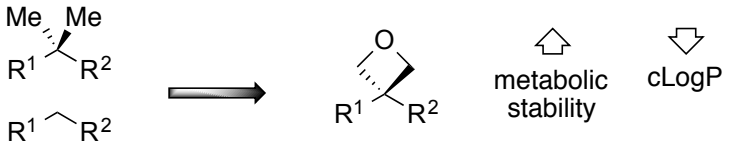
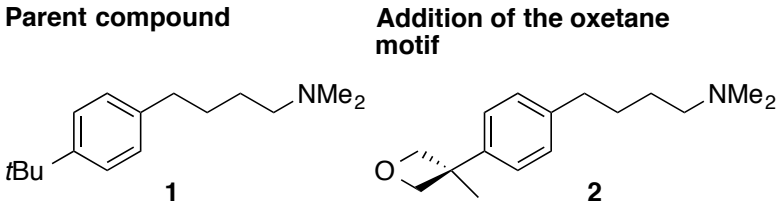


Figure 4. 3,3-Disubstituted Oxetanes as Replacement Group for *gem*-Dimethyl.

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 became considerably more polar and more soluble upon introduction of the oxetane. In addition, the metabolic stability was improved as indicated by reduced intrinsic clearance rates (CL_{int}; $min^{-1}mg^{-1}\mu L$) measured in human (h) and mouse (m) liver microsomes. Oxetane-containing compound **2** was also shown to be have reduced hERG inhibition (hERG IC_{50} 35 μM for **2**, vs 7.5 μM for **1**) due to the reduction in lipophilicity.[63,65]



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 an Oxetane.

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 alpha to the amine but interestingly a decrease of 0.3 pK_a units was still observed when the oxetane was at a position delta 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 a pH range of 1-10 over 2 h at 37 ºC.[63]

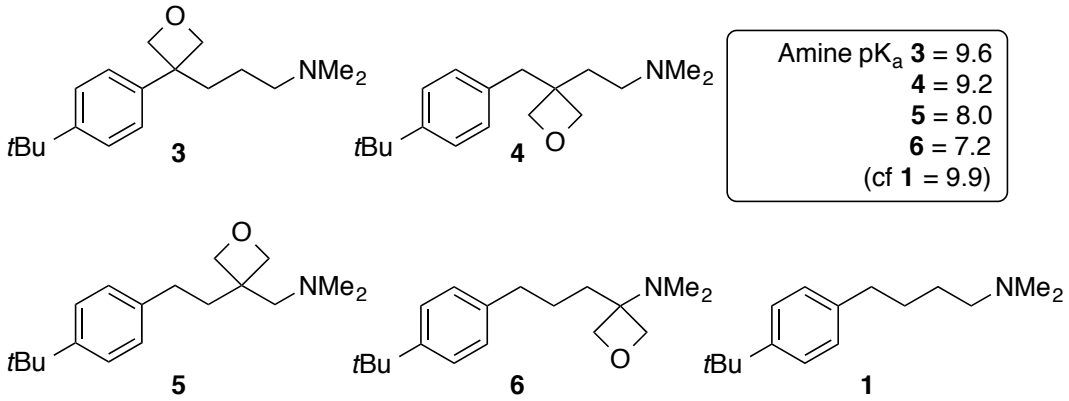


Figure 6. Effect of the Oxetane Motif on Amine Basicity.

In a subsequent series of papers, Carreira, Rogers-Evans and Müller investigated various properties of oxetanes as replacement groups resulting in a number of advantageous changes.[1,2,65,69] 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 carbonyl compounds (aldehydes, ketones and esters) are vulnerable to enzymatic attack and α-deprotonation/epimerization of stereogenic centres, the oxetane derivatives are stable to both of these concerns. The main difference between an oxetane and carbonyl motif is the length of the group. Fujishima employed this strategy and the increased size of the oxetane to improve the binding affinity of 1,25-dihydroxyvitamin D_3 analogues for the bovine thymus vitamin D receptor.[70,71]

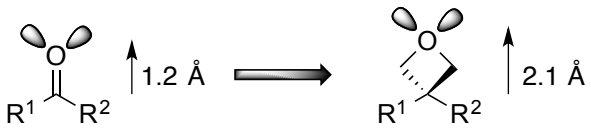
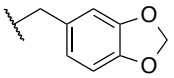
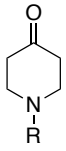
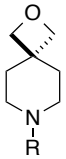
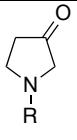
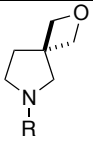
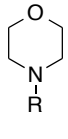


Figure 7. Comparison Between the Carbonyl and Oxetane Functional Groups, Representing Similar Arrangement of Lone Pairs and Change in Size.

Carreira studied the physiochemical and biological properties of various matched pairs of oxetane-containing spirocyclic compounds compared with the corresponding carbonyl containing heterocycle derivatives (Table 1).[69] In both the pyrrolidine and piperidine derivatives, **7**/**8** and **9**/**10**, the incorporation of the oxetane ring decreased the solubility. However, opposing effects on lipophilicity were observed. On the other hand, the metabolic stability was considerably improved for the oxetane spirocycles **8** and **10** compared to **7** and **9** in terms of the intrinsic clearance rate.

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

R = 	 **7**	 **8**	 **9**	 **10**	 **11**	 **12**
Solubility ($\mu g\ mL^{-1}$)	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} ($min^{-1}\ mg^{-1}\ \mu L$)[a]	120	6	100	2	9	3
mCL_{int} ($min^{-1}\ mg^{-1}\ \mu L$)[a]	88	22	580	27	8	7
pK_a	7.5	8.3	6.1	8.1	7.0	8.0

[a] Intrinsic clearance rates measured in human (h) and mouse (m) liver microsomes

Morpholine rings are often incorporated into drug scaffolds to improve aqueous solubility, but 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 whilst remaining metabolically stable towards oxidation (Table 1). Over recent years, Carreira and co-workers have also reported spirocyclic structures as structural analogues of heterocycles including piperazine,[72,] as well as piperidine and thiomorpholine analogues,[73] and other spirocyclic small ring heterocyclic systems targeting drug discovery.[74,75,76,77,78]

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

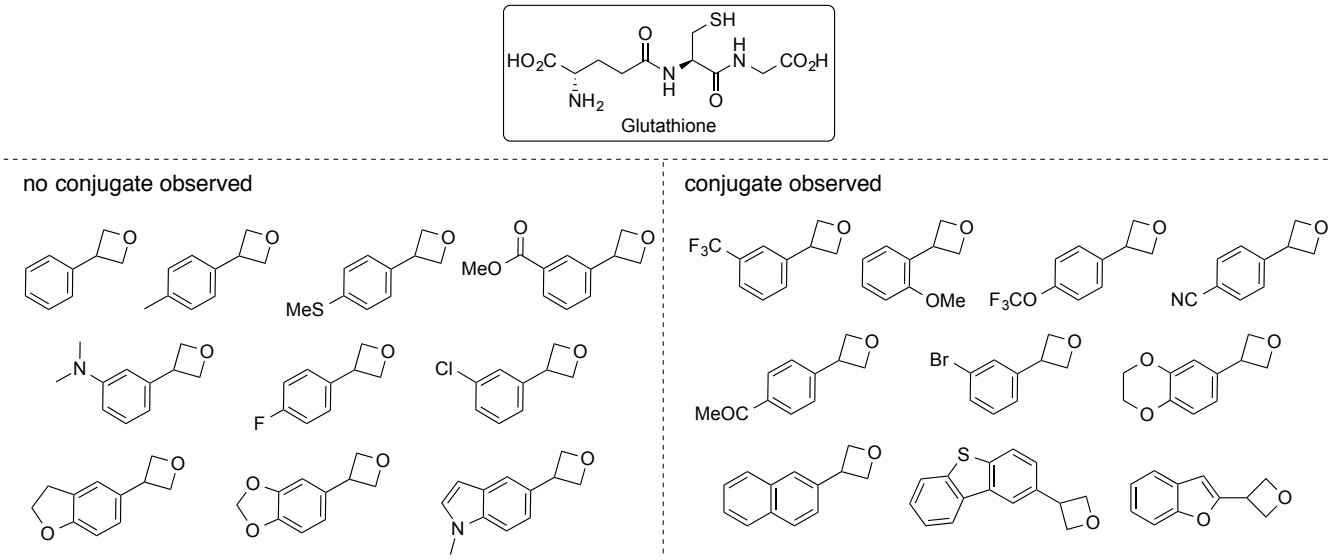
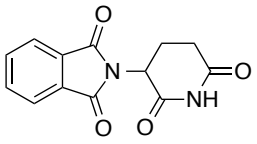
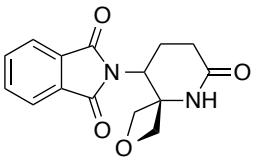


Figure 8. Examples of Oxetanes Tested with Human Liver Microsomes and Glutathione.

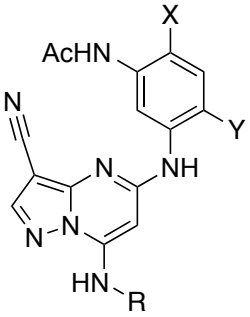
In 2013, Carreira explored the effects of structural modification of thalidomide and lenalidomide.[80] Infamously, while the *R*-isomer of thalidomide functions as an antiemetic and sedative, the *S*-isomer is a teratogen. Crucially, these readily interconvert under physiological conditions. When the imide C=O was replaced by an oxetane, an increase in solubility and decrease in lipophilicity, and no unfavorable difference in the intrinsic clearance rates in human microsomes was observed (Table 2).[80] Oxetano-thalidomide **13** was shown to be configurationally stable to racemisation 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 stereocentres.

Table 2. Comparison of the Physicochemical Properties of Thalidomide and Oxetano-thalidomide

	 Thalidomide	 **13** Oxetano-thalidomide
Solubility (μg mL^{-1})	29	78
Lipophilicity (logD)	0.24	0.00

Dowling and co-workers at AstraZeneca compared 3-amino oxetane motifs with other small rings through a series of matched pairs (Figure 9).[81] It was found that the introduction of the oxetane lowered the logD by ~0.8 units in comparison to amino-cyclopropane and amino-cyclobutane derivatives. In addition, the oxetane derivative significantly decreased the fraction of compound bound by human plasma proteins, increased the metabolic stability (rat liver microsome and hepatocyte), and reduced the hERG ion channel binding.



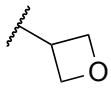
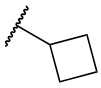
		logD		
	R			
X	**Y**			
Cl	H	2.2	3.1	nd
Me	H	1.6	2.4	2.9
Me	F	1.5	2.3	3.0
cPr	H	2.2	2.8	nd
cPr	F	2.1	3.0	nd

Figure 9. Matched Pairs Analysis of Log D for 5-Anilinopyrazolo[1,5-a]pyrimidine Inhibitors of CK2 Kinase.

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 (Pfizer) studied the effect of different carbocyclic and oxygen heterocylic derivatives on a series of *N*-substituted arylsulfonamides.[82] Progression from carbocyclic rings to 6- and 5-membered oxygen heterocycles and eventually oxetane rings gave an improvement in metabolic stability without reduction in potency (Figure 10). Across the THF derivatives, the 3-substituted example was more stable to human liver microsomes than the 2-substituted derivative; similarly the 3-mono-substituted oxetane was more stable than the 2-mono-substituted derivative. Metabolite identification studies, which initially identified *N*-alkyl substituents as metabolically labile, were able to identify sites of oxidative metabolism. For the 2-mono-substituted oxetane derivative, the compound underwent ring scission forming hydroxy acid and diol metabolites. For the 3-mono-substituted 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 mL/min/kg), whereas a *gem*-dimethyl group at the 3–position afforded a considerably less stable example (CL_{int} >293 mL/min/kg). This study concluded that the 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 the metabolic stability was directly linked to the intrinsic lipophilicity.[83,84] As such, the oxetane derivatives benefited due to the increased polarity compared to other cyclic ethers.

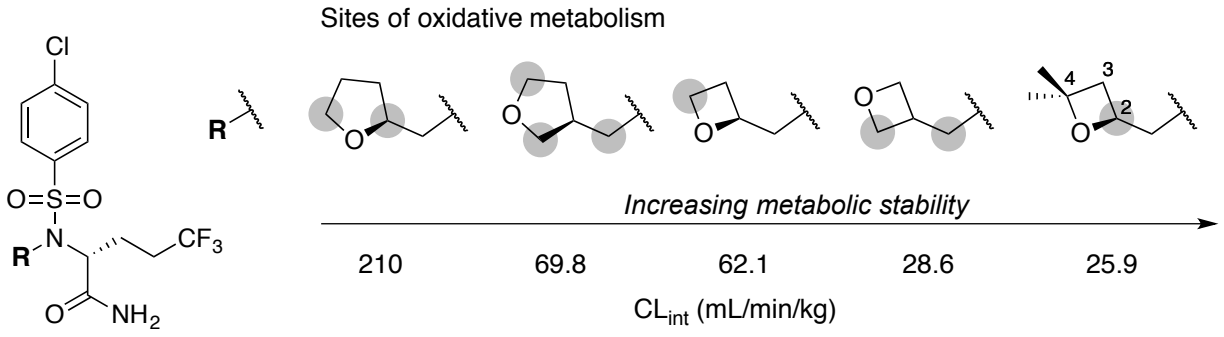


Figure 10. Comparison of Metabolic Stability of *N*-Substituted Arylsulfonamides. $CL_{int.app}$ is total intrinsic clearance obtained from scaling *in vitro* HLM half-lives.

Bull has reported studies into the chemical and metabolic stability of 2-sulfonyloxetanes, which were designed as novel fragments for fragment based drug discovery (FBDD).[85] Selected compounds were shown to be stable across the pH range (from pH 1-10), with half lives in the region of 4–5 days at 25 ºC. Similarly the intrinsic clearance of 2-(2-pyridylsulfonyl)oxetane was investigated in rat hepatocytes and shown to not present a metabolic liability. Oxetane δ-amino acid scaffolds, synthesized by Wessel and co-workers at Roche,[86,87,88] 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). The metabolic properties, in particular the oxetane derivatives' susceptibility towards degradation in human and mouse microsomes, were evaluated for a selection of substrates. All of the oxadiazoles tested displayed medium to low clearance in either human or mouse microsomes.

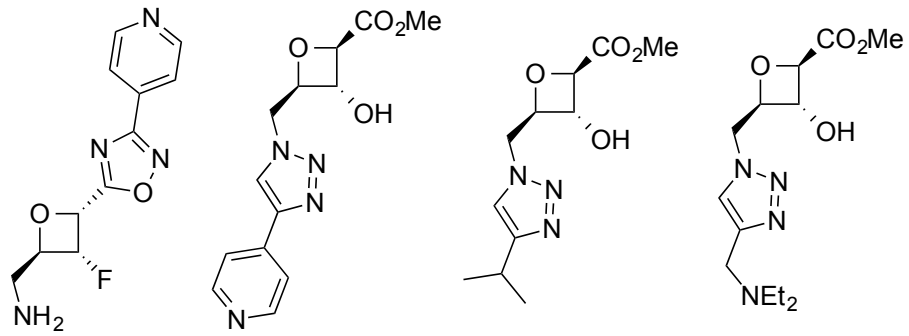


Figure 11: Examples from Wessel's Oxetane Library.

Wipf recently developed an oxetane–containing, neutral, solubilizing group by adapting an oxetanyl DMSO derivative which had proved effective as an additive to enhance the aqueous solubility of small organic molecules.[90,91] 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 HCl salt to improve

solubility, were converted into the corresponding oxetanyl sulfoxide carbamates. For a naproxen derivative, the oxetanyl sulfoxide derivative **14** showed a >10-fold increase in solubility and also a significant increase in cell permeability. A similar increse in solubility was achieved 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**.

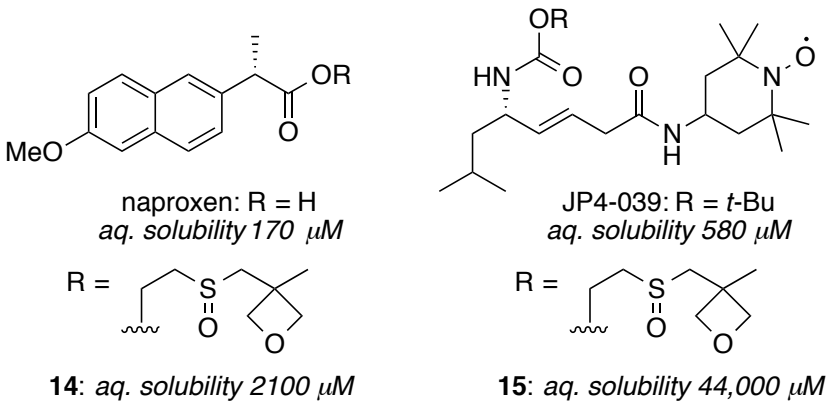


Figure 12. Wipf's Oxetane-Containing Neutral Solubilising Group.

The above studies and the presence of oxetanes in biologically active compounds have established the oxetane motif as an intriguing structure in medicinal chemistry. The 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 drug-like compounds (see Section 5 particularly).[92,93,94] 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;[95,96,97] the small, polar oxetane motif may offer opportunities towards these goals (Sections 2 and 5). The defined 3-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 (Sections 3.12 and 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 the oxetane products makes cyclization a fundamental synthetic challenge, and the kinetics of cyclization to form 4-membered saturated cyclic ethers are significantly slower than for the 3, 5 and 6-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, complemented by few but increasing C–C bond forming methods.

3.1 Cyclization Through C–O Bond Formation

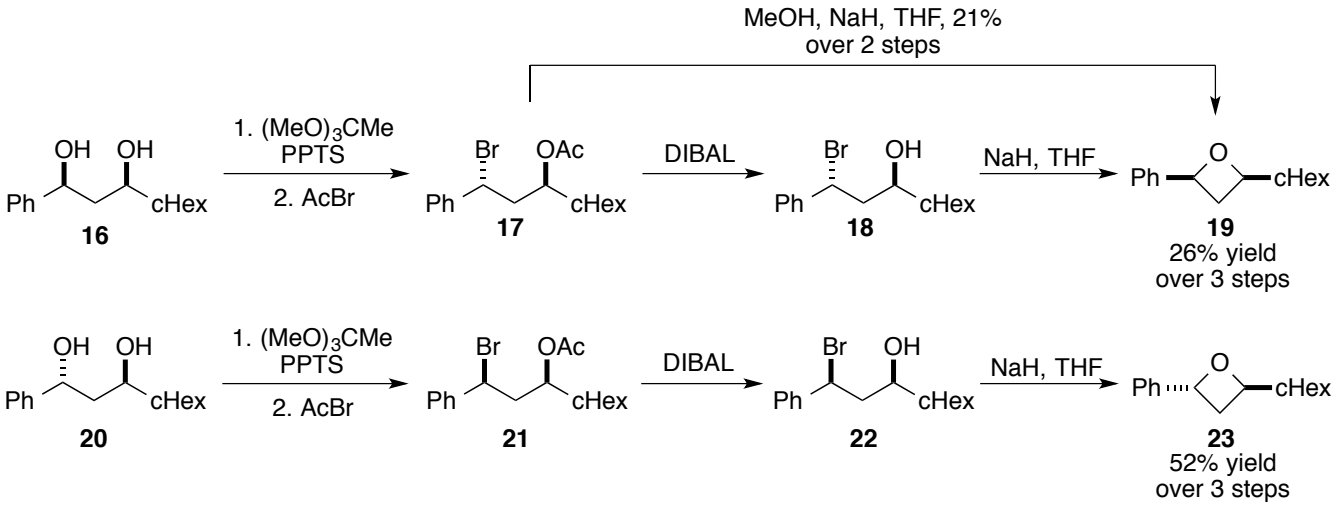
3.1.1 Intramolecular Etherification

Williamson etherification describes a general approach to ether synthesis by a base mediated nucleophilic substitution reaction between an alcohol and an aliphatic carbon centre, 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 the Grob fragmentation of the halo-alkoxide into an aldehyde and an alkene.[99,100] Consequently, the 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 Reboul[101] and remains the most commonly employed in the synthesis of complex oxetane-containing structures.[102,103,104,105]

Nelson reported a stereocontrolled synthesis of 2,4-substituted oxetanes from 1,3-diols (Scheme 1).[106,107] 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 orthoesters followed by treatment with acetyl bromide. The required 1-hydroxy-3-bromo relationship present in intermediates **18** and **22** was

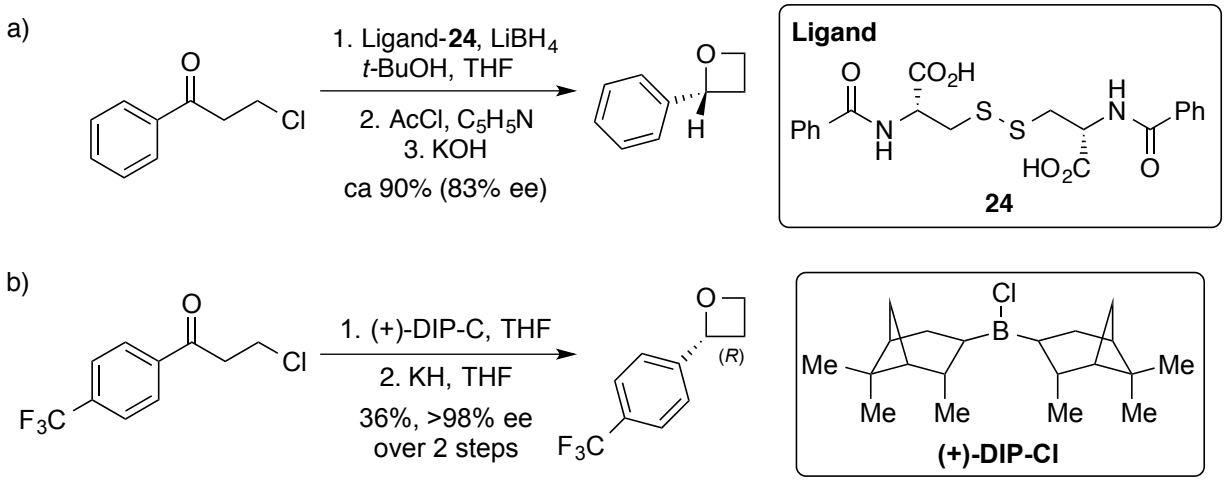
established using DIBAL to cleave the acetyl group. Intramolecular cyclization to oxetanes **19** and **23** was then achieved with complete inversion of stereochemistry using sodium hydride in THF resulting in an overall retention of stereochemistry (through double inversion at the benzylic centre) over the 3 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 the formation of a benzylic cation (not shown). A one-pot procedure for the conversion of **17** to **19** was also developed, removing the need for the DIBAL reduction, by the addition of 1 equiv of MeOH and excess base.

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



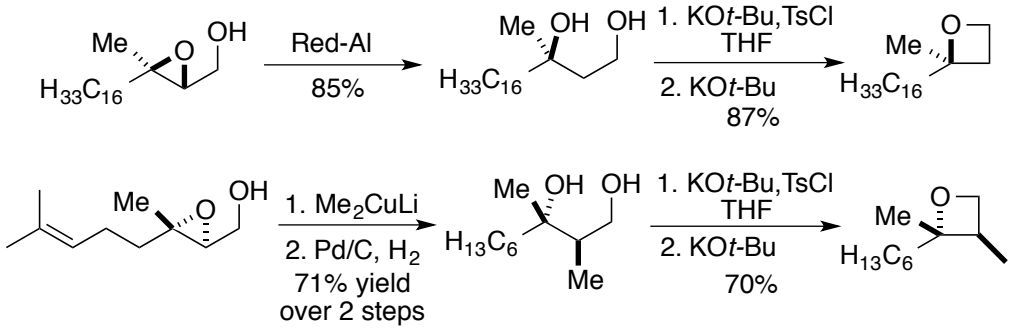
An important enantioselective synthesis of oxetanes was reported in 1986 from Soai. Three examples of enantioenriched 2-aryl substituted oxetanes were prepared through enantioselective reduction of β-halo-ketones followed by Williamson ether cyclization promoted by KOH.[110] Enantiomeric excesses of 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).

Scheme 2: Asymmetric Synthesis of 2-Aryl Oxetanes Using a Chiral Catalyst



More recently, Fu 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 using (+)-DIP-Cl (Scheme 2b).[111,112] The cyclization used KH, and while the yield was moderate, the ee was retained. Dussault reported the preparation of enantioenriched oxetanes via cyclodehydration of enantioenriched 1,3-diols, generated from 2,3-epoxy alcohols by ring opening with RedAl or dimethyl cuprate (Scheme 3).[113] The use of KO*t*Bu 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.

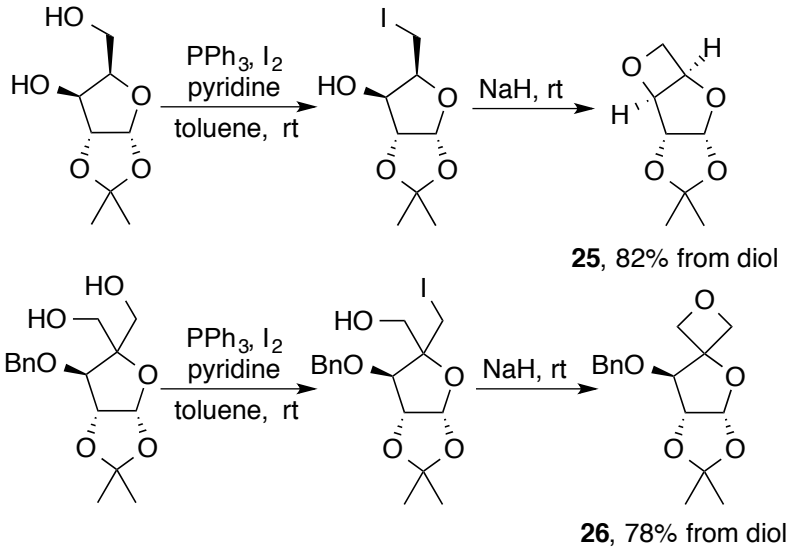
Scheme 3. Stereocontrolled Synthesis of Oxetanes from Epoxy Alcohols



In 2006, Mandal reported the one pot synthesis of a variety of cyclic ethers including oxetanes using a Williamson etherification protocol.[114] 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**

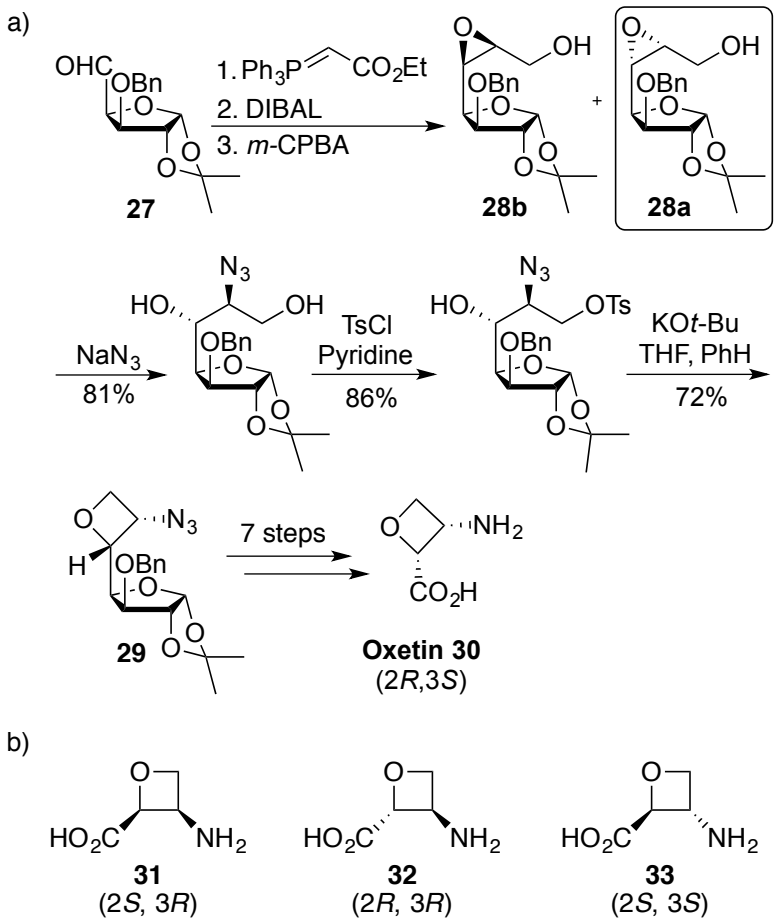
in 82% and 78% respectively (Scheme 4). (See sections 3.1.3 and 3.1.4 for oxetane-containing sugar derivatives and nucleoside analogues.)

Scheme 4. Synthesis of Oxetanes 25 and 26 Through an Iodination-Williamson Etherification Pathway



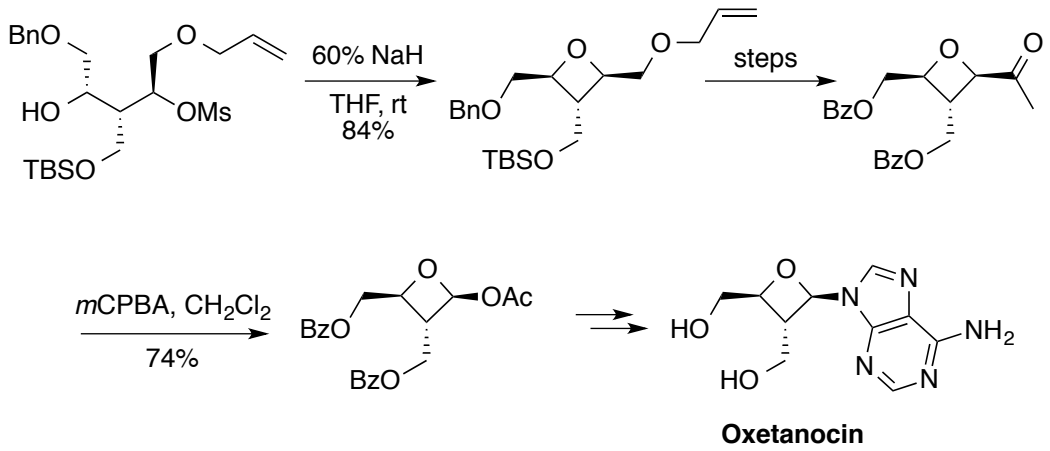
The first synthesis of oxetin employed a traditional Williamson etherification with a tosylate leaving group to give the oxetane ring motif with the desired stereochemistry.[115] Ōmura synthesized the natural product and its three stereoisomers, using a sugar as a chiral auxilliary (Scheme 5a). From aldehyde **27**,[116] a Wittig reaction afforded both *cis*- and *trans*- alkenes with poor selectivity (1.3:1 *cis*/*trans*), but which 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 using *m*-CPBA gave both possible stereoisomers of epoxide **28a/b**. Regio- and stereoselective ring opening of epoxide **28a** with NaN_3 afforded a single product with an excellent 81% yield. A selective tosylation of the primary alcohol, followed by a Williamson etherification using KO*t*Bu, afforded oxetane **29** in good yield. Functional group manipulation afforded the natural product **30** which was purified by ion exchange chromatography. The remaining 3 stereoisomers **31**–**33** (Scheme 5b) were all prepared using the same synthetic route. Subsequently, all 4 stereoisomers of oxetin were tested against *Bacillus subtilis*, but only the natural product oxetin **30** showed any activity.

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



The synthesis of oxetanocin was achieved by Yamamura using a Williamson etherification for the oxetane-forming step (Scheme 6).[117] A sodium hydride mediated cyclization was utilized to synthesize the oxetane scaffold of oxetanocin in a good yield of 84% using a mesylate leaving group. Interestingly, the 2-hydroxy methyl 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.

Scheme 6. Synthesis of Oxetanocin Using a Williamson Etherification for the Key Cyclization Step

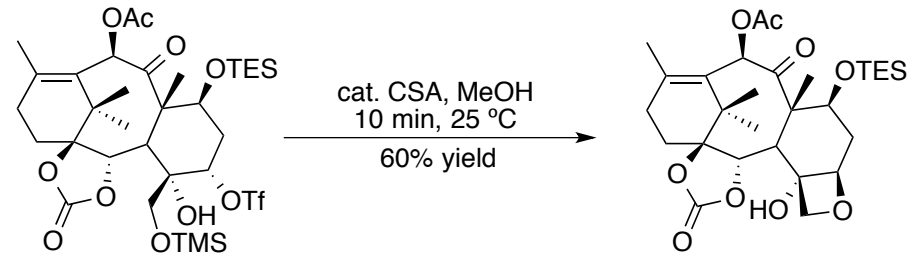


The total syntheses of taxol have primarily formed the oxetane ring midway through the sequence by an intramolecular Williamson etherification (Scheme 7).[119,120,121,122,123,124,125,126,127,128,129] The majority of total syntheses use base mediated approaches for formation of the oxetane on similar 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 Nicolaou's sequence, delivering the desired oxetane in just 10 minutes. Danishefsky's intermediate differed considerably as the oxetane was introduced in step 13 of 49,[127] considerably earlier than, for example, in Nicolaou's work (step 31 of 37) or in Wender's total synthesis (step 40 of 44). Danishefsky stated that this strategy would be important for an analog program. Treatment with ethylene glycol at reflux allowed the cyclization to occur, and it was speculated by Danishefsky that this transformation involved a hypervalent silyl ether to trigger the displacement of the required triflate.[127] Wender and Kuwujima both utilized a halide leaving group which allowed conversion to the oxetane in good yields of 95% and 86% respectively in a single step.[119,123] A base mediated cyclization step using DBU is a common and enduring approach with Holton (1994),[125,126] Kuwujima (2000),[123] Takahashi (2006)[120] and Nakada (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

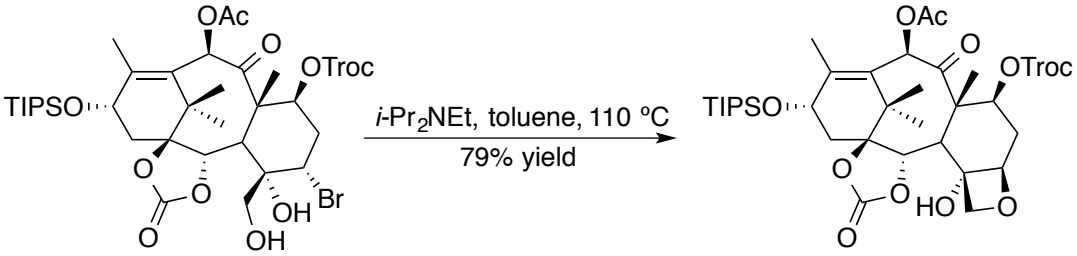
allowed the etherification reaction to proceed in good yield under a variety of conditions. Various synthetic studies have been reported on taxol mimics.[130,131,132]

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

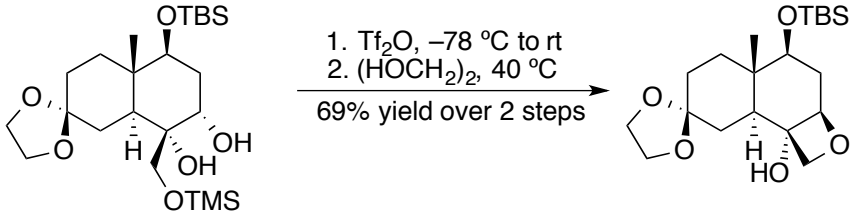
Nicolaou, 1994



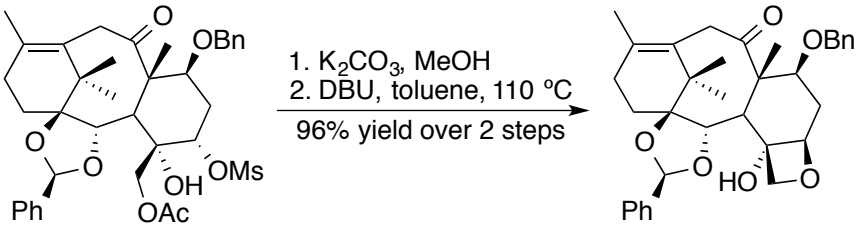
Wender, 1997



Danishefsky, 1998



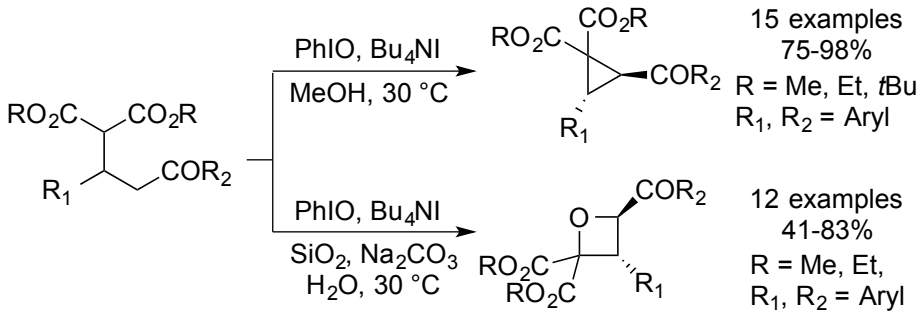
Nakada, 2015



In 2009, Fan and co-workers reported oxidative cyclization of malonate Michael adducts with chalcones to selectively access cyclopropanes and oxetane derivatives with high diastereoselectivity (Scheme 8).[133] Cyclization was only observed when iodosobenzene (PhIO) and tetrabutylammonium iodide (Bu_4NI) were utilized. During optimization, cyclopropanes were synthesized in shorter reaction

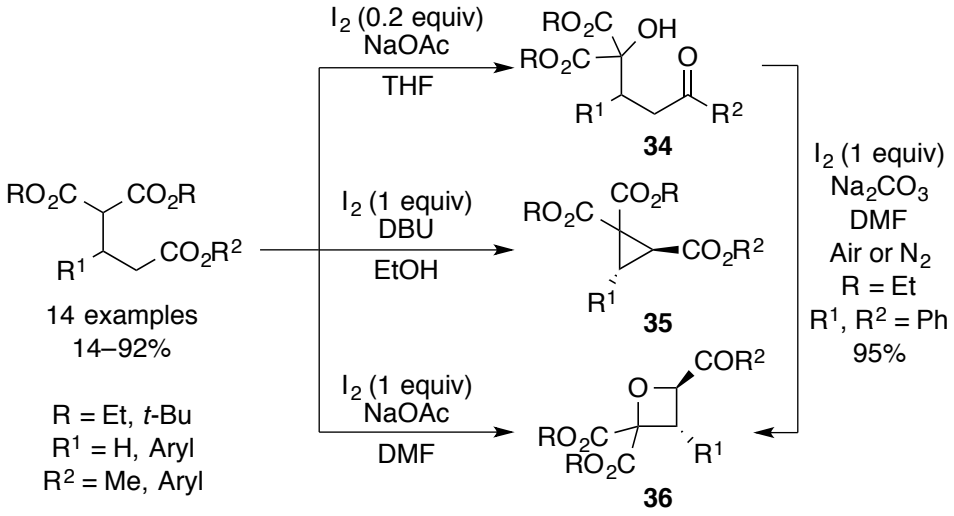
times when alcoholic solvents were used. Conversely, when the reaction was conducted in an open-air system with water, the oxetane was formed as the major product. Substrates bearing electron-rich aryl groups gave improved yields and selectivity for oxetane products, as did the addition of SiO_2 and Na_2CO_3.

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



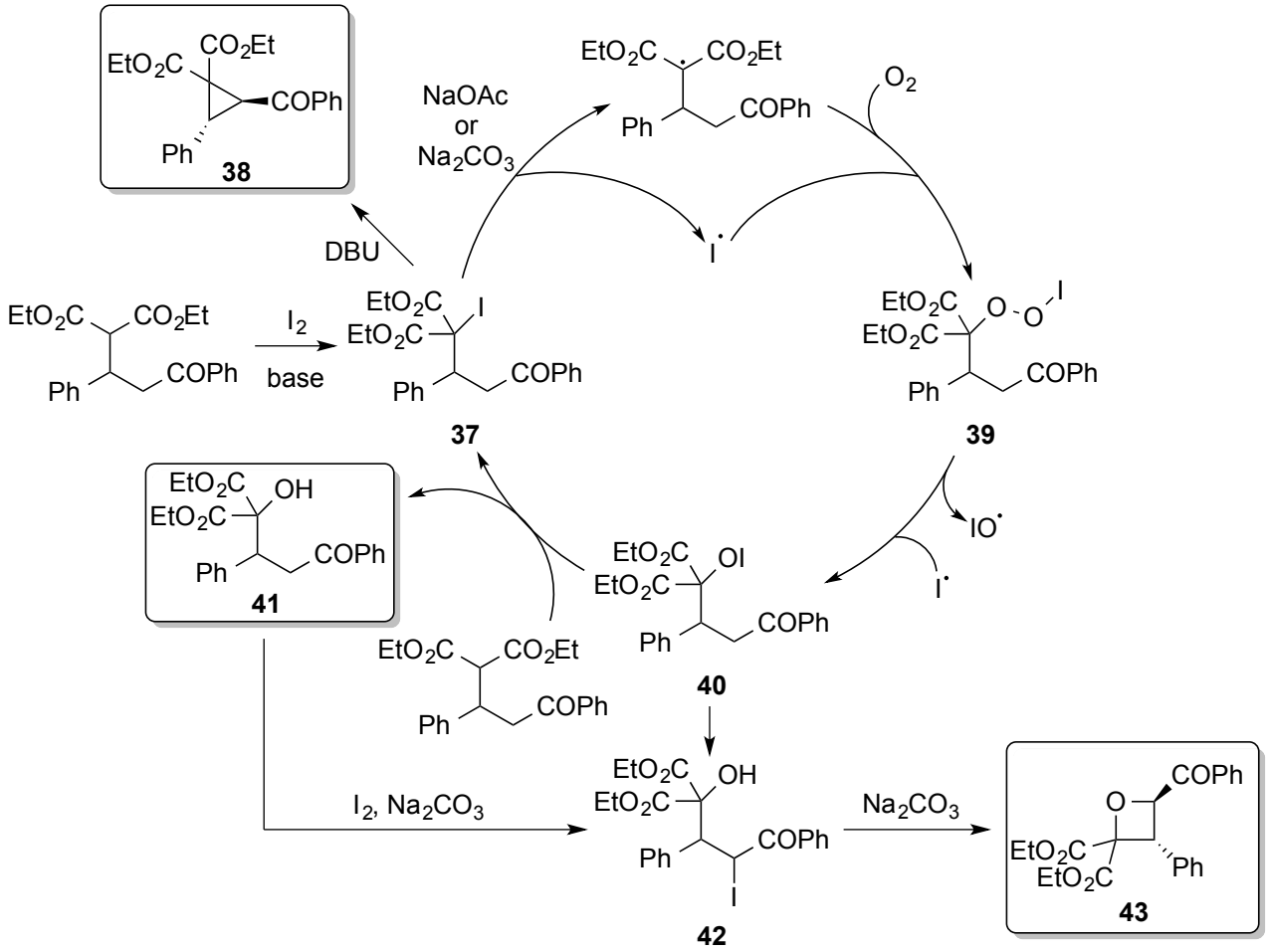
Two years later, Yang reported a similar iodine mediated conversion of Michael adducts of malonates with enones to either α-hydroxymalonate derivatives (**34**), cyclopropanes (**35**) or oxetanes (**36**) with high diastereoselectivity (Scheme 9).[134] The oxygen atoms in α-hydroxymalonates **34** and oxetanes **36** were derived from atmospheric O_2, and substoichiometric amounts of I_2 (0.2 equiv) could be used. Each of the three reactions proceeded well when both R_1 and R_2 were aryl groups with the nature of the substituents on the aryl ring having no significant impact on the reaction.

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



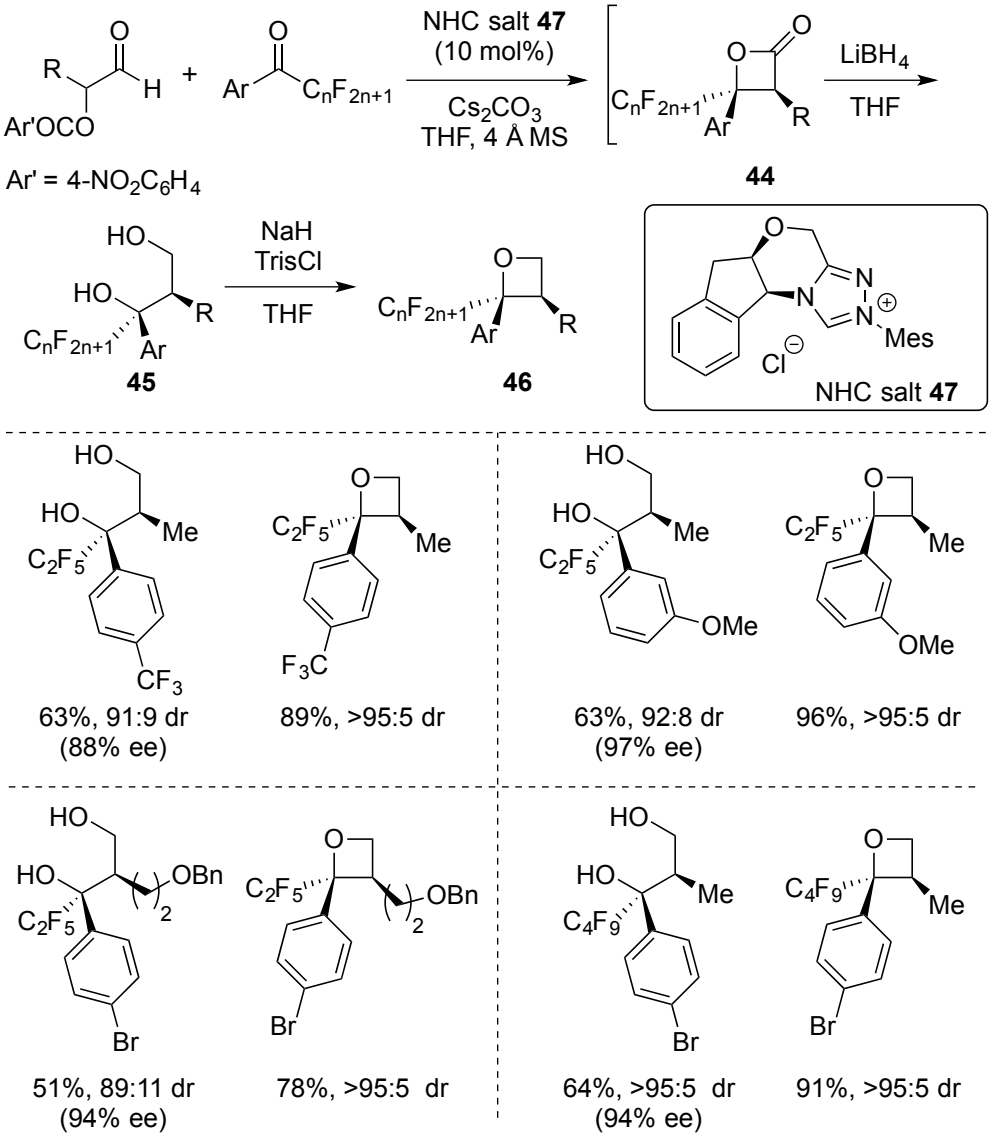
A radical mechanism was proposed involving initial iodination of the Michael adduct to give key intermediate **37** (Scheme 10). This intermediate could undergo a DBU mediated cyclization in the absence of O_2 to give cyclopropane **38,** or cleavage of the C–I bond and reaction with oxygen and an iodine radical to give iodoperoxide **39** then hypoiodide **40**. Iodine abstraction with the starting material would give α-hydroxymalonate **41** and regenerate key intermediate **37**. Treatment of **41** with I_2 and Na_2CO_3 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.

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



Recently, Smith developed an enantioselective formal [2+2] cycloaddition to form highly substituted, fluorinated β-lactones **44** from fluorinated ketones and α-aroyloxyaldehydes using a chiral NHC-catalyst **47**. Reduction to diols **45** using $LiBH_4$ and activation of the primary alcohol with TrisCl, followed by Williamson etherification, afforded the substituted fluorinated oxetanes **46** with excellent dr and ee (Scheme 11).[135]

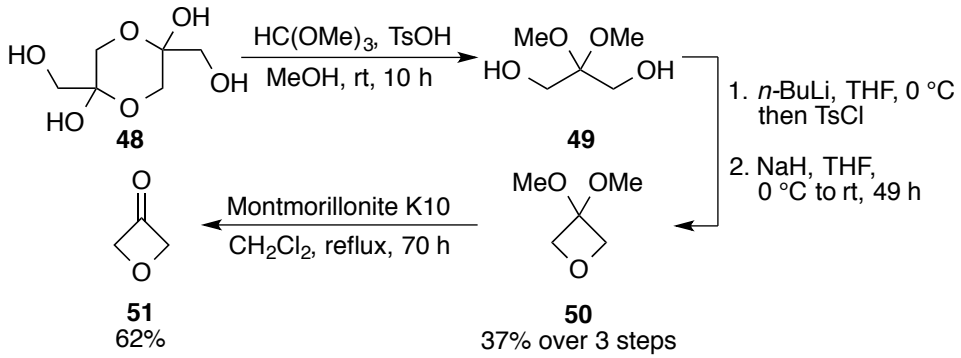
Scheme 11. Synthesis of Oxetanes via an NHC-Catalyzed Formal [2+2] Cycloaddition of Fluorinated Ketones and α-Aroyloxyaldehydes



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 developed a four-step synthesis of the cyclic ketone which involved an intramolecular cyclization to form the oxetane (Scheme 12).[63] The 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.

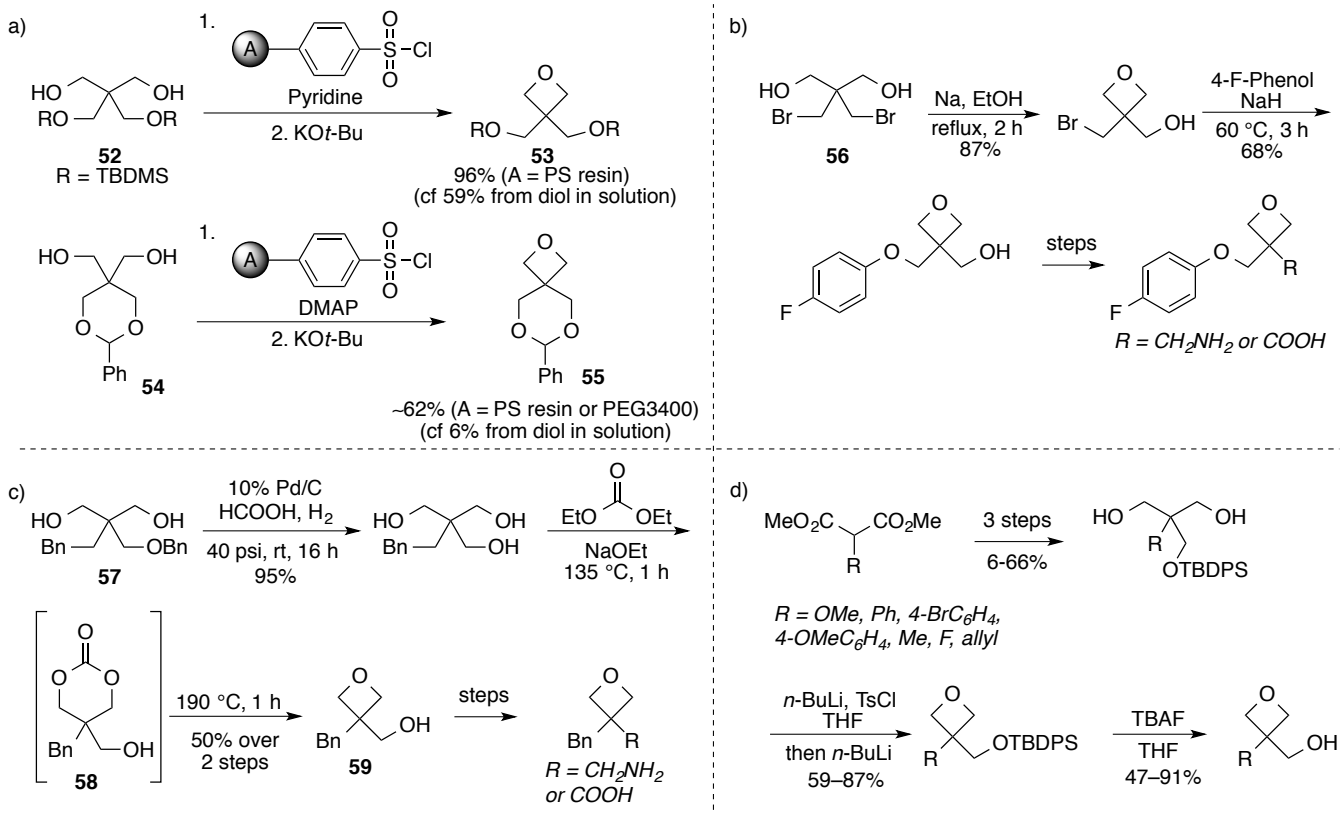
Scheme 12. Synthesis of Oxetan-3-one by an Intramolecular Cyclization



Use of solid phase synthesis for the preparation of 3,3-disubstituted oxetanes **53** and **55** was reported by Hailes in 2005.[136] Polystyrene and a novel PEG 3400 resin were used with a sulfone linker. The polymer bound precursors were synthesized from the polymer bound sulfonyl chlorides and the desired diols **52** and **54** with bead staining providing evidence for incorporation. Cyclization using sodium hydride proved unsuccessful, but treatment with KO*t*Bu resulted in much improved yields over the 2 steps when compared to the solution based synthesis for both resins and substrates used (Scheme 13a).

Vigo reported the synthesis of 3,3-disubstituted oxetanes with hydroxy, amino and carboxylic acid residues suitable for further functionalization.[137] From diol **56**, through a cyclization, nucleophilic substitution then functional group manipulation route, a variety of functionalized oxetanes were prepared (Scheme 13b).

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



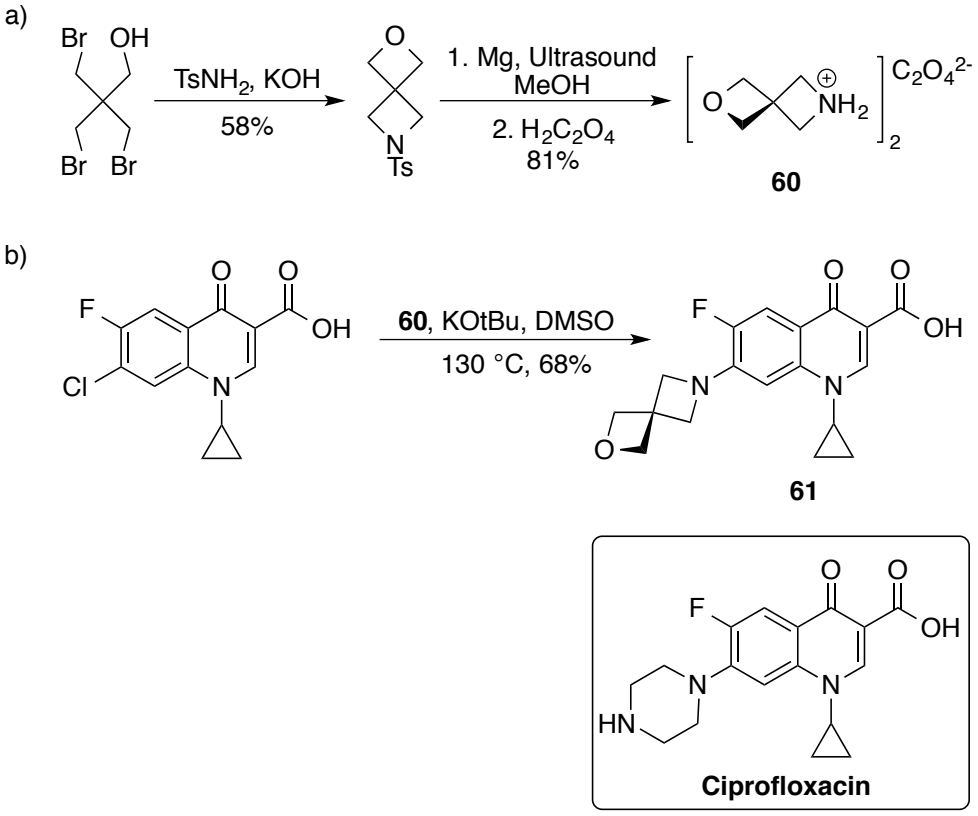
Development of a 3-step route from diol **57** via cyclic carbonate **58** allowed access to 3-benzyl oxetane **59** in a moderate yield (Scheme 13c).[137] Previous cyclization strategies and functional group manipulation had proved unsuccessful for this synthesis.

Further examples of medicinally relevant 3,3-disubstituted oxetanes were reported in 2014 by Boyd and Davis (AstraZeneca).[138] The 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 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.

The 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 on this subject appeared in 2014, and we will not replicate this material here,[2] but only to highlight a small selection of examples. The synthesis and biological testing of an analog 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 2 steps from 3-bromo-2,2-bis(bromomethyl)propan-1-ol (Scheme 14a). The synthesis of ciprofloxacin analog **61** was achieved in a yield of 68% using KO*t*Bu in DMSO at 130 °C (Scheme 14b). Oxetane analog **61** was then compared against an azetidine analog and the parent ciprofloxacin in a number of biological assays. Comparable activities were seen for the two spirocyclic analogs, and additionally there was no observable metabolism in human microsomal assays.

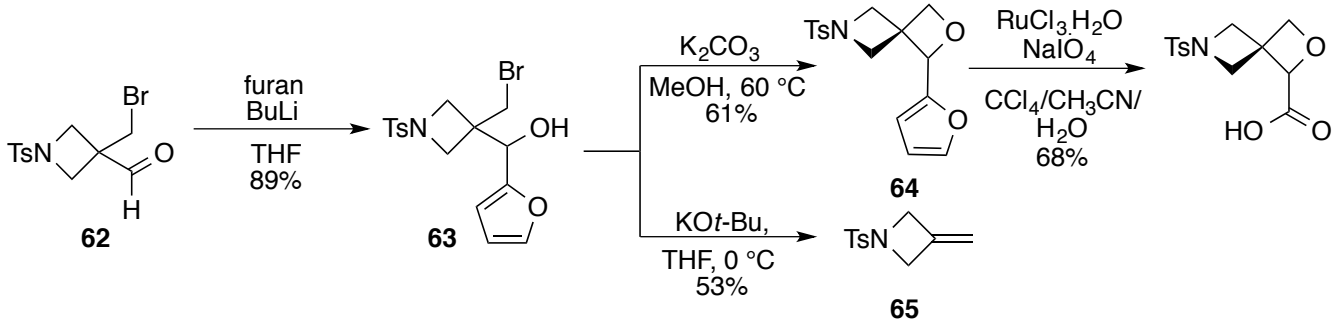
Scheme 14. Spirocyclic Building Block 60 and Use in a Ciproflozacin Analog



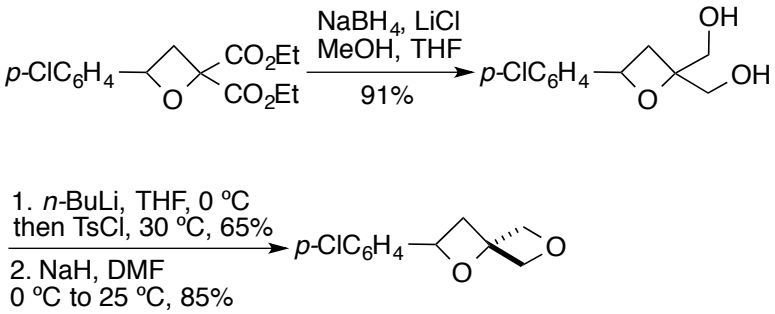
Carreira also reported the synthesis of 2-substituted spirocyclic oxetane azetidines (Scheme 15).[74] The addition of furyllithium to azetidine aldehyde **62**, synthesized in 3 steps from tribromopentaerythritol, afforded cyclization precursor **63** with the required 1,3-relationship between the alcohol and electrophilic carbon. Cyclization to the desired spirocyclic oxetane **64** occurred successfully using 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 KO*t*Bu in THF was used, Grob fragmentation occurred to give 3-*exo*-methylene azetidine **65** in a 53% yield. The likelihood of the 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 the Grob fragmentation occurring.[139]

Recently Bull and co-workers prepared an unusual bis-spirocyclic oxetane derivative (Scheme 16).[140] Reduction of an oxetane-diester to the diol using $LiBH_4$ 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.

Scheme 15. Preparation of Spirocyclic Oxetane Azetidines

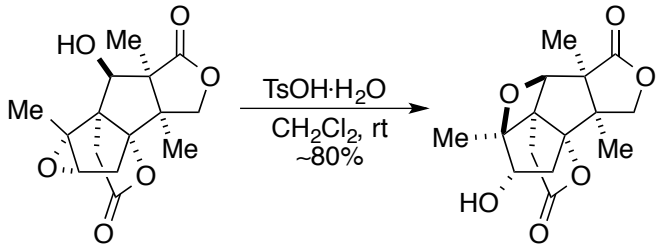


Scheme 16. Preparation of a Bis Spirocyclic Oxetane Derivative



Epoxides have also been used as leaving groups for the synthesis of oxetanes via intramolecular etherification. Kato demonstrated the synthesis of oxetanocin analogs involving base mediated ring opening of *cis*-epoxides of homoallylic epoxides using KOH to afford oxetanes (61–66% yield) along with the THF product (3.5:1 to 14.5:1 ratio, oxetane:THF).[141,142] Interestingly, *trans* and terminal epoxides gave only the THF product. Additionally, stoichiometric tributyltin methoxide was used by Chung in 1996 for the ring opening of a terminal epoxide by a hydroxy group to give 4-[(benzyloxy)methyl]oxetan-2-ylmethanol in 32% yield.[143] Subsequently, Carreira used this methodology for the synthesis of a bridged bicyclic morpholine,[69] also used elsewhere.[144] This disconnection has also been achieved under acidic conditions. In 2002, Danishefsky 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.[145] 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).[146,147,148,149,150]

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

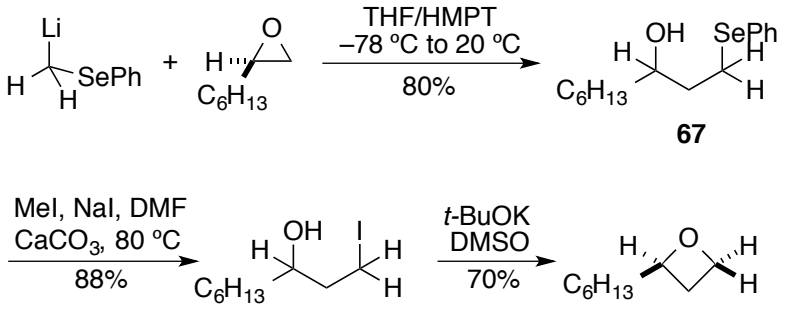


66 **merrilactone A**

3.1.2 Epoxide Ring Opening - Ring Closing

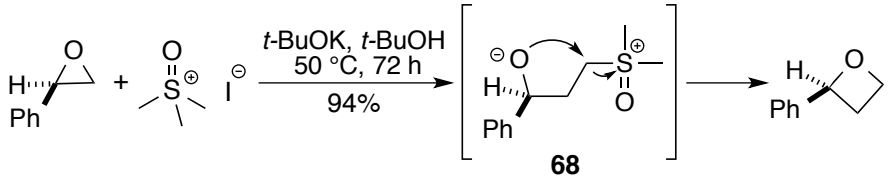
Epoxides can be ring expanded to oxetanes: as a variant of the Williamson etherification, the cyclization precursor has been accessed by opening an epoxide with nucleophiles bearing leaving groups. In 1980, Krief opened epoxides (2-hexyloxirane, 2-hexyl-2-methyl oxirane or 2-methyloxirane) with selenoalkyllithiums in THF/HMPT at –78 ºC then warmed to 20 ºC to afford ring opened hydroxy selenide **67** (Scheme 18).[151] These intermediates were converted to the halides which could be cyclized with a base such as KO*t*Bu or MeMgBr to access the oxetane. Selenoethyl- and selenopropyllithiums were also successful to introduce additional Me/Et groups at the oxetane C4 position.

Scheme 18. Oxetane Formation Through Epoxide Opening with Selenoalkyllithiums



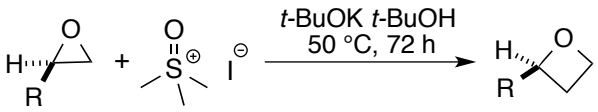
In 1983 Okuma reported a similar method to access the oxetane cyclization precursor by ring opening epoxides with a sulfoxonium ylide generated in situ from trimethyloxosulfonium iodide.[152] Attack of a 2-substituted or 2,2-disubstituted epoxide with the sulfur ylide accessed the ring-opened intermediate **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*-ClC_6H_5, Me or H substituents and an example using cyclohexanone.

Scheme 19. Oxetane Formation Through Epoxide Opening with Trimethyloxosulfonium Ylide



Okuma demonstrated that by increasing the equiv of trimethyloxosulfonium iodide, the oxetane motif could be accessed from the corresponding carbonyl compound through initial formation of the epoxide followed by ring opening.[152] A related method was reported using the sodium anion of an NTs-sulfoximine.[153,154] Fitton 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.[155] Treating mono substituted epoxides with dimethyloxosulfonium methylide resulted in oxetanes **69** in good yields (Table 3). The useful 2-hydroxymethyloxetane motif was formed in 74% following acetal deprotection (from Entry 1, Table 3), and the vinyl derivatives (Entries 2 and 4) successfully underwent bromination with Br_2 or epoxidation with *m*CPBA.

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



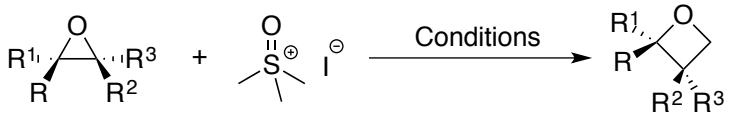
69

Entry	R	Yield (%)
1	$CH_2OCH(CH_3)OC_2H_5$	70
2	$CH_2OCH_2CH{=}CH_2$	65
3	$CH_2OC_6H_5$	83
4	$CH_2CH_2CH{=}CH_2$	56
5	$CH(OC_2H_5)_2$	59

Fokin modelled the ring expansion of an unsubstituted epoxide computationally at the DFT and MP2 levels of theory utilizing a polarizable continum model to account for solvent effects, determining that the formation of the oxetane ring from an epoxide required 13-17 kcal mol^{-1} activation energy; therefore moderate heating was required.[156] Subsequent ring expansion barriers were calculated for oxetane to THF at 25 kcal mol^{-1} and THF to THP at 38 kcal mol^{-1}. For 2-methyl and 2,2-dimethyloxirane the

methylenation of epoxides with dimethylsulfoxonium methylide was modelled and shown to proceed via an S_N2 transition structure and was sensitive to the epoxide substitution. Experimental findings were consistent with the computational results whereby enantioenriched chiral oxetanes were accessed from enantioenriched epoxides with full retention of enantiomeric purity (Table 4). 2-Alkyl and 2,2-dialkyl epoxides 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 applied this approach to *N*-Boc-azetidin-3-one where this transformation was successful in the generation of a spirocyclic azetidine-oxetane.[75] Aggarwal and McGarrigle reported the cyclization of a related intermediate to form a 2,2-disubstituted oxetane through the conjugate addition of a hydroxy malonate to a vinyl sulfonium salt forming an ylide, which underwent proton transfer and cyclization.[157]

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

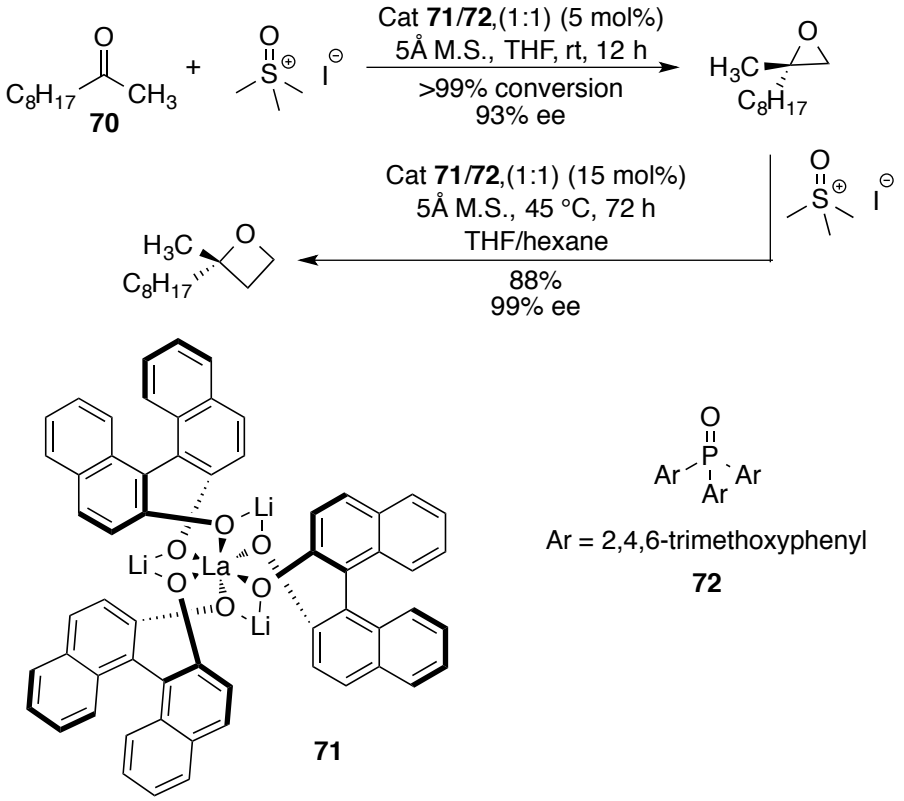


Entry	R	R^1	R^2	R^3	Conditions	Yield (%)	ee (%)
1	C_6H_5	H	H	H	NaH, DMSO, 70 ºC	85	>98
2	*n*-hexyl	H	H	H	*t*-BuOK, *t*-BuOH, 80 ºC	91	>98
3	H	CH_2OCH_2Ph	H	H	*t*-BuOK, *t*-BuOH, 80 ºC	80	>98
4	C_6H_5	Et	H	H	NaH, DMSO, 110 ºC	88	>98
5	C_6H_5	H	H	Me	*t*-BuOK, *t*-BuOH, 120 ºC	traces	n.d.

Shibasaki 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 a partial kinetic resolution and amplified ee.[158] The starting methyl ketone **70** was treated with 1.2 equiv of dimethyloxosulfonium methylide, 5 mol% of catalyst **71** and phosphorous oxide additive **72** in the presence of molecular sieves to afford the corresponding chiral epoxide, which was then treated with a further equiv of the sulfur ylide and 15 mol% of 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% in up to 99.5% ee employing both alkyl and aryl methyl ketones. When employing ethyl ketones such as propiophenone 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 the ketone substitution.

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

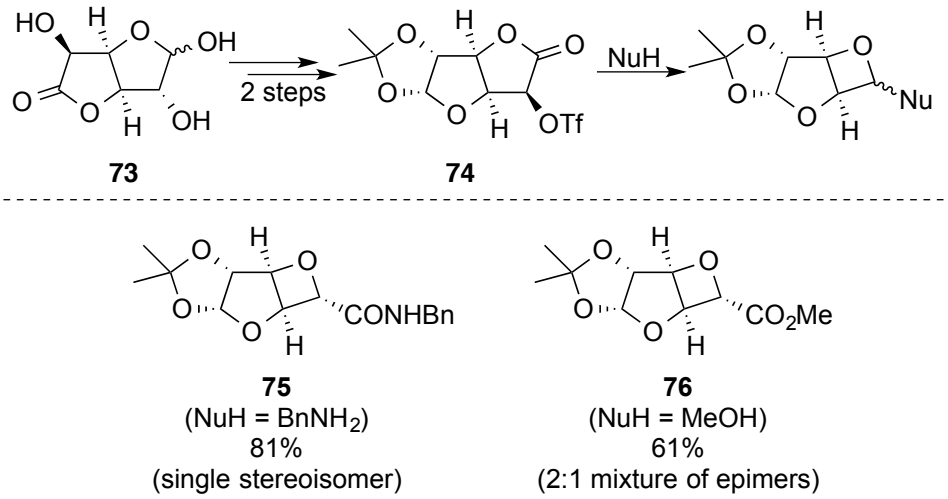


3.1.3 Synthesis of Oxetanes from Sugar Derivatives

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 as starting materials for the synthesis of enantioenriched oxetanes through ring contraction of the triflates of α-hydroxy-γ-lactones (Scheme 21).[160,161] These were formed from the corresponding α-hydroxy-γ-lactones which are, in turn, prepared from compounds derived from sugars.[162,163,164] 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]

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



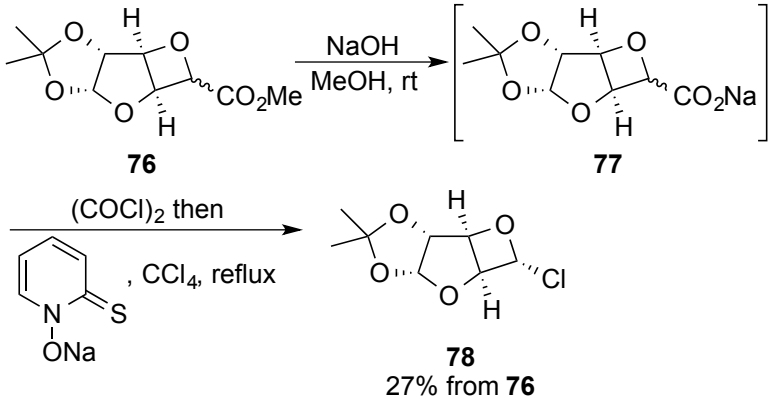
75
(NuH = $BnNH_2$)
81%
(single stereoisomer)

76
(NuH = MeOH)
61%
(2:1 mixture of epimers)

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 epimerisation prior to oxetane formation. Treatment of ester-oxetane **76** with benzylamine and hydrazine hydrate afforded the corresponding amide oxetanes, and reduction was achieved using $LiAlH_4$, both reactions proceeding without epimerisation.[161]

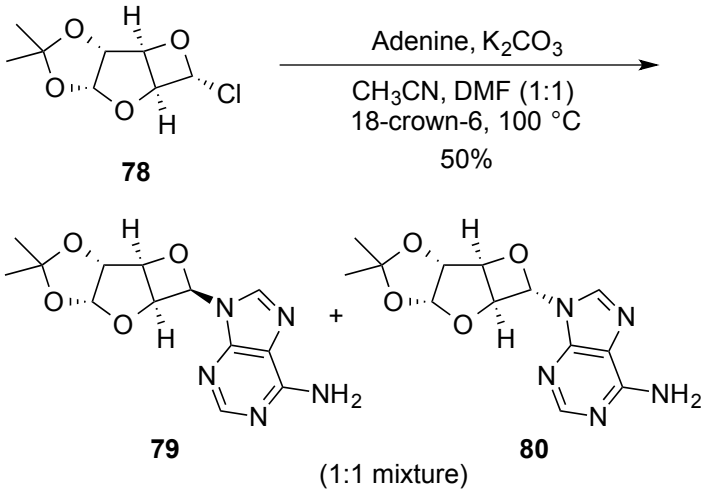
The synthesis of an unusual but stable α-chlorooxetane **78** was achieved by Fleet through a Barton modification of the Hunsdiecker reaction (Scheme 22).[165,166] Ester **76** was converted to the chloride with a yield of 27% through hydrolysis to the sodium carboxylate salt **77**, formation of the acid chloride and reaction with *N*-hydroxypyridine-2-thione sodium salt under reflux in CCl_4. The structure of this fascinating chloro-oxetane was proven by an X-ray crystal structure.[166]

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



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

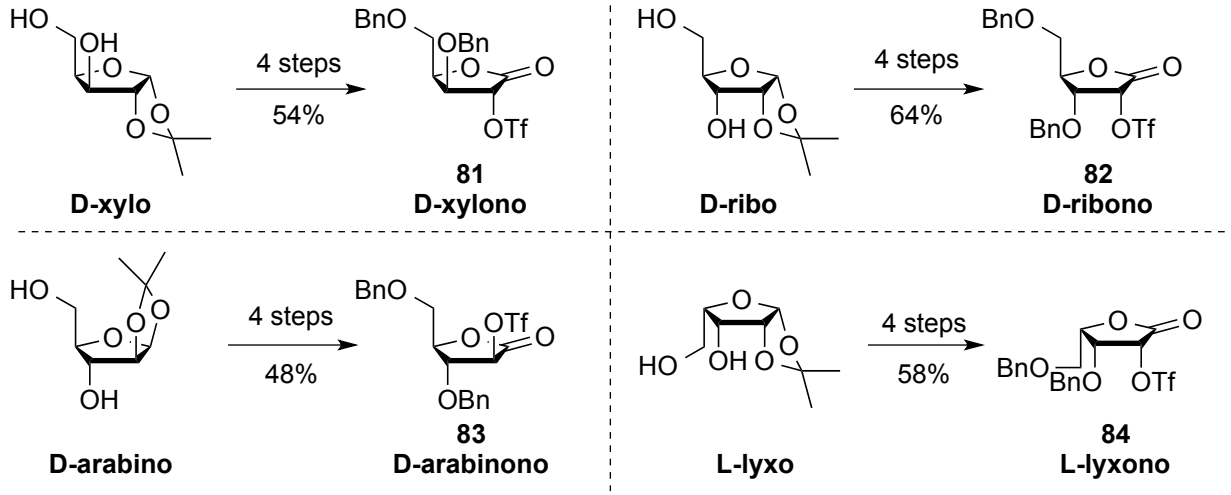
Scheme 23. Synthesis of Oxetane Nucleoside Analog from α-Chlorooxetane 78



A few years after the reaction with bicyclic lactones, Fleet expanded the scope of the ring contraction of α-hydroxy-γ-lactones to all 4 diastereoisomers of 3,5-di-*O*-benzyl-pentono-1,4-lactones.[168] These lactones were prepared from 1,2-*O*-isopropylidine pentofuranose sugars (Scheme 24). Triflates **81-84**

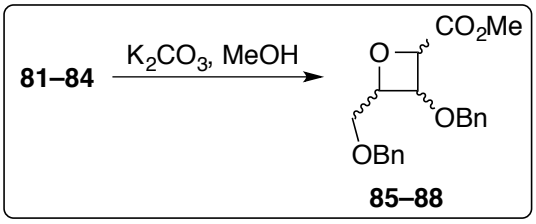
were prepared in 4 steps from the readily available diols of D-xylo, D-ribo, D-arabino and L-lyxo sugars with yields between 48% and 64%.

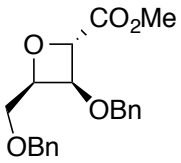
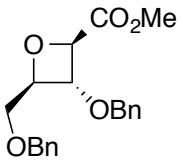
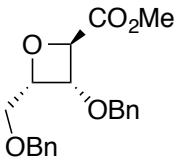
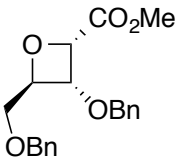
Scheme 24. Synthesis of Triflate Lactones 81–84 From Pentofuranose Sugars



Ring contraction was conducted on each example using the 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 substitutents on the oxetane ring. No deuterium incorporation was observed when the reaction was conducted in d_4-methanol, which implied that the stereochemical outcome of these reactions was not a consequence of an equilibrium of the oxetane products. Unfavorable interactions during the 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 the cyclization, which favored the *trans*-configuration.

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

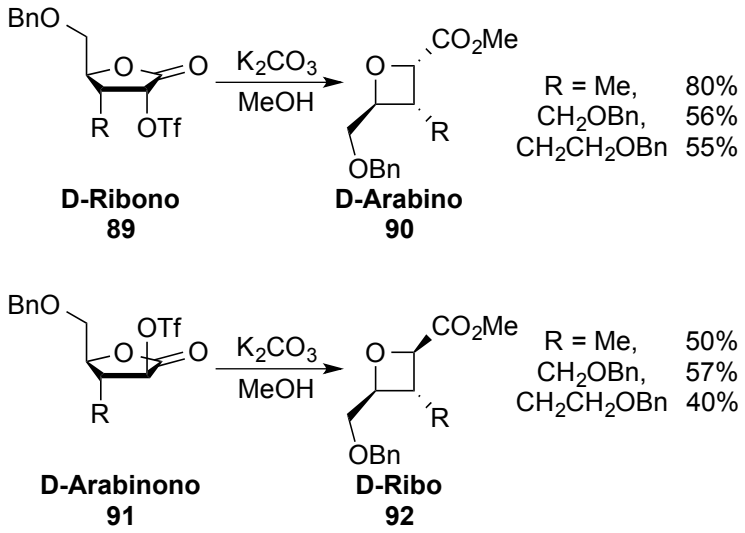


	Yield of Product (%)			
	 **85**	 **86**	 **87**	 **88**
Triflate				
D-xylono (**81**)	79 (inv)[a]	-	-	-
D-ribono (**82**)	-	73 (ret)[b]	-	9
D-arabinono (**83**)	-	70 (inv)[a]	-	-
L-lyxono (**84**)	-	-	80 (ret)[a]	-

[a] Inv: inversion of configuration on at C2 on cyclization. [b] Ret: retention of configuration on cyclization

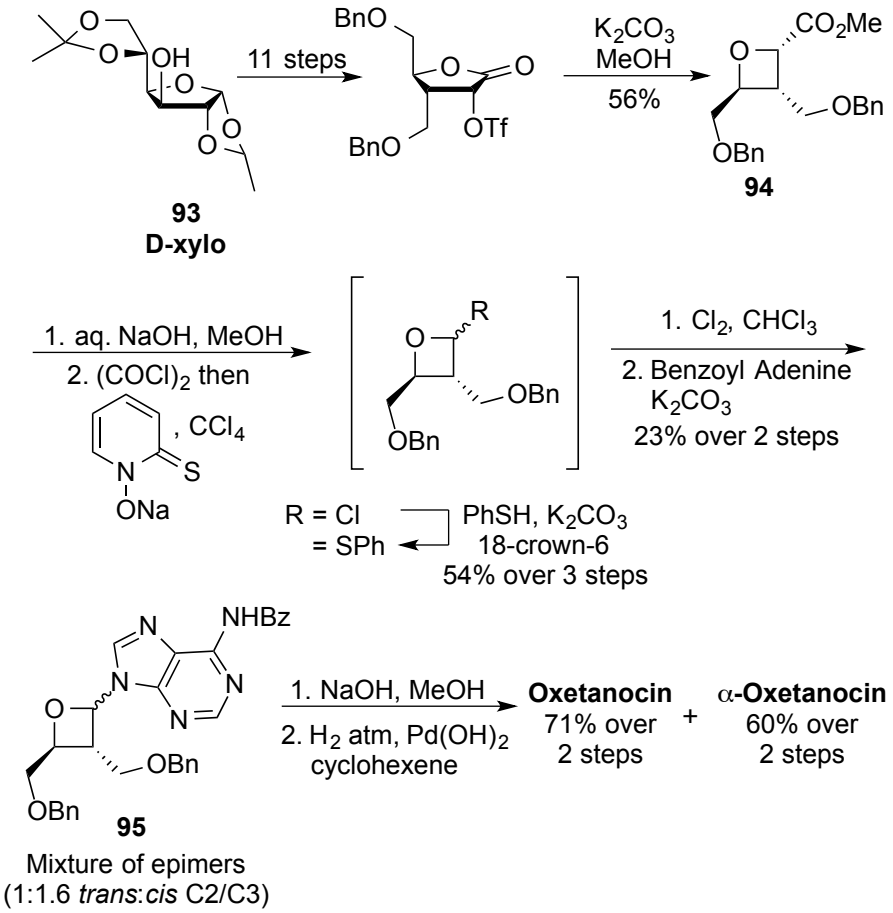
Fleet later demonstrated that the ring contraction occured with C3-deoxy 3-substituted oxetane products (Scheme 25).[169] In this case, inversion of configuration was observed for both D-ribono (**89**) and D-arabinono (**91**) derived substrates on the ring contraction The yields for the 3-alkyl oxetanes **90** and **92** were generally lower than that for the previously reported 3-ether substituted oxetanes due to the increased tendancy of the alkyl triflate lactones to undergo elimination reactions rather than ring contractions.

Scheme 25. Synthesis of 3-Alkyl Oxetanes 90 and 92



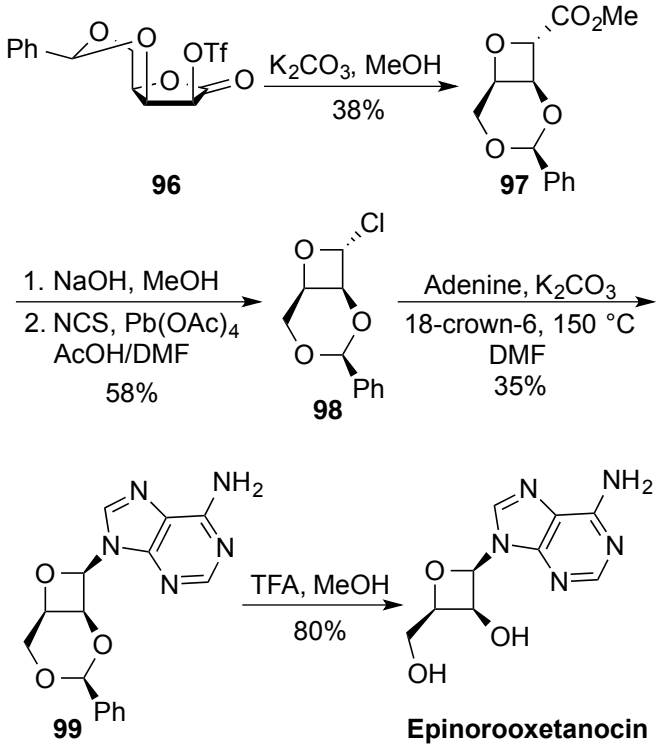
This ring contraction strategy enabled the synthesis of the natural product oxetanocin and the α-epimer (Scheme 26).[170] From the triflate lactone, derived from D-xylo **93**, ring contraction using K_2CO_3 in MeOH afforded oxetane **94** with inversion of configuration. The epimer of oxetane **94** could be formed from the same triflate lactone in 3 steps; treatment with sodium trifluoroacetate and MeOH gave the inverted α-hydroxy-γ-lactone (D-arabinono lactone), followed by conversion to the triflate and ring contraction. Radical decarboxylative chlorination gave unstable α-chlorooxetane, which was immediately trapped as the sulfide with PhSK to be purified. Regeneration of α-chlorooxetane was conducted using Cl_2 in $CHCl_3$ followed by addition of benzoyl adenine to give protected adenine oxetane **95** as an epimeric mixture in a 23% yield. Separation and subsequent deprotection afforded oxetanocin and α-oxetanocin in 71% and 60% yields respectively.

Scheme 26. Synthesis of Oxetanocin and its α-Epimer



Through an almost identical route, Fleet synthesized both epimers of norooxetanocin in 15 steps from diacetal glycose.[171] Both α- and β-norooxetanocin were inactive against HIV-1 (up to a concentration of 100 μgmL^{-1}).[172] In an improved sequence, epinorooxetanocin was prepared from lactone triflate **96**, itself prepared in 2 steps (Scheme 27).[172] Ring contraction using the standard conditions afforded oxetane **97**. To access α-chlorooxetane **98**, hydrolysis of the ester, followed by treatment with NCS and lead tetraacetate, gave a single stereoisomer in a 58% yield. The chloride was displaced with adenine to give nucleoside oxetane **99** as a single epimer, which was subsequently deprotected using TFA, affording epinorooxetanocin with an 80% yield. In vitro studies of epinoroxetanocin showed significant activity against HIV-1 (IC_{50} = 0.5–1.5 μgmL^{-1}) which was a similar activity to oxetanocin (IC_{50} = 0.5–1.5 μgmL^{-1}).

Scheme 27. Synthesis of Epinoroxetanocin



In 1992, Saksena developed the use of mesylate and tosylate groups for the ring contraction under aqueous hydrolytic conditions to form oxetane carboxylic acids with high yields.[173] Gumina and Chu used the conditions reported by Saksena in their synthesis of the enantiomer of oxetanocin.[174] 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.[170]

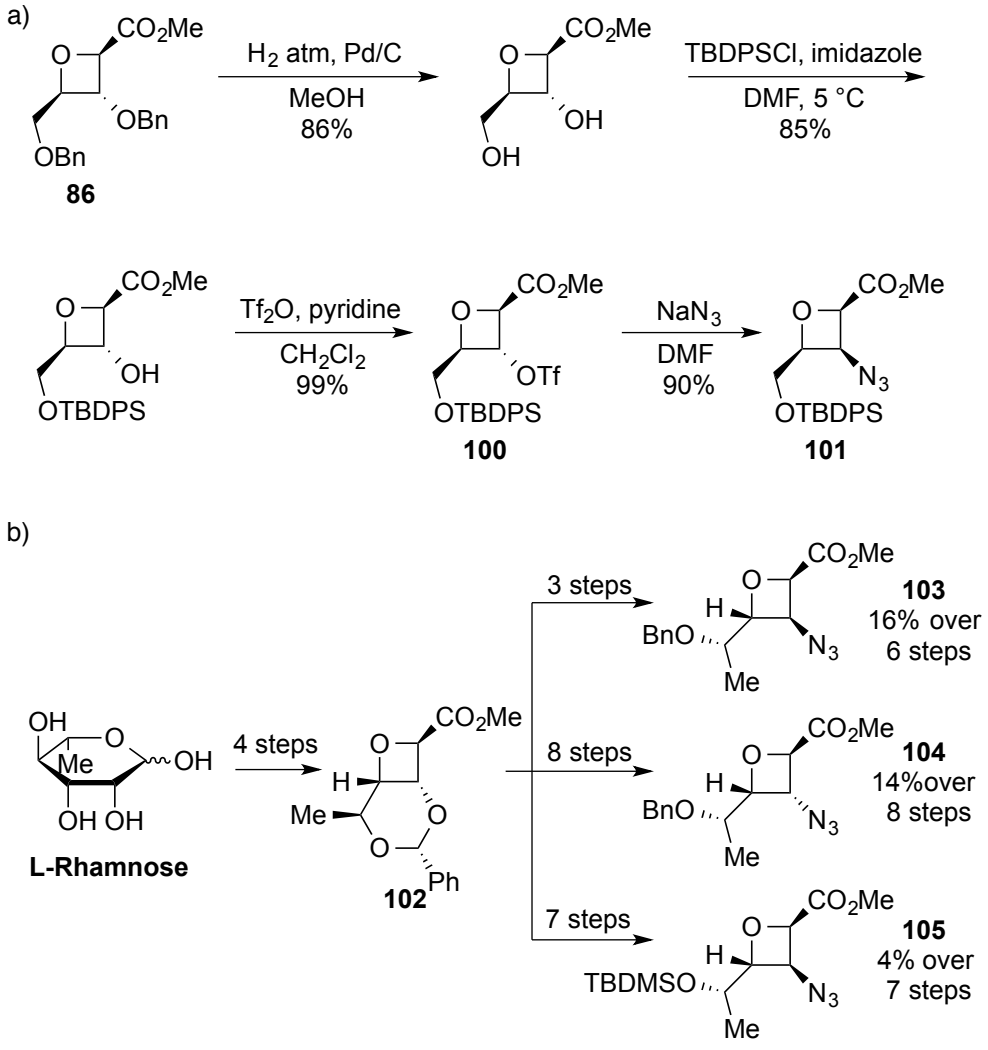
Functionalization and Applications of Oxetanes Derived from Sugars

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

C3 Functionalization. Fleet and co-workers showed that 2-ester oxetanes could undergo a variety of transformations at C3, particularly nucleophilic displacements.[175] 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-position of the oxetane ring could be converted to the triflate using Tf_2O, and triflate **100** could be displaced with inversion by a variety of nucleophiles. Initially this was achieved using NaN_3 to form oxetane **101** and no competing elimination reactions were observed. Oxetane **102**, prepared from L-rhamnose in 4 steps,[176,178] was used to access a range of 3-azido oxetanes **103–105** in a similar manner through reduction of the acetal protecting group, triflate formation and S_N2 displacement with NaN_3 (Scheme 28b).[177,178,179] A similar sequence was conducted using D-xylose.[177]

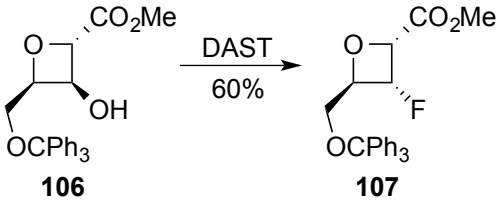
Scheme 28. Synthesis of Azido-Oxetanes



3-Hydroxyoxetane **106** was converted to a single isomer of fluoro-oxetane **107** through the use of diethylaminosulfur trifluoride (DAST), which proceeded with inversion (Scheme 29).[175] Recently,

Wessel and co-workers used DAST in the synthesis of 3-fluoro-oxetane δ-amino acids as interesting new rigid scaffolds for use in medicinal chemistry.[86] Fleet converted fluoro-oxetane and azido-oxetane derivatives to analogs of oxetanocin, and while the azido-analog showed significant anti-viral activity against HIV-1 (IC_{50} = 6 μgmL^{-1}), it was less than oxetanocin itself.[175]

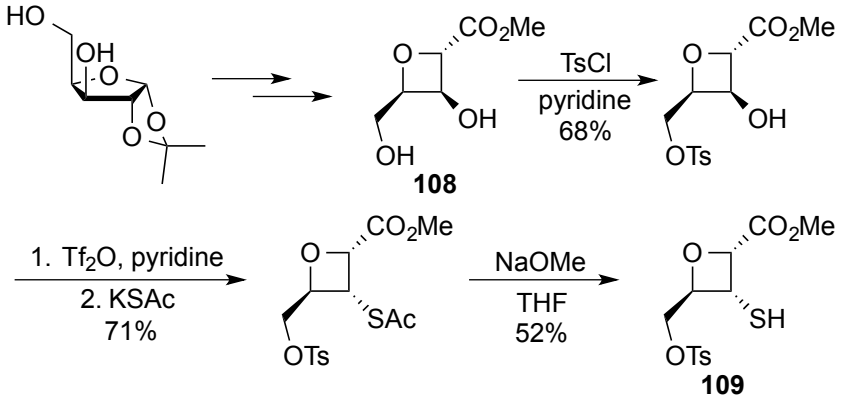
Scheme 29. Synthesis of Fluoro-Oxetane 107 using DAST



106 **107**

In 1997, Sakya and co-workers synthesized 3-thiol oxetanes from oxetane **108** (Scheme 30).[180] 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 formation followed by displacement with KSAc, selective for the secondary triflate, and deprotection.

Scheme 30. Synthesis of Thiol-Oxetane 109

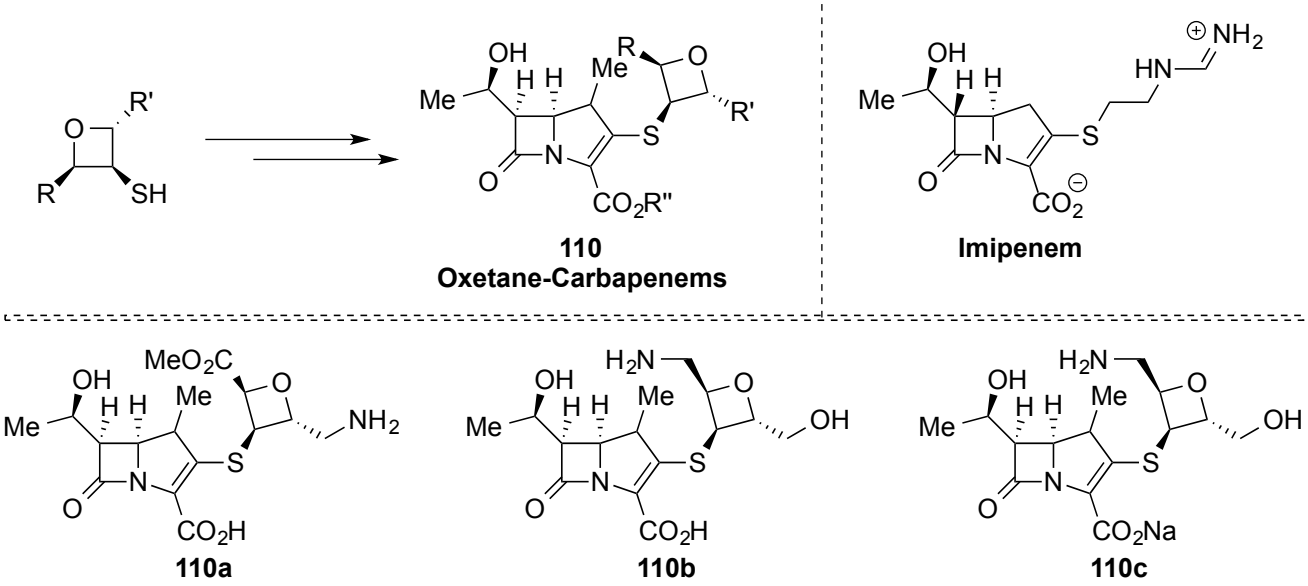


108 **109**

These thiol-oxetanes were subsequently used in the synthesis of a variety of oxetane carbapenems **110** and to determine their anti-bacterial 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 *S. aureus*) compared with the broad spectrum antibiotic imipenem,[181] but

showed similar activity against Gram-negative bacteria (*E. coli* and *P. aeruginosa*). Oxetane carbapenem **110a** was also shown to be more stable to hydrolysis by hog kidney dehydropepeptidase (DHP) than imipenem.

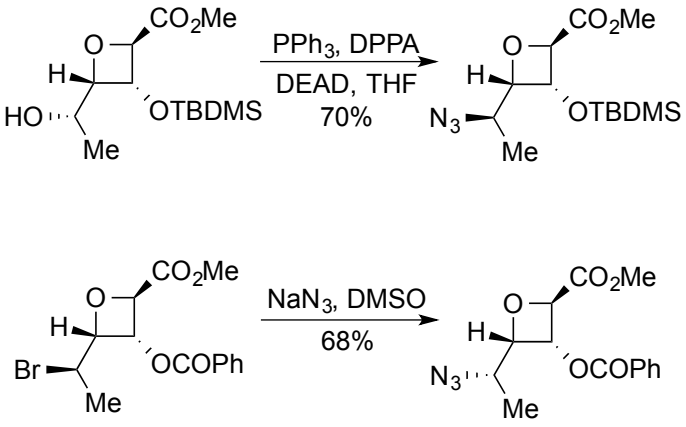
Table 6. Structual Activity Relationship of Oxetane Carbapenems



		Minimum Inhibitory Concentration (MIC) / μgmL^{-1}			
Organism	Strain	Imipenem	**110a**	**110b**	**110c**
E. coli	ATCC 25922	0.12	0.25	0.12	0.12
P. aeruginosa	ATCC 27853	2	128	16	64
S. aureus	ATCC 28213	≤ 0.06	1	0.12	0.12
Relative hydrolysis to hog DHP		100	< 1	-	-

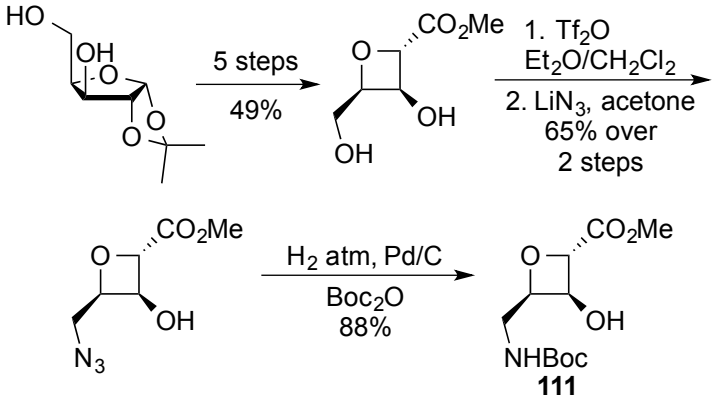
C4-Functionalization. Oxetane derivatives have been developed as isosteres for dipeptides.[182] Towards this aim, Fleet incorporated an azide group at the C4 position by two routes: a Mitsunobu reaction with PPh_3, DEAD and diphenylphosphorylazide (DPPA) and also a displacement reaction of an alkyl bromide using sodium azide (Scheme 31).[183]

Scheme 31. Synthesis of Alkyl Azide-Oxetanes



Towards novel oxetane amino acids, Wessel and co-workers from Roche reported that the azide moiety could be incorporated through the displacement of a triflate (Scheme 32).[86,87] These primary azides were subjected to hydrogenolysis followed by in situ protection using Boc_2O to give protected primary amino-oxetane **111** in good yields.

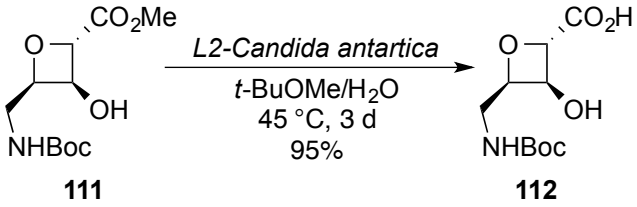
Scheme 32: Synthesis of a Protected Amino-Acid Oxetane



Wessel achieved hydrolysis of the methyl esters using 1 N LiOH in THF with a quantitative yield, and it could also be achieved enzymatically with pig liver esterase (Scheme 33).[86] Acidic aqueous work up led to degradation of oxetane **112**; therefore, the reaction was screened in microaqueous reaction systems (organic solvents with a small amount of water added). It was shown that lipase L2 from *Candida antartica* provided the best activity, and carboxylic acid oxetane **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 yield was obtained. A related oxetane monomer was incorporated into a β-turn region of cyclo-decapeptide gramicidin S, which caused a well-defined cyclic hairpin structure in solution.[184]

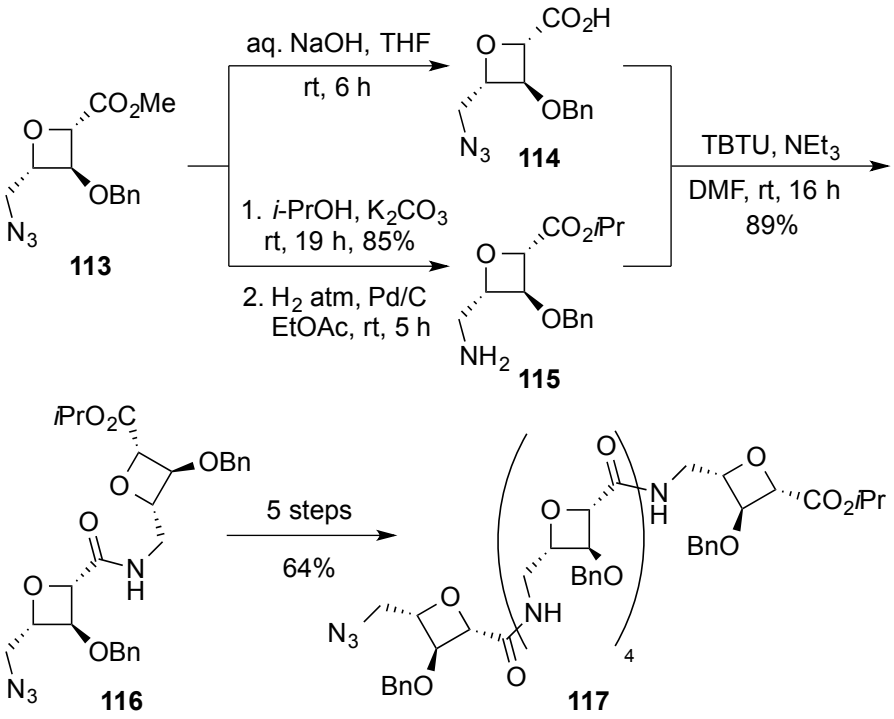
Scheme 33. Hydrolysis of Ester Oxetane using L2-*Candida antartica*



While investigating the preferred secondary structures of homo-oligomers 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 lactamisation and oligomerisation which was observed with the 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 homo-oligomers up to the hexamer were successfully synthesized. Hexamer **117** was built up over 5 steps with a very good yield of 64% from dimer **116** (Scheme 34). Conformational analysis of these oxetane β-amino acid oligomers by IR and NMR, involving NOE, TOCSY and 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-OTBS substituent did display a defined conformation in chloroform and 2,2,2-trifluoroethanol, enforced

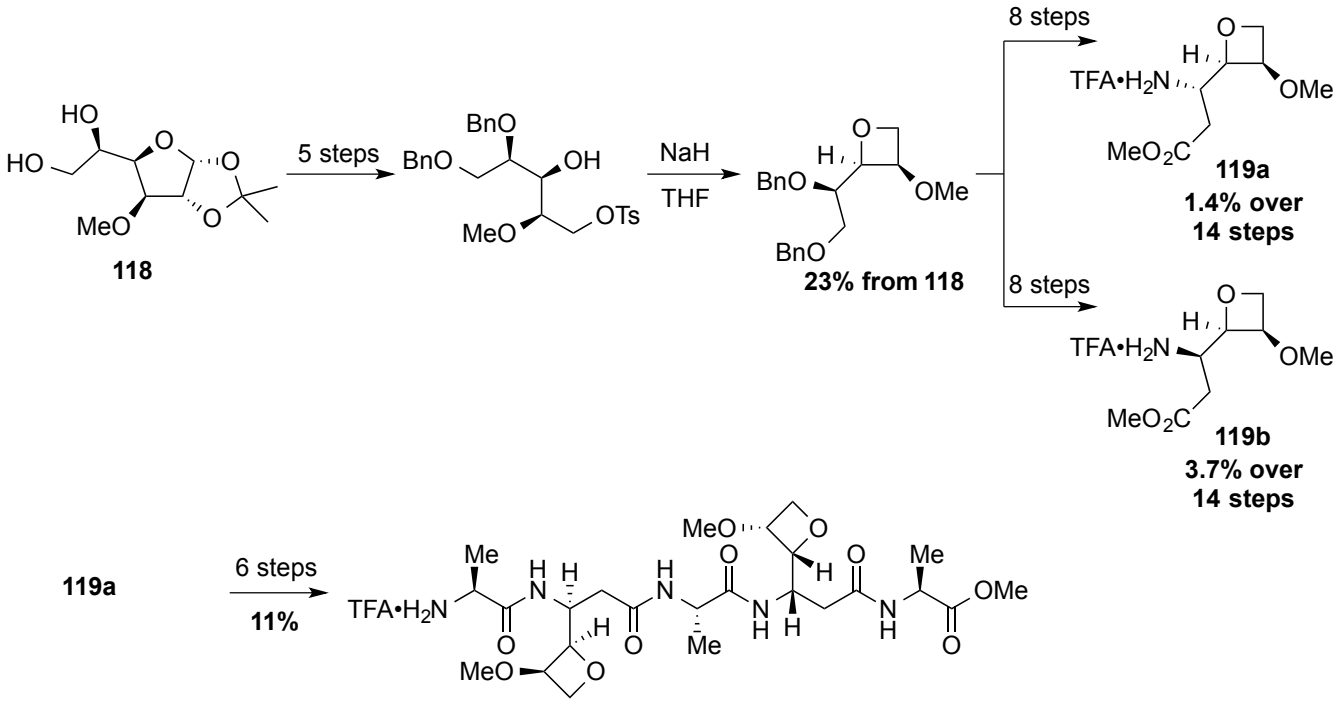
through steric interactions without the influence of H-bonding.[188] Cyclic tetrameric derivatives have also been prepared.[189]

Scheme 34. Synthesis of Oxetane Hexamer 117



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 **119** were prepared from sugar derived diol **118** in 14 steps with an overall yield of 1.4% and 3.7%, respectively (Scheme 35). Oxetane formation was achived via a Williamson etherification using NaH in THF. The amine stereocentre was introduced using an aza-Michael addition. Oxetane β^3-amino acid **119a** was incorporated into tri– and penta-α,β-peptides using standard peptide coupling conditions,[191] with L-ala derivatives. Conformational analysis using NMR, molecular dynamics and circular dichroism indicated the presence of a well-defined folded conformation that involved hydrogen-bonding.

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



3.1.4. Synthesis of Oxetane-Containing Nucleoside Analogs

Nucleoside analogs 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 the treatment of the herpes simplex virus,[194] zidovudine (AZT),[195] approved in 1987 as a treatment for HIV, and more recently entecavir[196] (2005) and sofosbuvir[197] (2013) as approved treatments for hepatitis B and C, respectively (Figure 13).

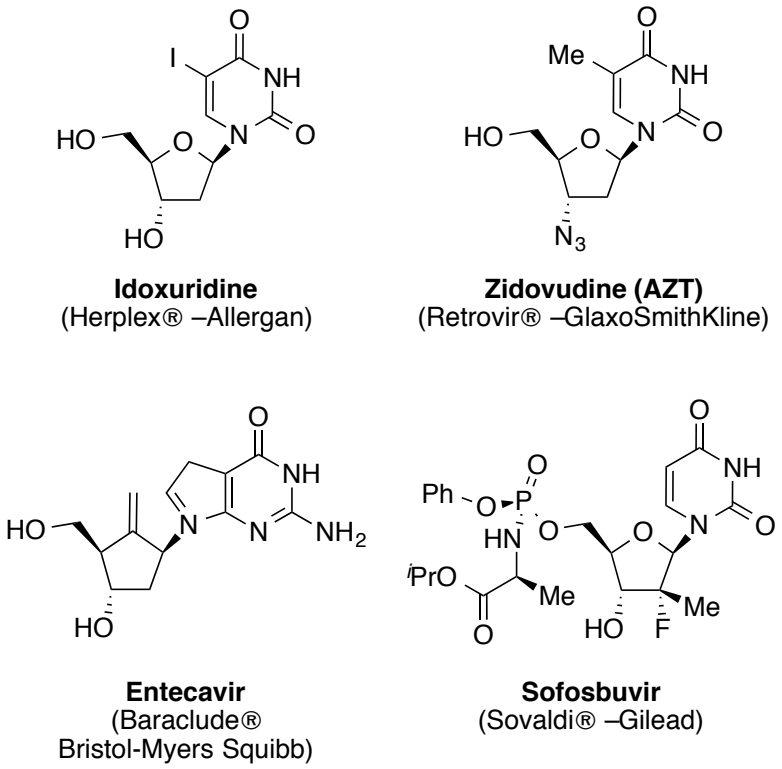
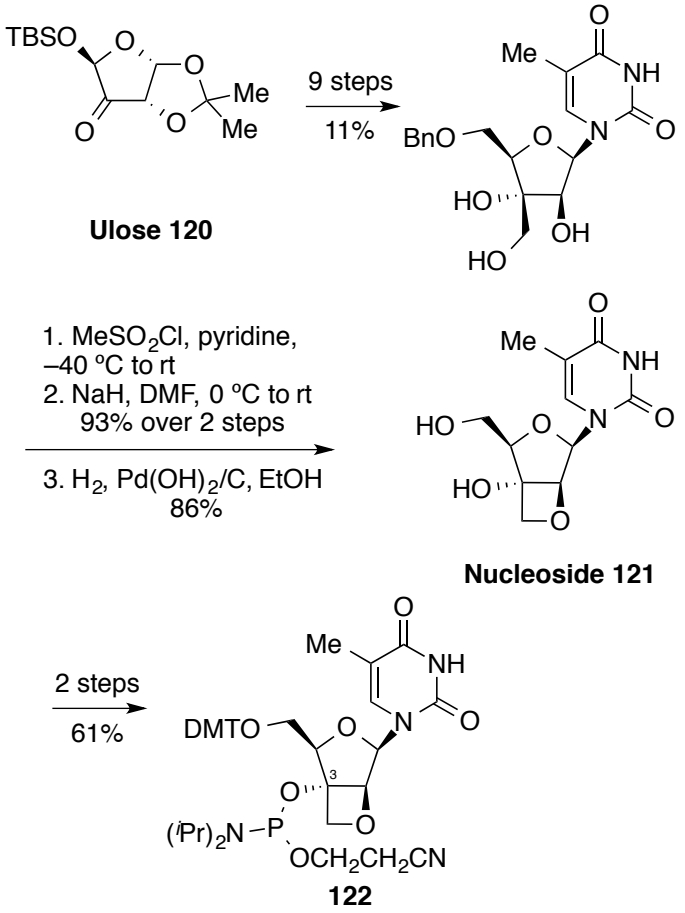


Figure 13. Examples of Marketed Nucleoside Antivirals.

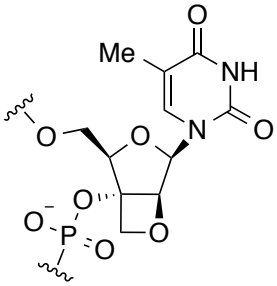
Toxic side effects and development of resistance to existing therapies[198,199] means there has been a continued drive in this area to find novel nucleoside based therapeutics with optimal physicochemical properties. Several groups in recent years have investigated incorporating oxetanes, in addition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

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

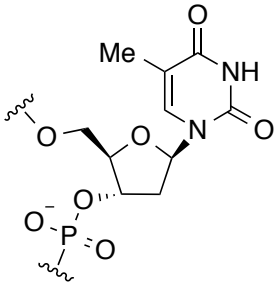


Several modified 14-mer ONs were synthesized along with a 9-mer variant, and the thermal stabilities of their duplexes with single stranded DNA and RNA were determined by melting point analysis and compared to that of unmodified ON (Table 7).[201] It was found that the majority of the modified 14-mer ONs resulted in a decrease in thermal stability against both DNA and RNA with lower melting points being reported. However, 5'-X_{13}T 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.

Table 7. Melting Point Experiments to Determine the Thermal Stability of Modified Oliglionucleotides Compared to the Unmodified Reference[a]



Monomer "X" derived from 122



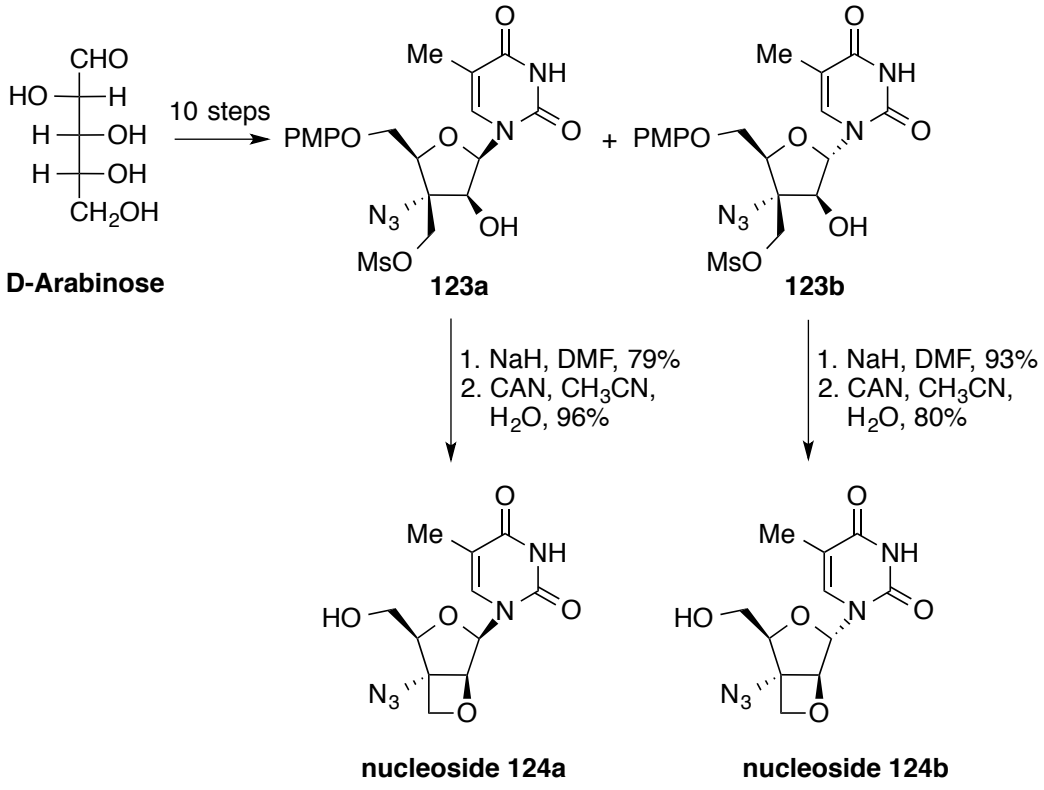
Thymidine Monomer "T"

		ssDNA duplex	ssRNA duplex
Entry	Oligonucleotide	T_m/°C	T_m/°C
1	5'-T_{14} (reference ON)	36.0	34.0
2	5'-T_7**X**T_6	36.0	33.5
3	5'-T_6**X**$_2T_6$	34.5	33.0
4	5'-T_6**X**T**X**T_5	35.5	32.5
5	5'-T_5**X**$_4T_5$	31.5	37.0
6	5'-T_3(T**X**)$_4T_3$	35.5	31.5
7	5'-**X**$_{13}$T	58.0	49.0
8	5'-GTGATATGC (reference ON)	26.0	26.5
9	5'-G**X**GA**X**A**X**GC	34.5	34.5

[a]Measured at 260 nm in medium salt buffer: 1 mM EDTA, 10 mM Na_3PO_4, 140 mM NaCl, pH 7.2. Concentration of each strand 2.5 μM; G = 2'-deoxyguanosine monomer; A = 2'-deoxyadenosine monomer; C = 2'-deoxycytidine monomer; T_m = melting point determined as the maximum of the first derivative of the absorbance vs temperature curve.

In 2001, Nielson published a study exploring the anti-HIV activity of a conformationally restricted nucleoside analog of AZT featuring an oxetane motif.[202] 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** were then tested against HIV-1 in MT-4 cell lines, in both cases, no anti-HIV activity was observed at 300 μM.

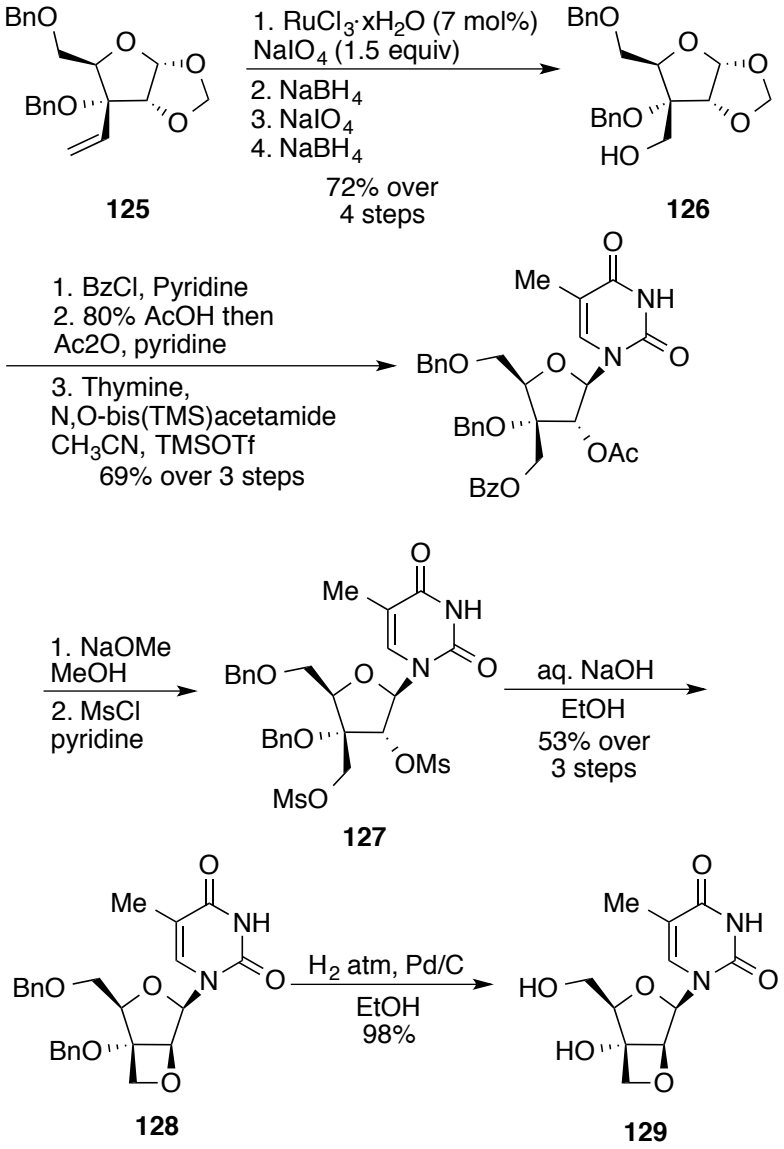
Scheme 37. Overall Synthetic Strategy for the Synthesis of Nucleosides 124a/b



In 2004, Sharma and Nielsen reported the synthesis of oxetane-containing [3.2.0]bicycloarabinonucleoside **129** of interest for potential in anti-sense and anti-gene technology, from alkene **125** (Scheme 38).[203] The key step of the synthesis involved the oxidative cleavage of the

terminal alkene to give alcohol **126** using in situ formed RuO_4 (from $RuCl_3 \cdot xH_2O$ and $NaIO_4$). In the second step of this oxidative cleavage, the addition of $NaBH_4$ re-converted the α-ketol (formed from over oxidation) back to the diol as well as reducing any active Ru species. After protecting group manuipulation, thymine was used to displace the acetate at the anomeric centre. Deprotection of the benzoyl and acetyl protecting groups followed by mesylation afforded di-mesylate **127**. Selective hydrolysis of the primary sulfonate ester of the primary mesylate followed by a Williamson etherification afforded oxetane bicycle **128**. Benzyl deprotection gave oxetane **129**.

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



Chattopadhyaya explored the synthesis and anti-sense effects of 1',2'-locked oxetane-containing nucleosides.[204,205] Extensive studies on the effects of replacing either thymine or cytosine residues in antisense oglionucleotide (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 towards endonucleoase with stability increasing with increasing levels of modification. The modifications led to a loss in thermodynamic stability, which could be improved by introduction of a dipyridophenazine (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 by nucleoside **131** was significantly improved compared to AON-RNA duplexes modified with nucleoside **130**.[205]

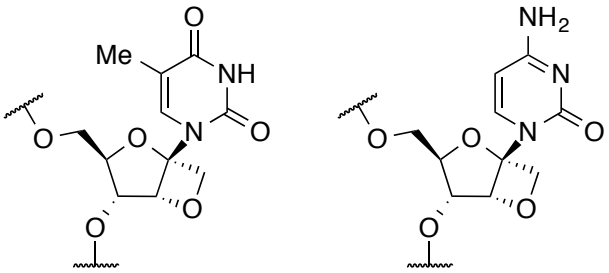
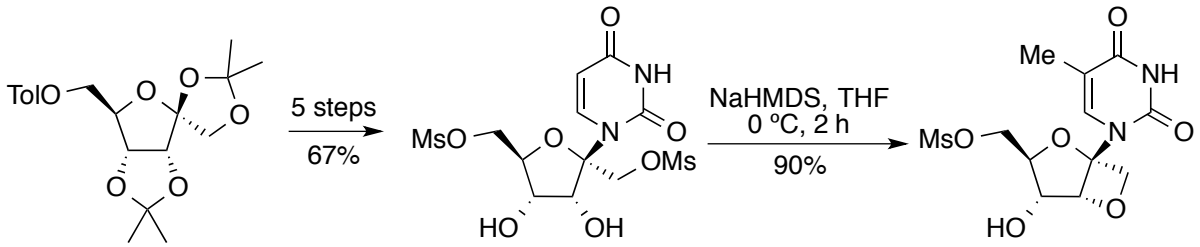


Figure 14. Structures of 1',2'-Locked Oxetane-Containing Nucleosides **130** and **131**.

In 2005, Chattopadhyaya developed routes to oxetane-containing 1',2'-locked nucleosides from protected furanose derivatives.[206] The oxetane ring forming step involved base mediated Williamson etherification with either a mesyl or tosyl leaving group, for example the synthesis of the uracil derivative **132** (Scheme 39). Synthesis of guanine and adenine derivatives was achieved via a similar strategy, which allowed the synthesis of the oxetane-containing nucleosides on multigram scale.[206] In 2014, Komsta 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 (IC_{50} = 10 μm).[207]

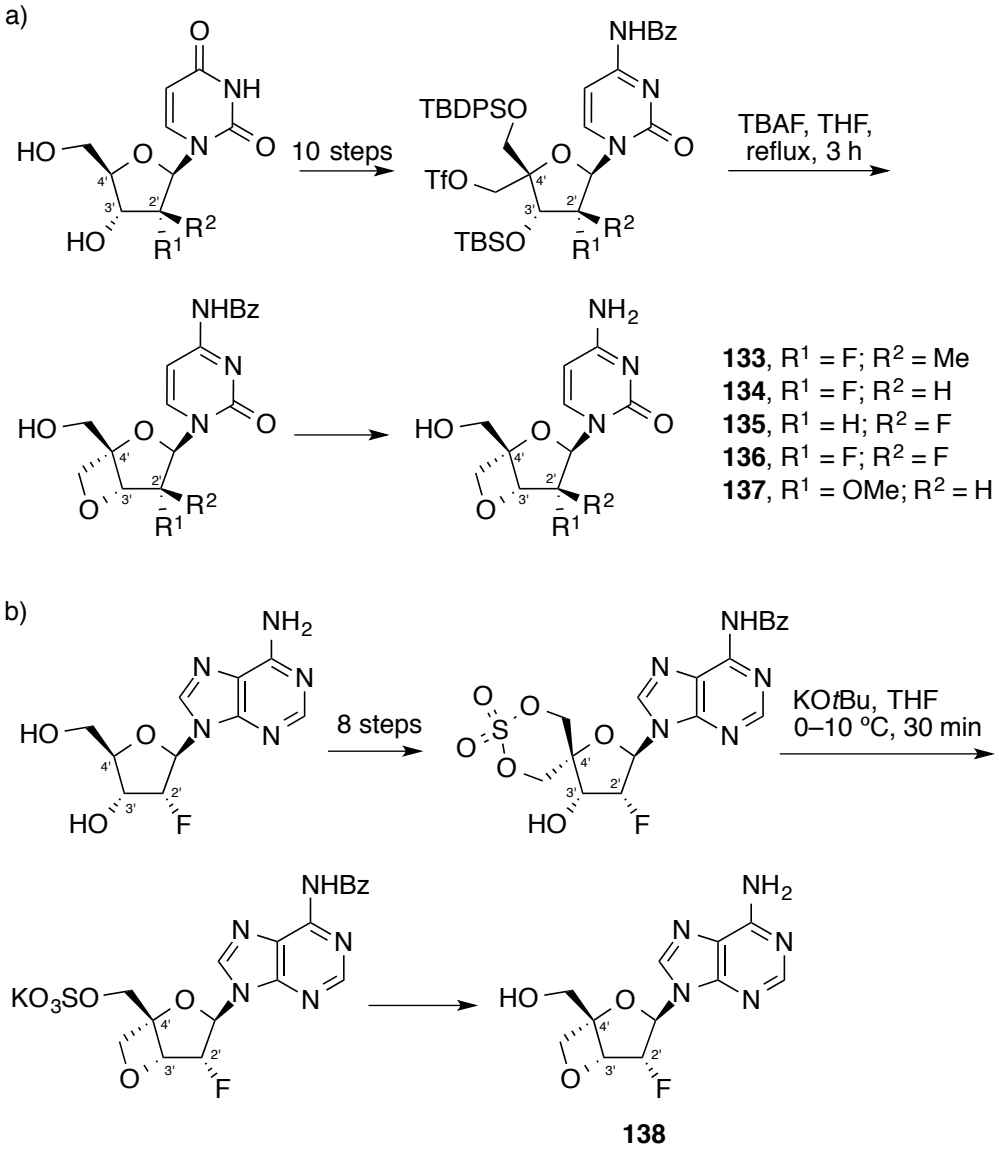
Scheme 39. Synthesis of 1',2'-Locked Oxetane Nucleoside



Nucleoside 132

Interest in nucleosides including an oxetane moiety as antivirals for treatment of the 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 in 2010.[208] 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. The synthesis of the cytosine-based analogs 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-fluoro-adenosine (Scheme 40b). In both cases the key ring forming cyclization was a base mediated displacement of a triflate (Scheme 40a) or a cyclic sulfate group (Scheme 40b).

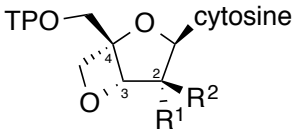
Scheme 40. Synthesis of Cytosine and Adenine Oxetane-Containing Nucleoside Analogs



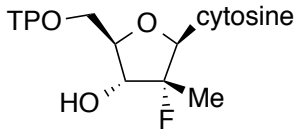
When subjected to the subgenomic replicon assay, none of the oxetane derivatives showed significant antiviral activity compared to several related non-oxetane-containing analogs. This lack of activity was postulated to be due to an inability of the modified nucleosides to be anabolised to the triphosphate derivative, an essential step for antiviral efficacy. Therefore, the triphosphate derivatives of **134**–**136** were prepared and their activity relating to the inhibition of HCV polymerase (NS5B) explored and compared to 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 the whole cell replicon studies.

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



139, R^1 = F; R^2 = H
140, R^1 = H; R^2 = F
141, R^1 = F; R^2 = F

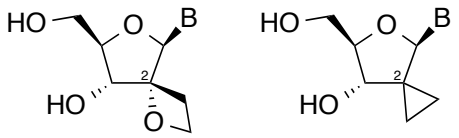


PSI-6130

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

In 2014, both Du[209] and Jonckers[210] published anti-HCV data for nucleosides furnished with a pendant oxetane group at the 2'-position. Jonckers' study indicated disappointing results for 4'-hydroxy methyl 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).

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



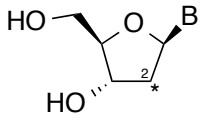
142, B = uracil
143, B = cytosine

144, B = cytosine

Nucleoside	EC_{50} (μM)
142	>98
143	17.1
144	7.3

In Du's similar study, several 2'-oxetane derivatives were compared, unfavorably, to the 2'-tetrahydrofuran derivatives in a luciferase based genotype 1b replicon assay in Lunet cells (Table 10).[209] Only one example, compound **143**, indicated any anti-HCV activity, and this was significantly lower than the best 2'-tetrahydrofuran example. In the two studies, different anti-HCV activites were calculated for nucleoside **143**; this was likely due to the different assays used in the studies.

Table 10. Anti-HCV Activity of Pyrimidine Nucleosides

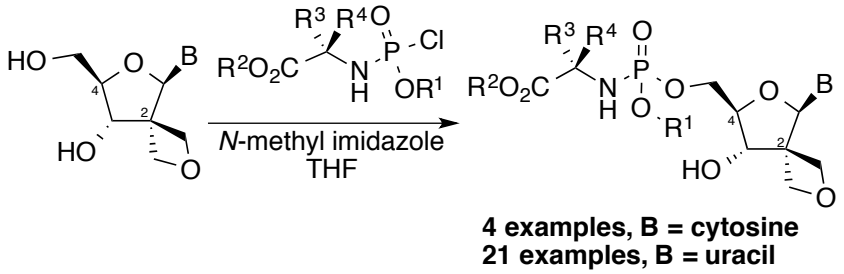


Nucleoside	B	*	EC_{50} (μM)
142	Uracil		>100
145	Uracil		>100
143	Cytosine		56.6
146	Cytosine		>100
147	Uracil		>100
148	Uracil		14.9
149	Cytosine		>100
150	Cytosine		>100

In both studies, by Du[209] and Jonckers,[210] a prodrug strategy was successfully exploited to bypass the restrictive phosphorylation steps. In Jonckers' study 25 phosphoramidate derivatives were prepared from the 4'-hydroxymethyl derivative, using *N*-methyl imidazole (Scheme 41). The anti-HCV activity of each compound was investigated, and generally very promising EC_{50}'s in the low μM range were

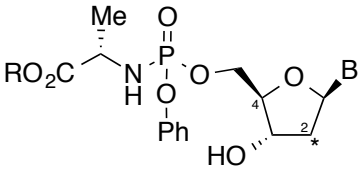
observed.[210] Additionally, cytotoxicity up to a 98 μM concentration was only observed in one of the compounds.

Scheme 41. Synthesis of Oxetane-Containing Nucleoside Prodrugs



Du 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).[209] Once again no cytotoxicity was observed up to concentrations of 100 μM. As with Du's 2010 study, triphosphate derivatives **153**-**154** were also prepared. These examples demonstrated more promising results than the corresponding tetrahydrofuran-containing analogs and the 4'-hydroxymethyl derivatives against NS5B polymerase and its S282T mutant (Table 12).[209]

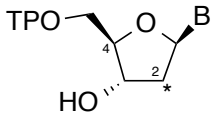
Table 11. Anti-HCV Activity Data for the Prodrug Nucleoside Analogs in Du's Study



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

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

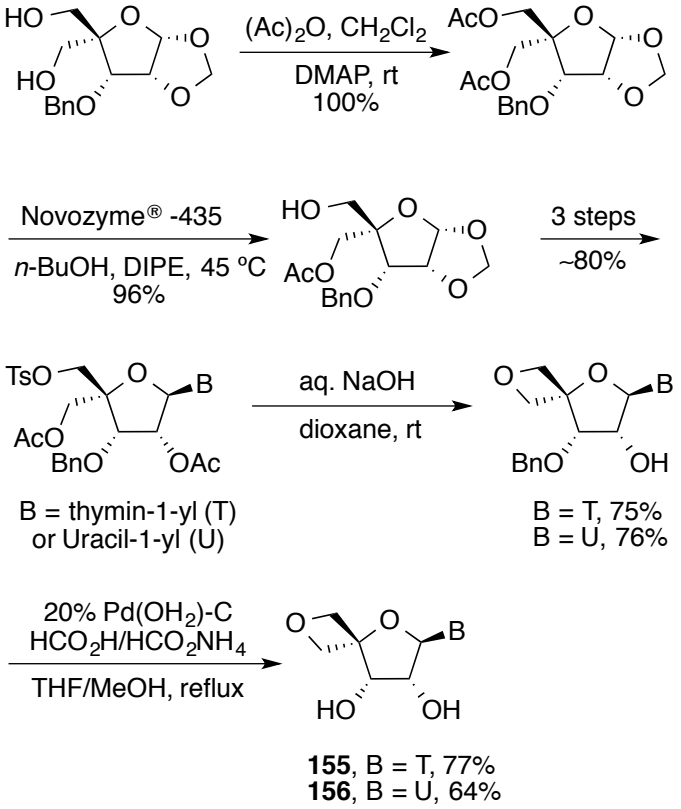


153a-b, B = uracil
154a-d, B = cytosine

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

Prasad and co-workers identified oxetanoribonucleosides as potentially interesting antiviral agents and in 2014 developed a synthesis of *C*-4'-spiro-oxetanoribonucleosides utilizing a diastereoselective Novozyme-435 catalyzed deacylation step. In just 7 moderate to high yielding steps both the thymine and uracil spironucleoside derivatives **155** and **156** could be formed (Scheme 42).[211]

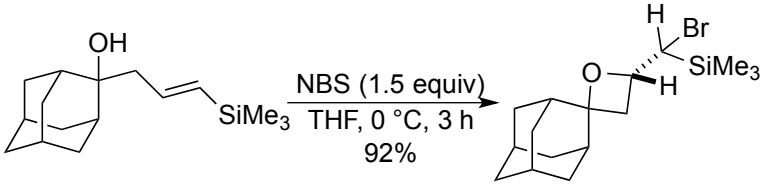
Scheme 42. 7 Step Synthesis of *C*-4'-Spiro-Oxetanoribonucleosides 155 and 156



3.1.5. Oxetane Synthesis Through Electrophilic Halo-Cyclization of Alcohols

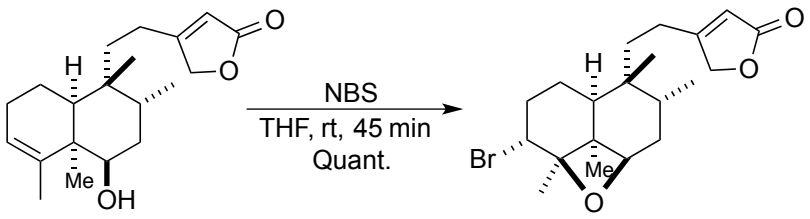
Intramolecular halo-etherification has been shown to be a viable strategy for the synthesis of oxetanes, but has received relatively little investigation. Throughout the 1980s and early 1990s a variety of 4-*exo*-*trig* electrophilic cyclizations to form oxetanes were discovered largely using NBS and often with constrained structures. In 1980, Magnus found that vinyl silane **157** favored an *exo*-cyclization process giving adamantyl oxetane **158** in a very good yield of 92% (Scheme 43).[212] The THF that would result from the *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, Nishino formed oxetane **159** in a quantitative yield using NBS (Scheme 44).[213] The same reaction was used by Paquette in the synthesis of a [5.9.5]-tricyclic system closely related to jatrophatrione.[214]

Scheme 43. Synthesis of Adamantyl Oxetane through an NBS Mediated 4-*exo-trig* Cyclization



157 **158**

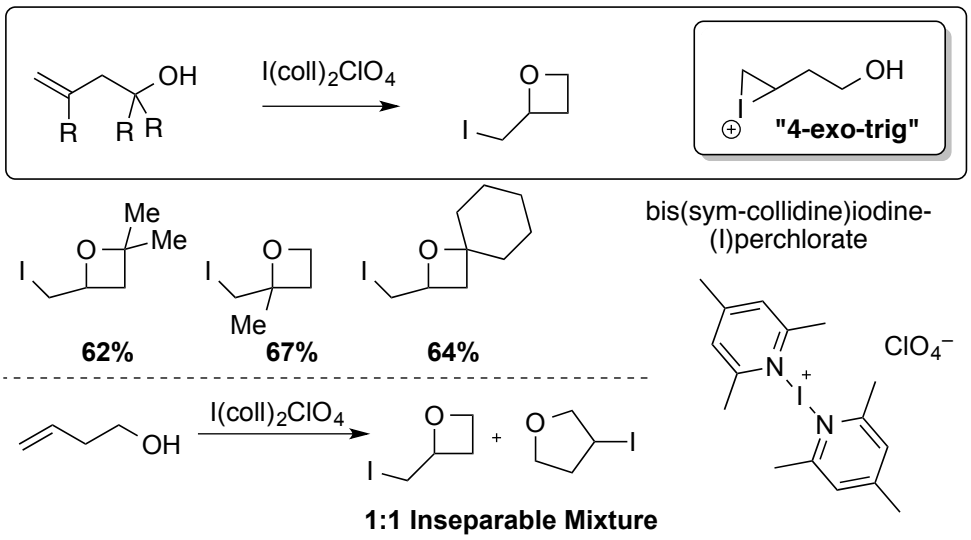
Scheme 44. Synthesis of Oxetane-Containing Diterpene Derivative



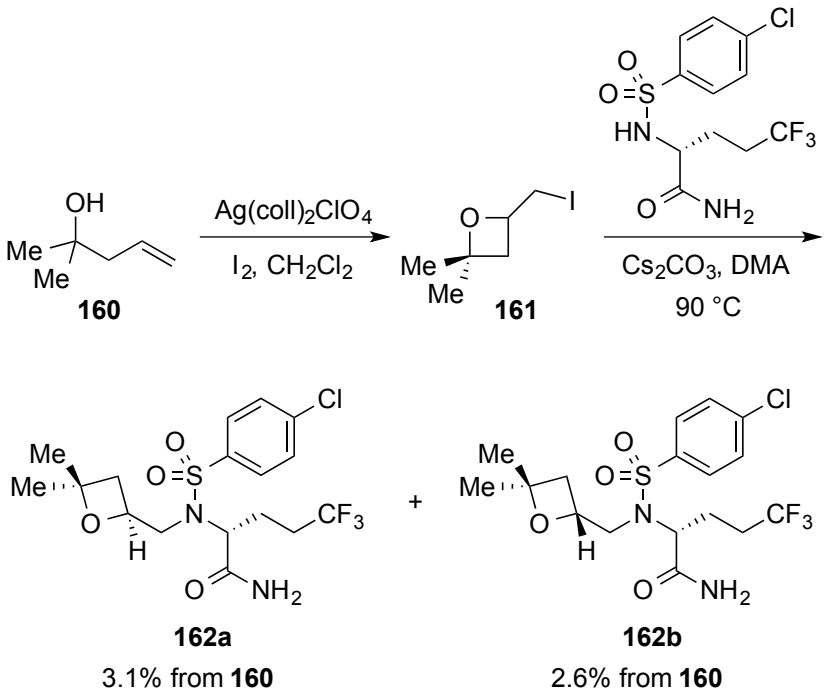
159

In the late 1980s, bis(*sym*-collidine)iodine perchlorate [$I(coll)_2ClO_4$] 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, could provide three to seven-membered ring ethers using 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 the oxetane and THF was observed (no yield given). Stepan 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).[82]

Scheme 45. Synthesis of 2-Alkyl Iodo-Substituted Oxetanes via a 4-*exo-trig* Cyclization



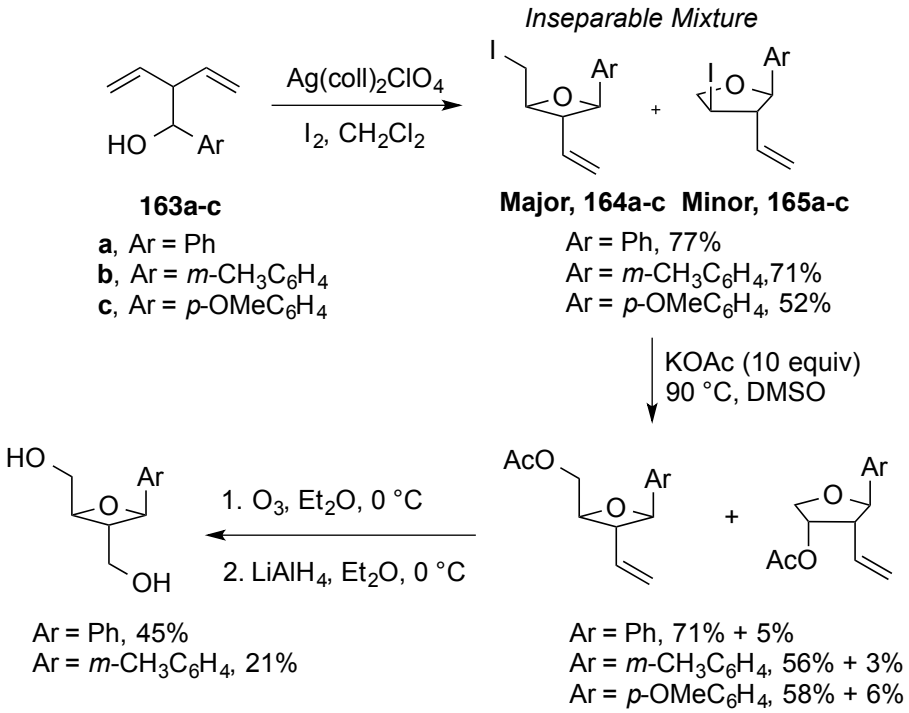
Scheme 46. Synthesis of γ-Secretase Inhibitor 162 via an Iodonium Mediated Oxetane Cyclization



Nichols used this 4-*exo-trig* halo-etherification cyclisation strategy to synthesize racemic oxetanocin A analogs, predicting that the aryl and vinyl groups on the alcohol substrate **163** would be enough to promote oxetane formation.[216] Cyclization from alcohols **163a-c** occurred using the in situ formation of bis(collidine)iodine(I) perchlorate from the silver salt to afford good yields and selectivity (oxetane:THF) for each substrate (Scheme 47). *trans*-Substituted oxetanes **164** were the major products,

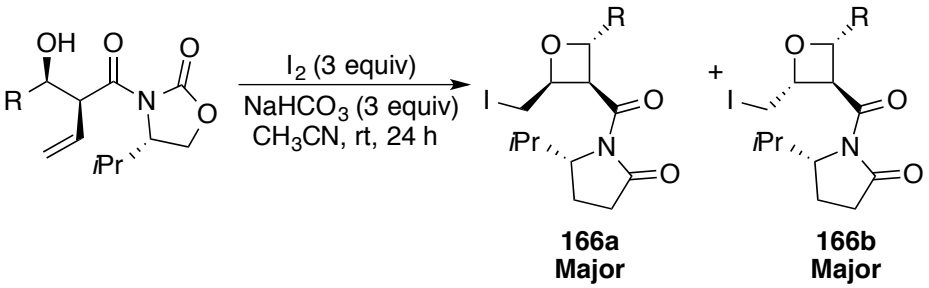
as determined by NOESY experiments, but reductive deiodination of **164a** with $LiAlH_4$ indicated that all four possible isomeric oxetane products formed in a ratio of 10:2:1.5:1. Oxetanes **164** and the respective THFs **165** could be separated after the displacement of the alkyl iodide with acetate; ozonolysis followed by reduction gave oxetanocin A analogs.

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



In 1997, an asymmetric variant of this process was achieved through the incorporation of an oxazolidinone auxilliary.[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 study, using methyl esters preferentially gave THF products.[218] Good facial selectivity was observed in the cyclization step, proposed to be due to minimising 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).

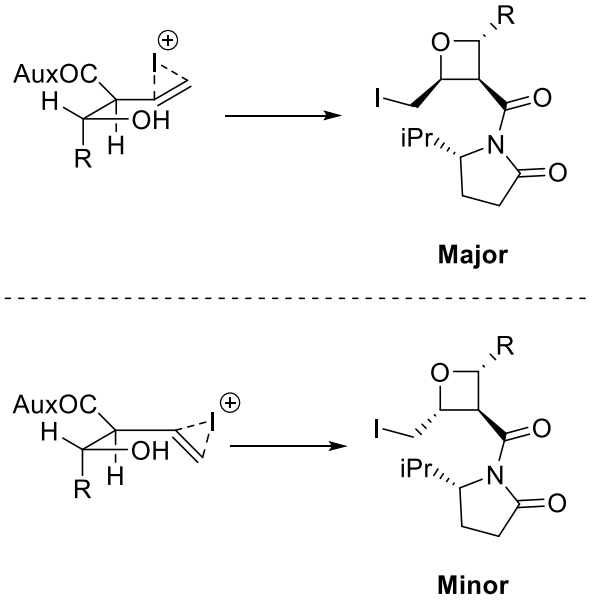
Table 13. Iodine-Mediated Cyclization of Enantioenriched Oxetanes Through the Incorporation of an Evans Auxillary



Entry	R	Yield **166** (%)	Ratio (**a**:**b**)
1	Me	63	>98 : <2
2	Et	90	82:18
3	*i*Pr	77	81:19
4	Ph	85	-[a]

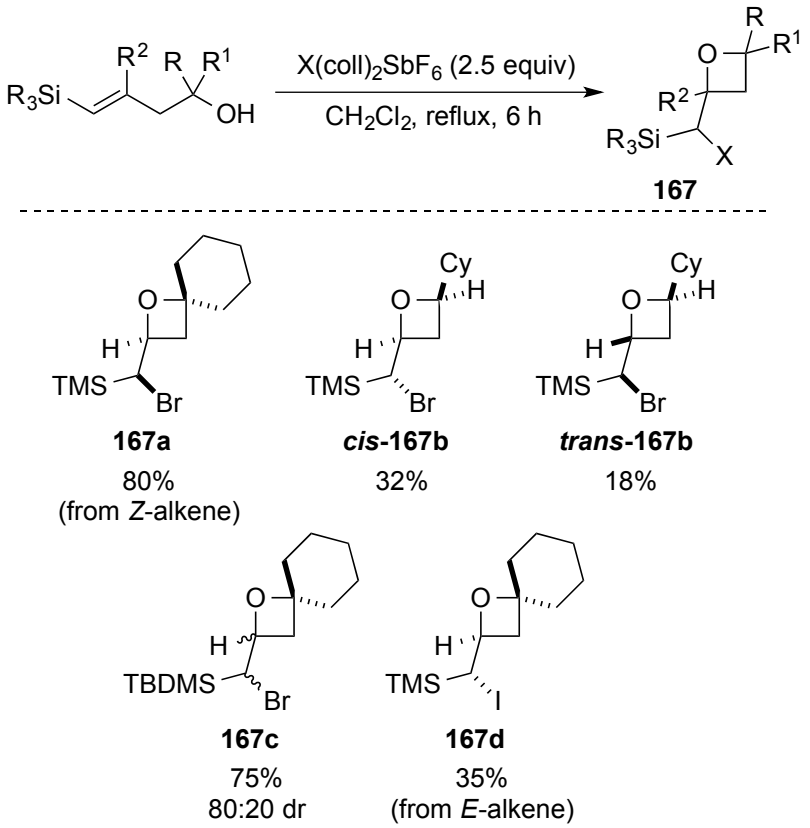
[a]Decomposition occurred.

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



exo-Cyclization of vinyl silanes was later investigated by Rousseau (Scheme 49).[219] 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**) on reaction with the bromonium reagent, $Br(coll)_2SbF_6$, 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 C=C double bond led to mixtures of diastereomers (**167c**), which could not be identified. Finally, the reactivity of the iodonium salt, $I(coll)_2SbF_6$, was investigated, but a reduced yield was obtained (**167d**).

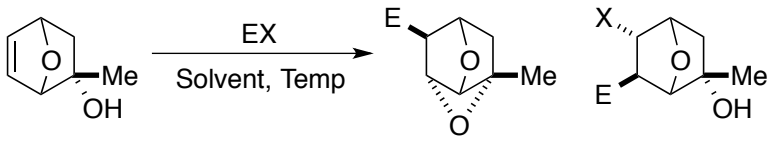
Scheme 49. Electrophilic Halo-Cyclization of Functionalized Vinyl Silanes



Similar transformations have been reported by *exo*-cyclisation using electrophilic S and Se reagents to generate oxetanes. The electrophilic addition of PhSe, using PhSCl, and etherification was first reported as an unwanted side reaction in the synthesis of a *cis*-hydrindenone, a bicyclic natural product scaffold.[220] Arjona shortly afterwards reported electrophilic addition using both PhSCl and PhSeCl with

a variety of 7-oxanorbornenic substrates.[221] The use of PhSCl was more effective at promoting etherification and gave oxetane **168a** as the major product, whereas the use of PhSeCl 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 the Electrophilic Cyclization of a 7-Oxanorbornenic Substrate



168a **168b**

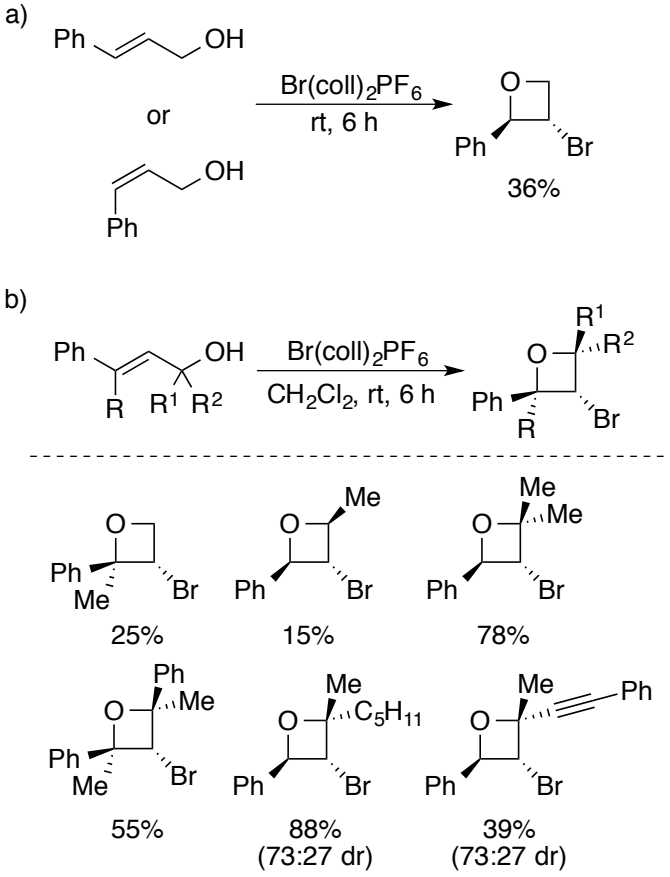
Entry	Electrophile (EX)	Solvent	Temp (**°C**)	Yield **168** (%)	Ratio **a**:**b**
1	PhSCl	$CHCl_3$	rt	-	4:1
2	PhSCl	CH_2Cl_2	–50	93	1:0
3	PhSeCl	$CHCl_3$	rt	-	1:4
4	PhSeCl	CH_2Cl_2	–78	84	9:1

The synthesis of 4-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, Rousseau showed that oxetanes (as well as other 4-membered rings) could be synthesized in reasonable yields from cinnamic alcohols through a 4-*endo trig* cyclization by using bis(collidine)bromine(I) hexafluorophosphate (Scheme 50a).[223] The *E*- and *Z*-alkenes gave the same oxetane, with the stereochemistry determined to be *trans* due to a coupling constant of 6 Hz (*cis* expected to be larger).

Examination of the influence of substituents on the 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≠R' then mixtures of diastereoisomers were observed.

These oxetanes were further functionalized in order to access oxetin derivatives, for example, through oxidative cleavage of the phenyl group with $NaIO_4$ and catalytic $RuCl_3$ (not shown).

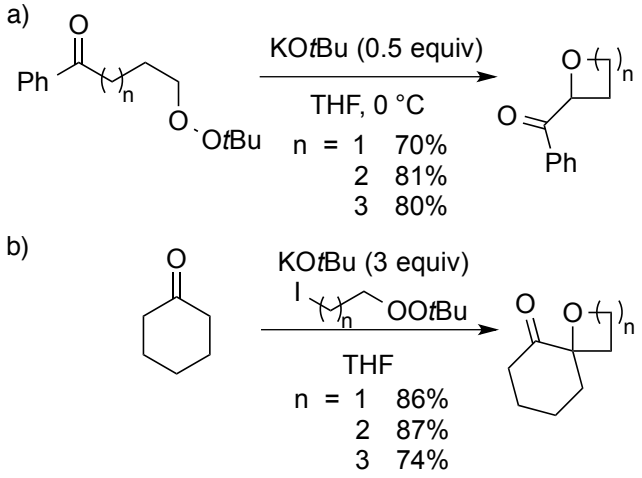
Scheme 50. Oxetane Synthesis via a 4-*endo-trig* Halo-Electrophilic Cyclization. a) Initial Result with Cinnamic Alcohols. b) Substrate Scope Accessing Highly Substituted Oxetanes



3.1.6 Other C–O Bond Forming Cyclization Approaches

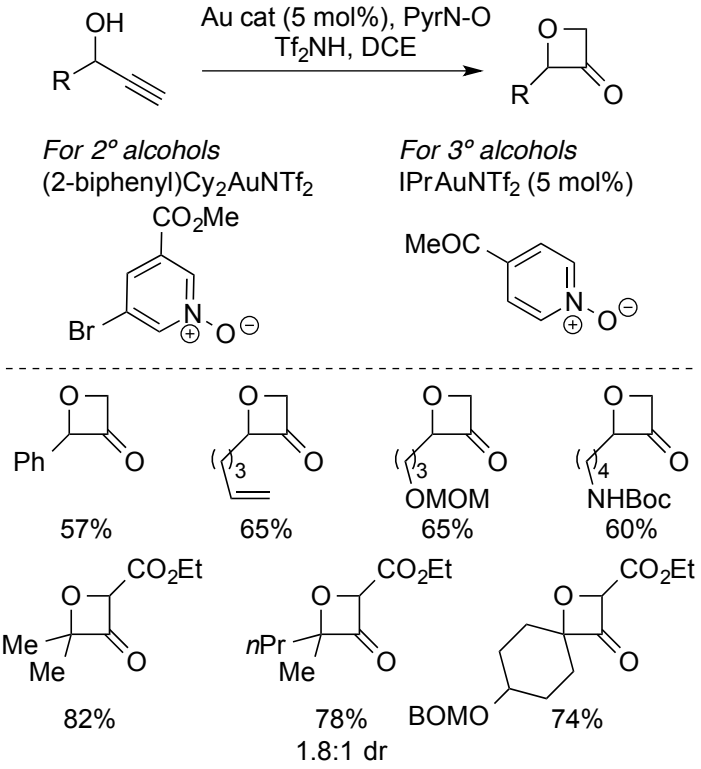
In 2014, Dussault reported the synthesis of cyclic ethers through a C–O bond formation with reversed polarity. Unlike the traditional Williamson etherification (oxyanion and electrophilic carbon), carbanions as enolate anions and electrophilic oxygen in the form of a peroxide were used.[225] Cyclization proceeded rapidly in the presence of KO*t*Bu 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).

Scheme 51. Synthesis of Oxetane, THF and THP Rings Through a Reverse C–O Bond Formation



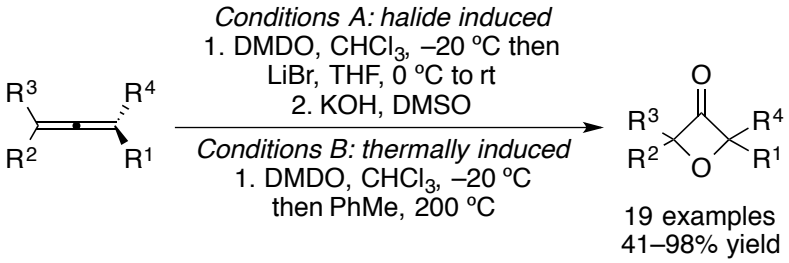
Commonly, oxetan-3-ones have been formed by intramolecular OH insertion of diazo compounds which has been previously reviewed.[5,226] In 2010, Zhang reported an alternative, whereby a gold carbene was generated from an alkyne which formed oxetan-3-ones from propargylic alcohols in one-step, using a Au(I)-catalyst (Scheme 52).[227] Functionalized secondary and tertiary propargylic alcohols were successfully employed though they required a slight modification to the catalyst and pyridine *N*-oxide additives.

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



Sharma and Williams demonstrated the formation of oxetan-3-ones in a two step sequence from allenes (Scheme 53).[228] Double epoxidation of the allene and then halide or thermally induced rearrangement of the spirodiepoxide gave the desired oxetan-3-one analogs. The different conditions for the rearrangement gave different diastereomers as the major product.

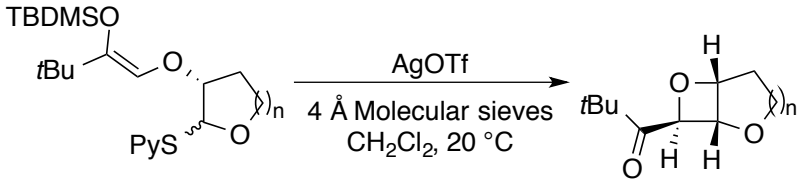
Scheme 53. Synthesis of Oxetan-3-ones in 2 steps from Allenes.



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 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).[229,230] 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 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 using either the original conditions or thiophenyl glycosides with tin chloride or ethylaluminium dichloride.[231,232]

Scheme 54. An Intramolecular *C*-Glycosidation Route to Oxetanes

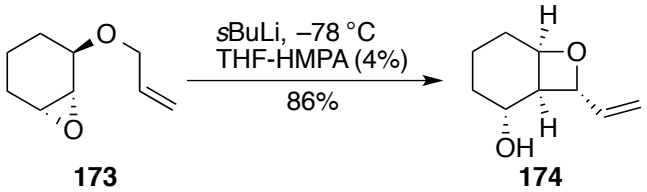


169, n = 1
171, n = 2

170, n = 1, 53%
172, n = 2, 50%

Intramolecular cyclization with epoxide opening through C–C bond formation has been used to form oxetanes. First reported in 1976 by Still, *trans*-epoxy allylic ether **173** was treated with *s*BuLi in THF-HMPA at –78 °C to form vinyl oxetane **174** regioselectively, via stereospecific cyclization of the resulting allyloxycarbanion (Scheme 55).[233] Formation of the more strained 4-membered ring over the isomeric 5- or 6-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 the intramolecular epoxide ring opening as, 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 of with *s*BuLi.

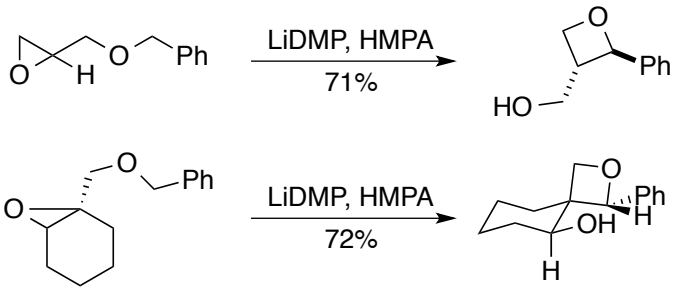
Scheme 55. Vinyl Oxetane Formation via an Intramolecular Epoxide Ring Opening Cyclization



173 **174**

Bird reported a similar outcome on treating allyl glycidyl ethers with *s*BuLi in THF-HMPA at –78 ºC; the 4-membered oxetane or 7-membered oxepane products were favored over the isomeric THF or THP.[234] In general, the oxepane product was favored, but two examples gave the oxetane as the major product due to substitutent effects. In 1986 Williams reported the intramolecular epoxide ring opening of substrates bearing a benzyl substituent to afford various cyclic ethers.[235] For oxetane examples, treatment of epoxides with 3 equiv of lithio-2,4-dimethylpiperidide (LiDMP) and 3 equiv of HMPA in THF at –78 ºC, followed by warming to 22 ºC for 2 h, resulted in cyclization (Scheme 56). Good stereocontrol was observed with the phenyl ring preferring orientations that minimized unfavorable steric interactions.

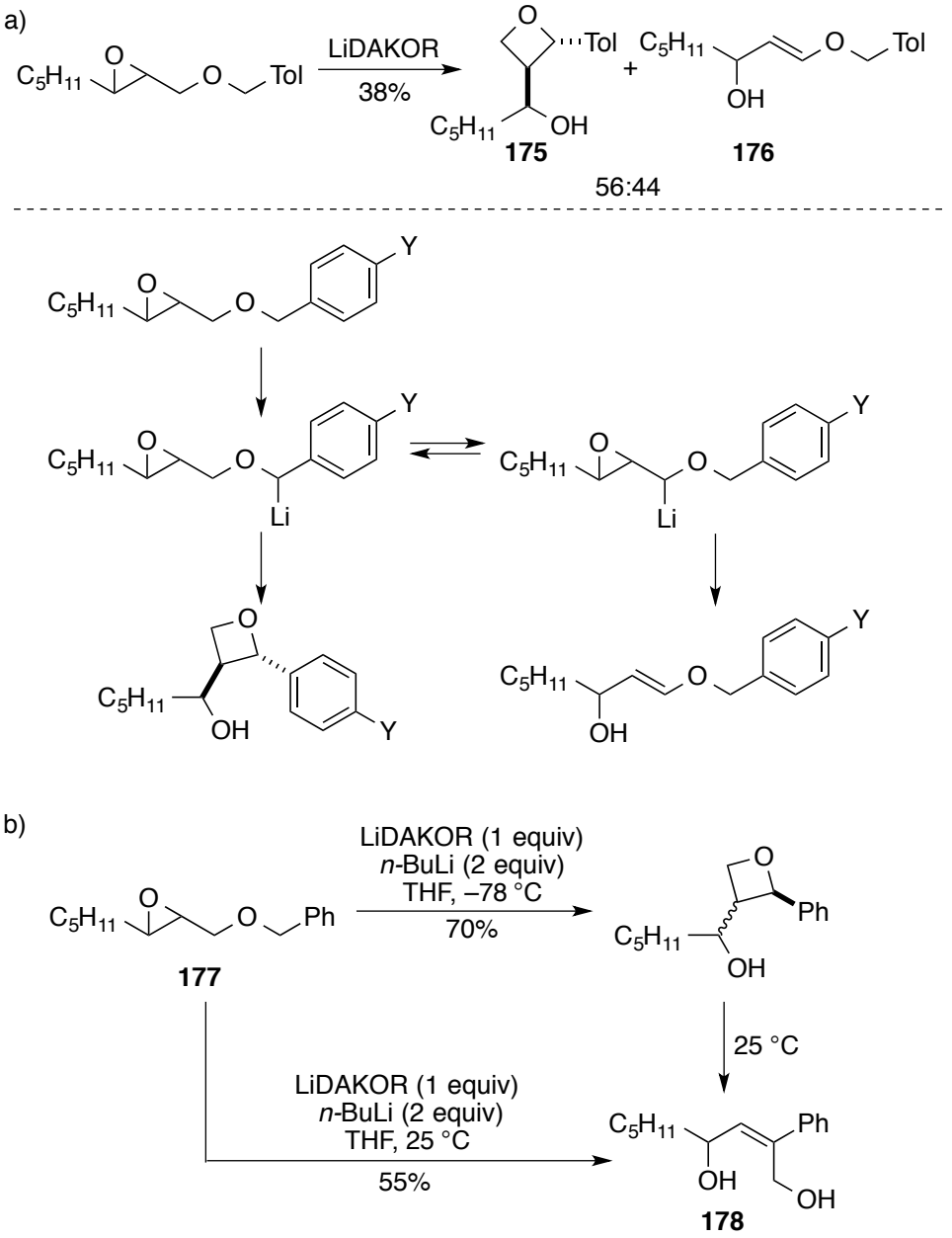
Scheme 56. Intramolecular Cyclization of Epoxy Ethers Bearing a Benzyl Substituent



Mordini 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 ºC for 15 h. Cyclization of the benzylic anion by attack at the epoxide formed 2,3-disubstituted oxetanes with complete *anti* selectivity between the C2 and C3 substituents, but in low yields due to a competing elimination reaction to form vinyl ethers **176** (Scheme 57a).[236] The electronics of the aryl group were important in determining the reaction outcomes. With electron rich examples,

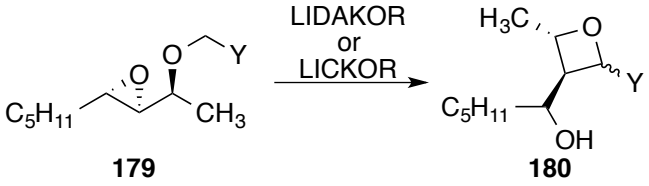
migration of the lithiated anion from the benzylic position occurred, resulting in formation of the vinyl ether product (Y = OMe, Me, and *t*Bu). Electron-withdrawing substituents favored oxetane formation unless the anion was too stable; the *p*-nitro substituent gave no reaction. When a phenyl ring was present (Y = H), the oxetane could be accessed as the only product in a 70% yield. When benzyloxy ether **177** was treated with LiDAKOR and a large excess of *n*BuLi at higher temperature, 25 ºC, *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% on treating the epoxides with LiDAKOR.[238] Subsequent treatment with *n*BuLi (4 equiv) resulted in diol formation with stereocontrol.

Scheme 57. Oxetane Formation from the Cyclization of Benzyl Epoxides



α-Substituted epoxy ethers **179** prohibited the 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 in THF at –50 ºC resulted in excellent yields of the trisubstituted oxetanes (Table 15, entry 1).

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

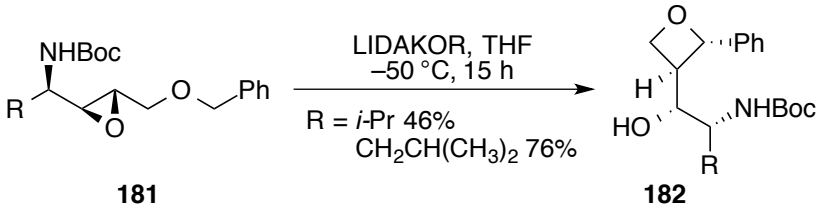


179 **180**

Entry	Y	2,3-*syn*:2,3-*anti*	Yield **180** (%)
1	C_6H_5	13:87	80
2	*p*-F-C_6H_5	12:88	81
3	CH_2=CH	2:98	80
4	C_6H_5S	78:22	86

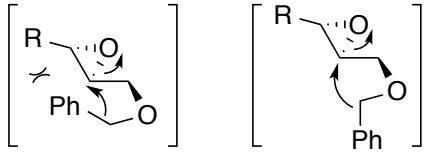
In 1997 Mordini expanded these studies to access amino alcohols bearing an oxetane moiety.[240] Benzyl epoxy ethers derived from valine, leucine and serine were treated with LiDAKOR at –50 ºC to generate the amino alcohol substituted oxetanes (Scheme 58). Employing the *E* isomers of **181** resulted 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 a 65% yield as a mixture of the *syn* and *anti* (30:70) configurations was observed.

Scheme 58. Regio- and Stereoselective Synthesis of Amino Hydroxyoxetanes



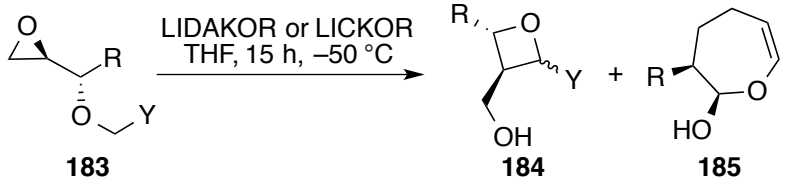
181 **182**

proposed transition states (TS)



Trisubstituted oxetanes with an hydroxymethyl substituent could be generated from mono-substituted epoxides. Terminal epoxy α-substituted ethers **183**, on treatment with LiCKOR or LiDAKOR at –50 ºC, afforded **184** (Table 16).[241] When Y was a phenyl ring or an alkyne, 2-phenyl or 2-alkynyl-oxetanes were the major products, demonstrating the preferred formation of the 4-membered ring over the isomeric THF. The relative stereochemistry of the oxetane products at C2/C3 was determined by consideration of the stereochemistry of the epoxy ether substrates, and selectivity for the *anti*-configuration of the 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 the lithiation of allyl ether and epoxide opening; however, selectivity and yield for the desired oxetane were low.[243,244]

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

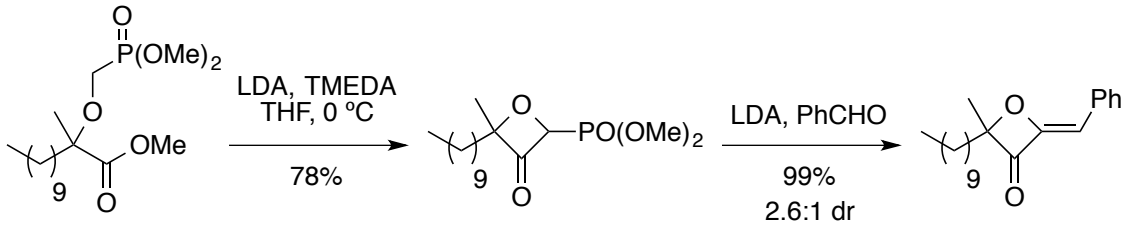


183 **184** **185**

Entry	R	Y	**184** (*syn/anti*): **185** (*syn/anti*)	Yield (%)
1	C_5H_{11}	C_6H_5	98 (*5:95*):2	53
2	CH_2OSiMe_2tBu	C_6H_5	98 (*2:98*):2	55
3	C_5H_{11}	CH≡C	98 (*20:80*):2	55
4	CH_2OSiMe_2tBu	CH≡C	98 (*15:85*):2	50
5	H	CH_2=CH	2:98 (*98:2*)	45
6	C_5H_{11}	CH_2=CH	2:98 (*98:2*)	65
7	CH_2OSiMe_2tBu	CH_2=CH	2:98 (*98:2*)	53

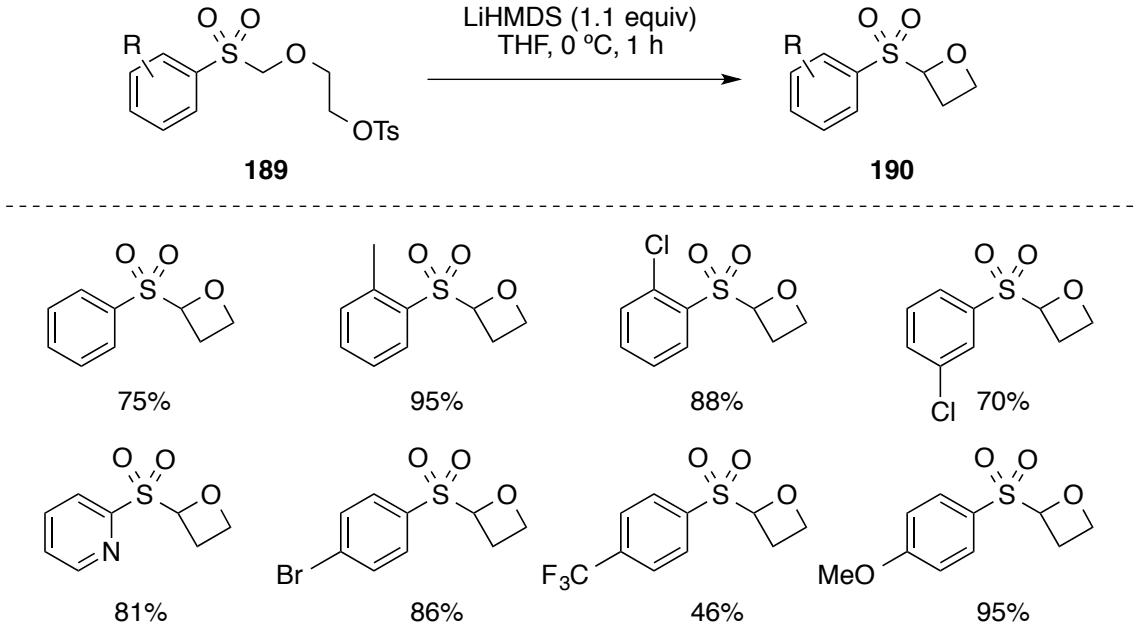
Fujioka developed a C–C bond forming route to highly substituted 2-phosphonato-oxetan-3-ones by intramolecular ester condensation (Scheme 59).[245] Cyclization precursors such as **186** were prepared from the corresponding MOM ether with TMSOTf and $P(OMe)_3$, and the cyclization was then promoted with LDA in the presence of 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 2-step procedure.

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



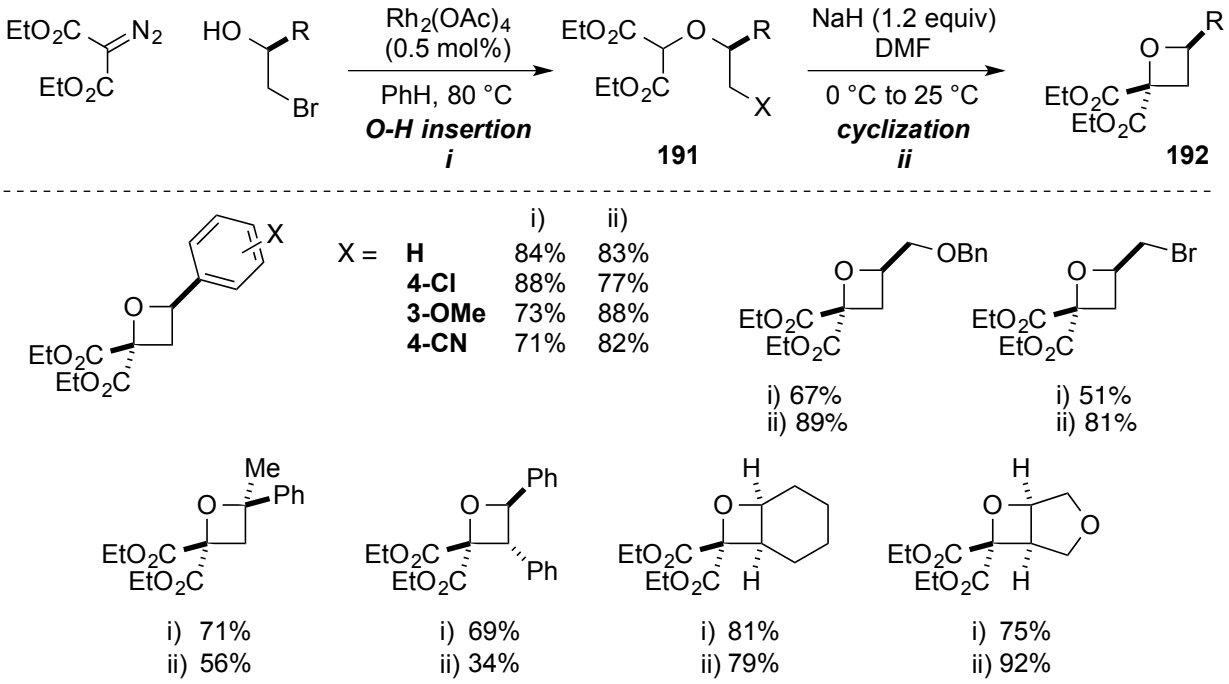
In 2014 Bull reported an anionic substitution cyclization reaction to form 2-functionalized oxetanes, forming the C2–C3 bond. 2-Sulfonyl oxetanes were targeted as unusual fragments for fragment based drug discovery, but presented unsuitable substrates for C–O bond forming cyclization approaches.[85,246] This prompted more extensive investigation of a C–C bond forming approach. The required cyclization precursors **189** were accessed in 3-steps from readily available chloromethyl aryl-sulfides. Treatment of aryl sulfones **189** with LiHMDS resulted in the 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 ºC and was successful on gram scale. The aryl group could be readily varied to build a collection of 2-sulfonyl oxetanes. The sulfonyl oxetane fragments were further derivatized through deprotonation on the ring, aided by the sulfonyl group (section 8), 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 sulfinyl oxetanes, which cyclized under modified conditions on deprotonation adjacent to the sulfoxide.[247]

Scheme 60. Synthesis of 2-Sulfonyl Oxetanes



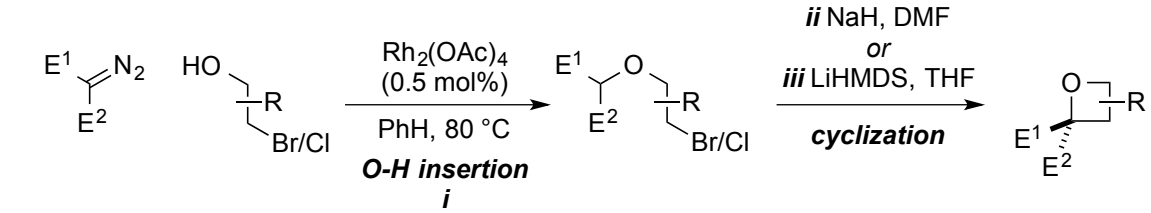
The C–C bond forming strategy was extended to a 2-step approach to 2,2-disubstituted oxetane derivatives.[140,248] A rhodium acetate catalyzed O–H insertion between ethyl diazomalonate and *β*-bromohydrins rapidly constructed suitable cyclization precursors **191** (Scheme 61). Cyclization forming the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

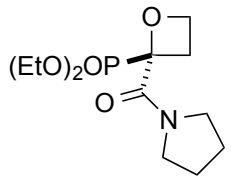
Scheme 61. Oxetane Synthesis by O–H Insertion/C-C Bond Forming Cyclization



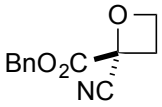
The use of other diazo compounds gave a series of novel functionalized oxetane motifs. From the corresponding diazo compounds, varied functional groups were introduced into the oxetane products, including amides, nitriles, phosphonates and sulfones (Scheme 62).[249] More substituted examples were also demonstrated, with low to good diastereoselectivity. Using 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. Ester hydrolysis was again demostrated, and amide coupling using nitrile and aryl substituted examples accessed new amide derivatives.

Scheme 62. Synthesis of Functionalized Oxetanes from Unsymmetrical Diazo Compounds

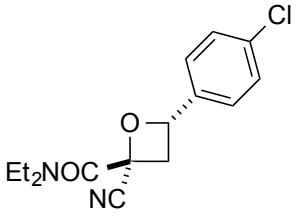




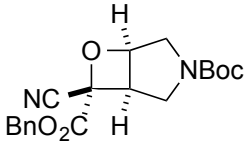
i) 84%
ii) 72%



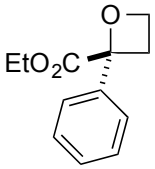
i) 93%
ii) 93%



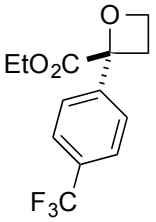
i) 63%
ii) 86% 74:26 dr



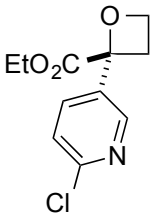
i) 65%
ii) 95% 83:17 dr



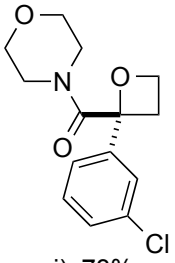
i) 86%
iii) 93%



i) 64%
iii) 77%



i) 54%
iii) 76%



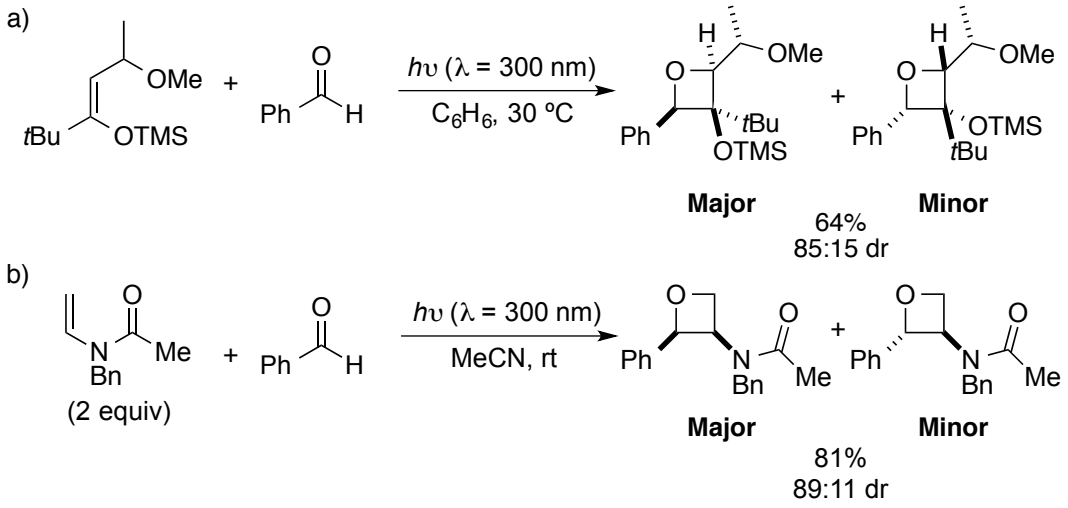
i) 73%
iii) 90%

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,[3,4,250,251,252] 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.

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 non-concerted or concerted pathway. Where the reaction occurs through the triplet state carbonyl, the reaction is non-concerted 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 non-concerted mechanism.[3,4,253,254,255,256] While regio-, site- and stereoselectivity can be challenging, such selectivities have been achieved, for example, in the extensive work by Bach targeting 3-silyloxy[257,258] and 3-aminooxetane derivatives[259,260,261,262,263] (Scheme 63a and b).[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.

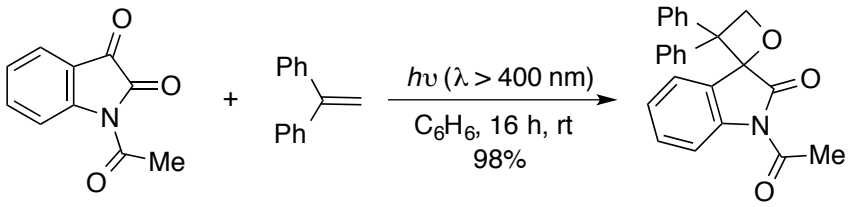
Scheme 63. Synthesis of 3-Silyloxyoxetanes (a) and 3-Aminooxetanes (b) via Paternò-Büchi Photochemical [2+2] Cycloadditions



Recently, Griesbeck has formed fused oxetane-isoxazolines by a Paternò-Büchi reaction of methyl substituted isoxazoles with aryl aldehydes with high regioselectivity and *exo*-diastereoselectivity.[266] Zhang reported the [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.[267] Furthermore, the Paternò-Büchi reaction has been conducted on designed chiral templates with dihydropyridones,[268,269] using 8-phenylmenthol as an auxiliary,[270] and directed by chiral hydroxy groups.[271] Additionally, the synthesis of a variety of natural products e.g. oxetanocin[272] 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 reported the synthesis of a 3,3-diphenyl oxetane in 98% yield using a Paternò–Büchi reaction (Scheme 64).[274] Prior to this work 3,3-diaryl oxetanes were not known in the literature.

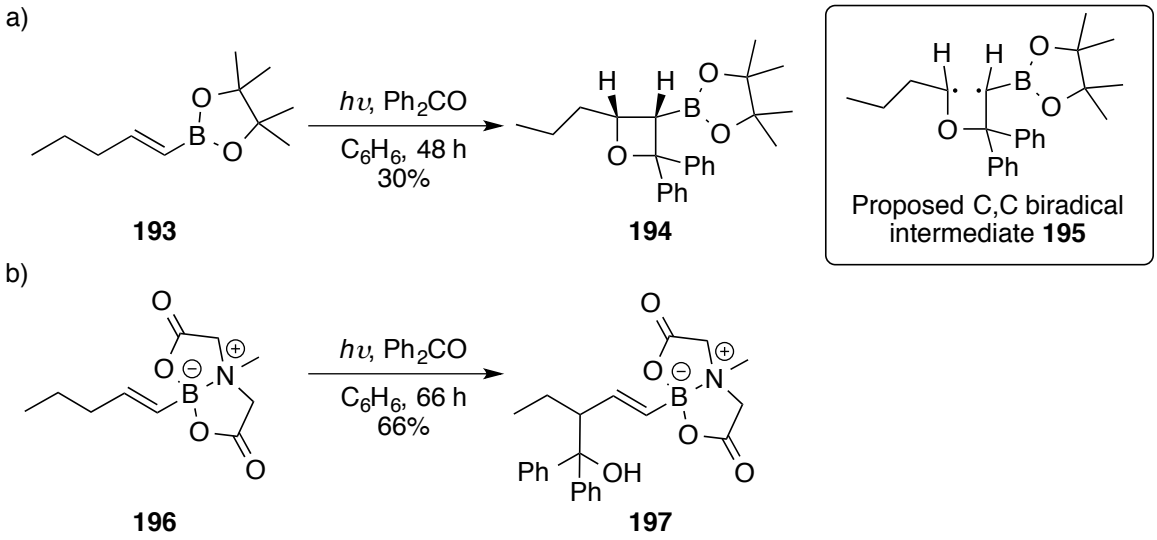
Scheme 64. Synthesis of a 3,3-Diphenyl Oxetane by a Paternò–Büchi Reaction



Subsequently, Inoue used [2+2] photo-cycloaddition methods for the synthesis of 3,3-diphenyl oxetanes 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).[275,276] Non-intercovertible diastereomeric pairs of excited state complexes were generated with different ratios depending on excitation, and the dr was carried through to the oxetane products. The mode of excitation was controlled by simply changing the irradiation wavelength.[275, 276]

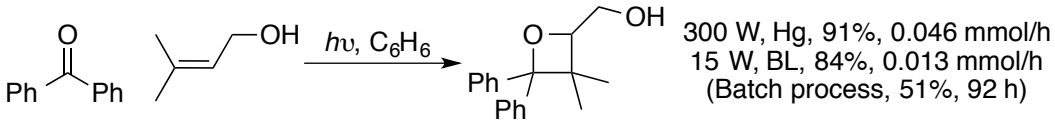
D'Auria examined the Paternò-Büchi reaction with alkenyl boronates and benzophenone.[277] When pinacol boronate **193** and benzophenone were irradiated in benzene at 310 nm the product oxetane **194** was observed in a 30% yield (Scheme 65a). Interestingly, when the *N*-methyl-iminodiacetic acid (MIDA)-boronate derivative **196** was submitted to the same conditions, allylic alcohol **197** was observed in a 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 the 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 of the observed products were the kinetically favored products and not thermodynamically preferred.[277]

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



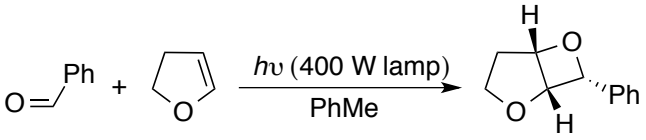
Photochemical reactions, although often powerful as a synthetic tool, may involve long irradiation times that can lead to reduced yields of the product due to undesired reactions over the extended time period. In recent years, reactions in continuous flow have been described as a strategy to achieve 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 using a 300 W mercury lamp and a residence time between 2 and 3.2 h.[279] The equivalent reaction on a model substrate in batch 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 the synthesis of oxetanes. In 2011, Ryu 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).[280] 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]

Scheme 66. The First Example of a Paternò-Büchi Cycloaddition in Flow



A single example of a Paternò-Büchi cycloaddition in flow was published by the Booker-Milburn group in 2014 (Scheme 67).[281] After 3 hours, the batch process (run at a 0.3 M concentration) gave 14.05 g of product (67% yield). Under optimised flow conditions using a flow rate of 3 mL min^{-1}, 20.52 g of product was isolated after 3 hours (72% yield), representing an increase in productivity of 50%.

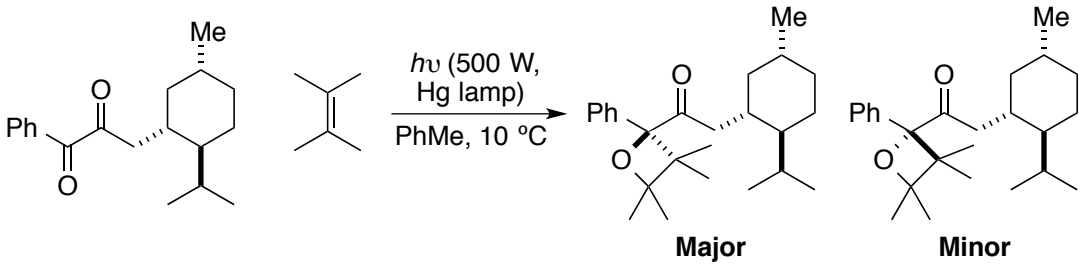
Scheme 67. Booker-Milburn's Example of a Paternò-Büchi Cycloaddition in Flow Compared to the Batch Process



Batch: 67% yield, 14.05 g/ 3 h
Flow: 72% yield, 20.52 g/ 3 h

In 2014, Kakiuchi 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.[282] Three different modes of flow were investigated and compared to the batch reaction: normal flow, slug flow using the substrate solution/N_2, and slug flow using the substrate solution/H_2O. 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 using the substrate solution/H_2O combination gave the highest efficiency. Suggested reasons for the increase in efficiency include light dispersion effects, a stirring effect caused by the 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.

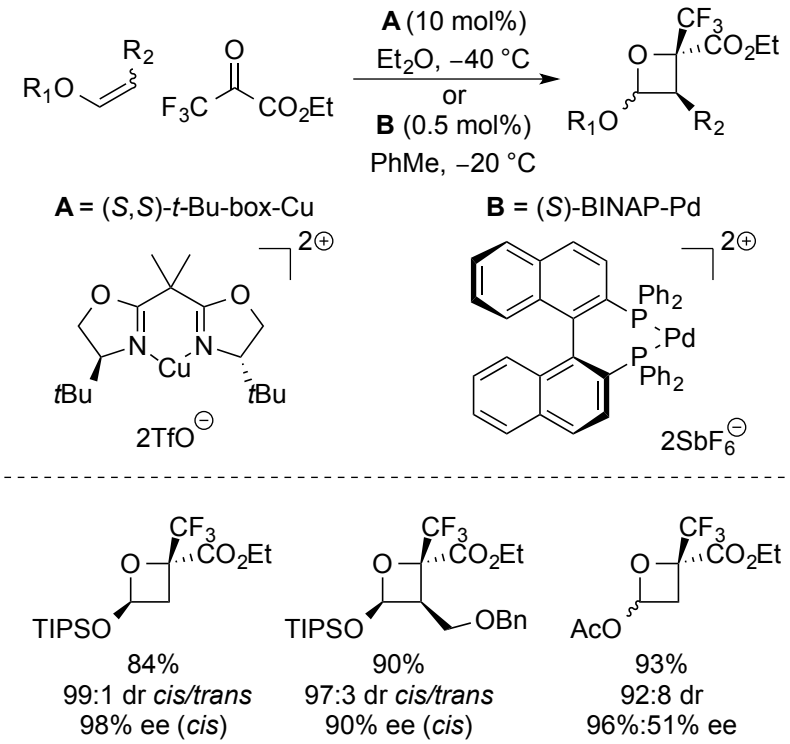
Table 17. Effect of Normal Flow Conditions and Slug Flow Conditions on the Efficiency of the Paternò-Büchi Cyclization



Reactor	Yield (%)	Irradiation time (sec)	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 using H_2O and substrate solution	45	15	21.6	1.376

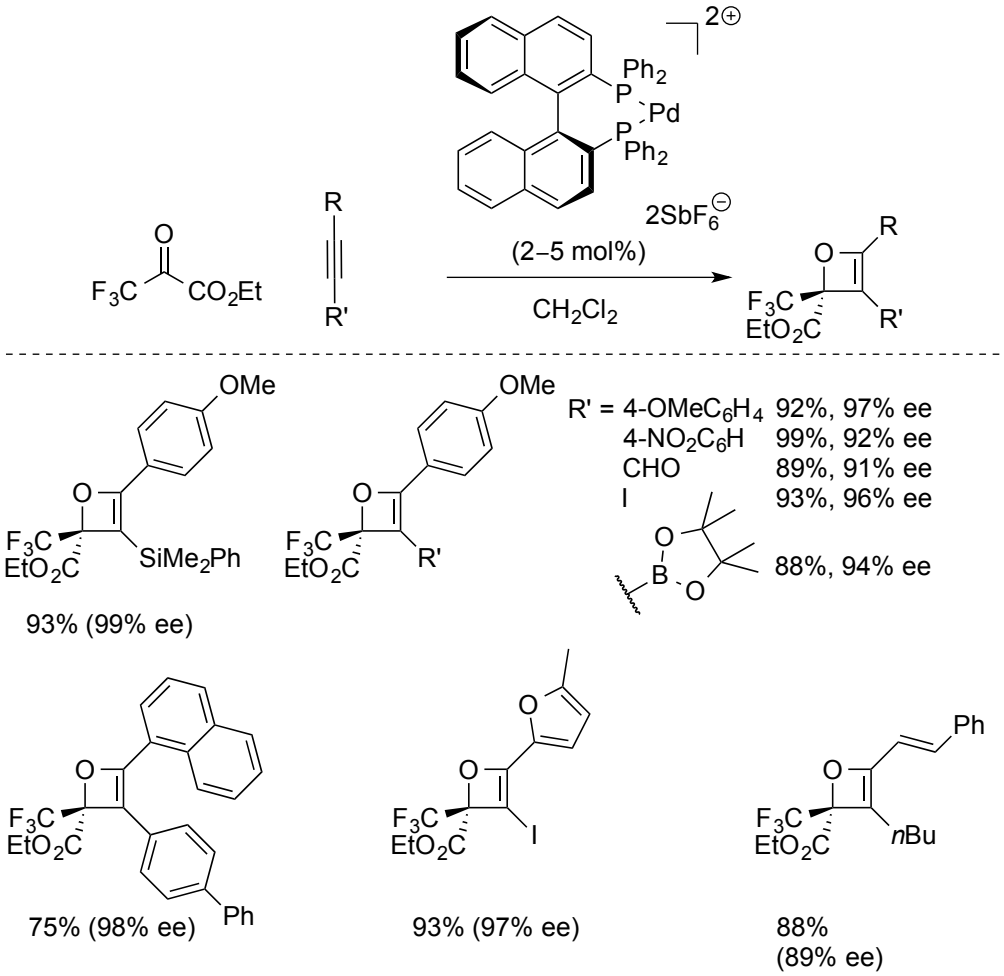
Formal [2+2] Cycloadditions In 2011, Mikami reported a Lewis acid-catalyzed asymmetric formal [2+2] cycloaddition to form 2-trifluoromethyloxetanes from trifluoropyruvate and activated alkenes (Scheme 68).[283] This transformation was achieved using either Cu(II) or Pd(II) complexes depending on the vinyl substrate: silyl ethers required Cu-bisoxazoline complex **A**, whereas Pd-BINAP complex **B** was required for the less reactive vinyl acetate.

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

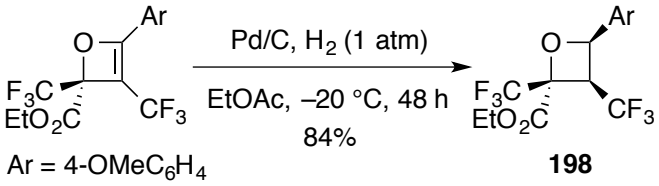


This Lewis acid-promoted strategy was also used to synthesize unusual, yet stable oxet*ene* derivatives. Mikami demonstrated that using alkynylsilanes bearing electron-rich *p*-methoxyphenyl groups underwent the formal [2+2] cycloaddition to afford oxetenes with high ee using a chiral cationic BINAP-Pd complex (Scheme 69).[284,285] 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-substituted, heteroaryl-substituted 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 of transformations, including reduction of the double bond using Pd/C and H_2 to give oxetane **198** (Scheme 70).[284]

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



Scheme 70. Reduction of Trifluoromethylated Oxetene to the Corresponding Oxetane



5. Synthesis of Oxetane Derivatives from Oxetane-Containing Building Blocks

Partly due to the 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, or 3-hydroxyoxetane are inexpensive; yet other simple substitution patterns remain very costly e.g. oxetane-3-carboxylic acid.

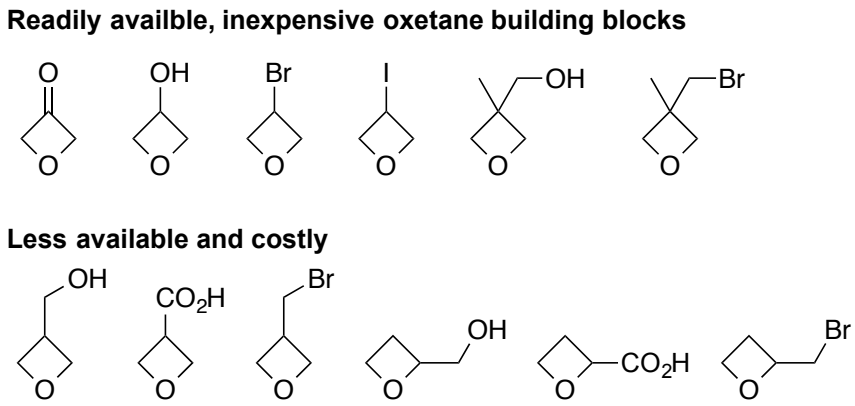
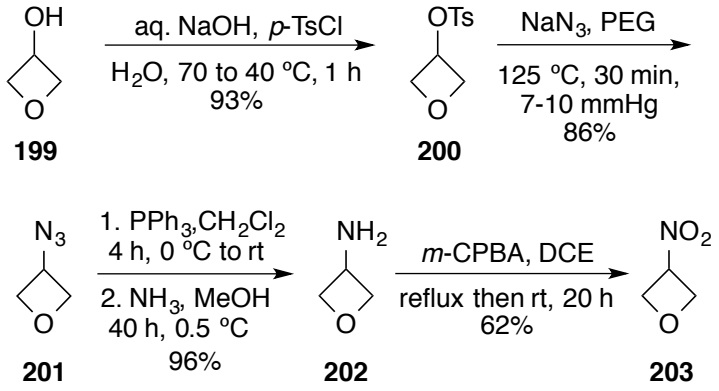


Figure 15. Some Commercially Available Oxetane-Containing Building Blocks.

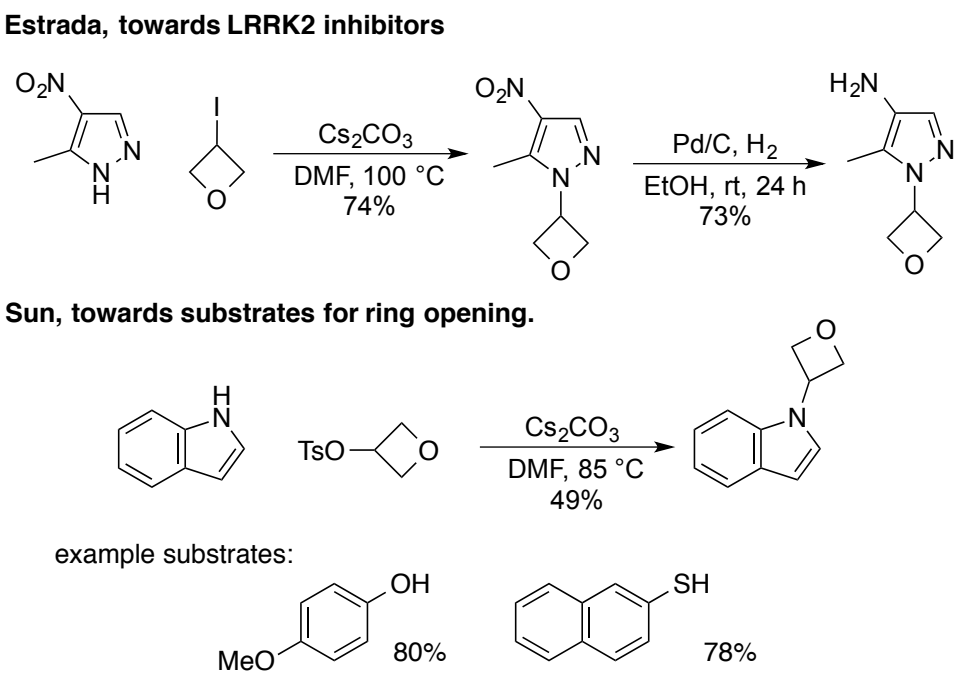
Reactions of 3-hydroxyoxetane **199** were demonstrated by Baum in 1983 via the tosylate, formed using aqueous sodium hydroxide and tosyl chloride (Scheme 71).[286] Reaction of 3-(tosyloxy)oxetane **200** with sodium azide yielded 3-azidooxetane **201** in an 86% yield. Subsequent reaction with triphenylphosphine and then ammonolysis using liquid ammonia gave 3-aminooxetane **202** in an excellent 96% yield. Oxidation to 3-nitrooxetane **203** was successful using *m*-CPBA. This could be then converted to the 3,3-dinitrooxetane using aqueous methanol and tetranitromethane.[286]

Scheme 71. Synthesis 3-Amino and 3-Nitrooxetane



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 4-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 for additional examples of similar reactions on more substituted substrates).

Scheme 72. SN2 Reactions on Simple Oxetane Building Blocks.



Nonetheless, outside the patent literature, there remain relatively few reactions on these simple substrates that maintain the oxetane ring. An example is the oxidation of oxetane-3-methanol to the

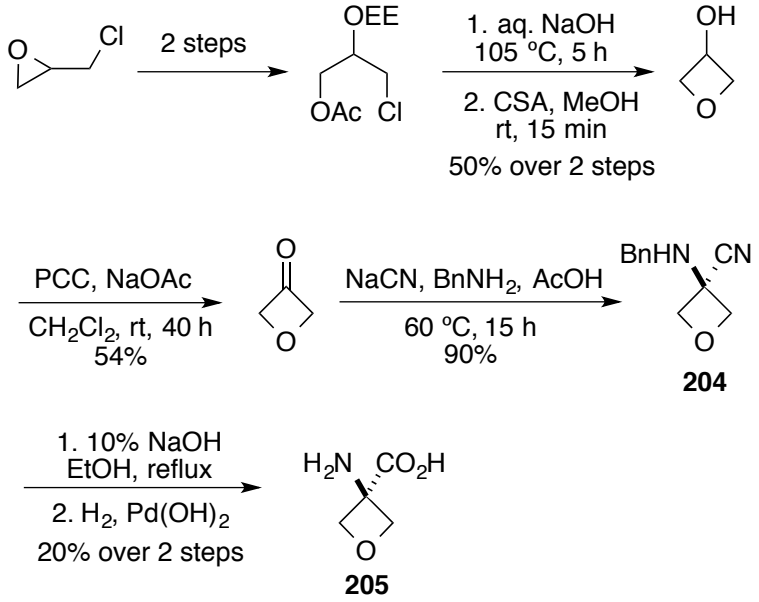
aldehyde, which has been achieved with Dess-Martin periodinane[290,291] or PCC.[292] This section will give an overview of the transformations available on key oxetane building blocks and provide examples of their use in drug discovery efforts, including a survey of examples from the patent literature.

5.1 Carreira's Oxetan-3-one

Oxetan-3-one was originally reported in 1973;[5,287] however, Carreira's studies since 2006 have developed this unit as an attractive electrophilic building block for the incorporation of oxetanes.[63,65] There have been a large number of examples since, exploiting this ketone in reactions to incorporate an oxetane into a selection of important molecules.

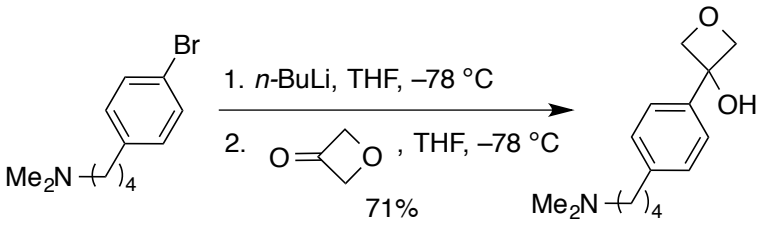
In 1991, prior to Carreira's studies, Kozikowski and Fauq published a route to synthesize oxetane-containing amino acid derivatives as inhibitors for the glycine binding site of the NMDA receptor complex (Scheme 73).[293] Oxetan-3-one was identified as a key intermediate and was synthesized in 5 steps from epichlorohydrin. A Strecker synthesis was then used to deliver the desired amino acid derivatives. Base hydrolysis of aminonitrileoxetane **204** at 95 ºC for 2.5 hours, then hydrogenolysis over $Pd(OH)_2$, delivered the amino acid **205** (Scheme 73). Alternatively, base hydrolysis at 50 ºC for 30 minutes and then hydrogenolysis over $Pd(OH)_2$ resulted in the amino carboxamide.

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



Carreira developed a general procedure for the synthesis of 3-aryloxetan-3-ols from halogenated aromatic species, through a halogen-lithium exhange and then addition to oxetan-3-one (Scheme 74).[63,64] This has been shown to be general for a large number of aromatic and hetereoaromatic groups, including but not limited to, pyridine, pyrimidine, pyrazole, *ortho*, *meta* and *para* substituted phenyl containing examples.[289,294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309] Similarly, alkynyl[289,310,311,312] and vinyl[313,314] organometallics have been added directly.

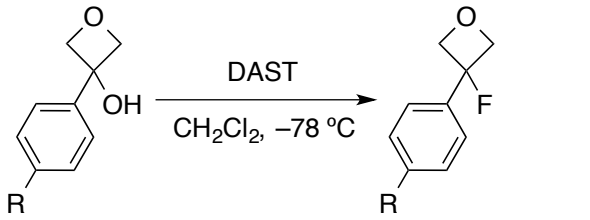
Scheme 74. Example Synthesis of a 3-Aryl Oxetan-3-ol by Organometallic Addition



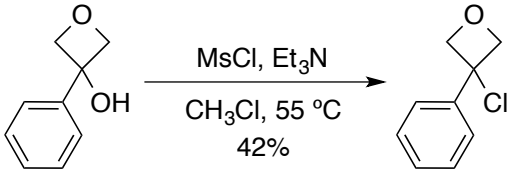
The 3-hydroxy group has provided a useful handle for further reactions, making 3-aryloxetan-3-ols interesting reactive intermediates. The earliest demonstration of the replacement of a tertiary alcohol at the 3-position of an oxetane with a suitable nucleophile was in 2006 by Carreira.[63] Fluorination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

methodology has been adopted and reported in numerous industrial medicinal chemistry patents for the synthesis of 3-fluoro oxetanes.[315,316,317,318,319,320,321,322,323,324,325-339] Fluorinating agents such as XtalFluor[325, 326] and Deoxo-Fluor[327, 328, 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*-CN,[330,331,332] *m*-I,[333] and *p*-Br phenyl,[334,335] and pyridyl[336,337,338] examples. Additionally, examples have been reported with pyrimidines,[329] pyrazoles[339,326] and more complex diaryls.[340,341,342] Chlorination of an oxetan-3-ol was also shown to be feasible by Carreira; using mesityl chloride and triethylamine at 55 ºC formed the desired 3-chlorooxetane in 42% yield (Scheme 76).[64] This remains the only example of this transformation.

Scheme 75. Fluorination of an Oxetan-3-ol using DAST

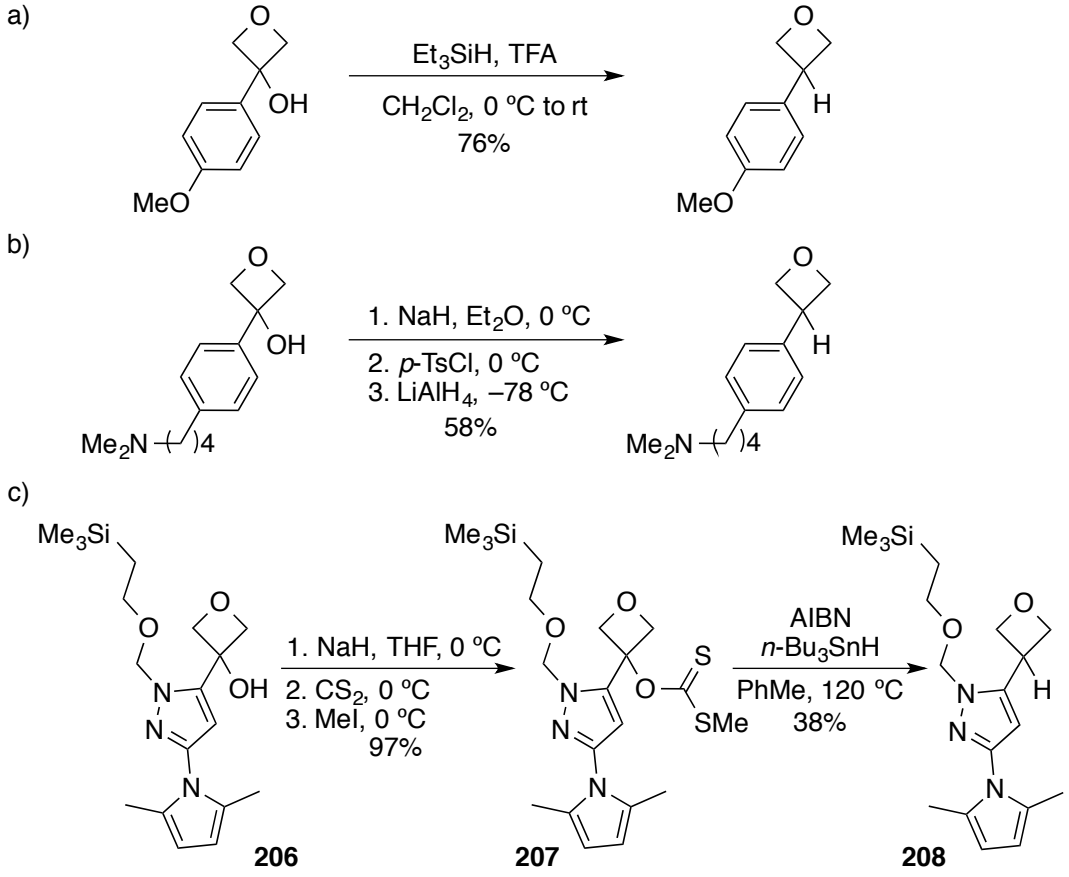


Scheme 76. Chlorination of 3-Phenyloxetan-3-ol using MsCl and Triethylamine



Acid mediated dehydroxylation of 3-aryloxetan-3-ols has been successfully achieved using 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 using 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]

Scheme 77. Dehydroxylation of Oxetan-3-ols

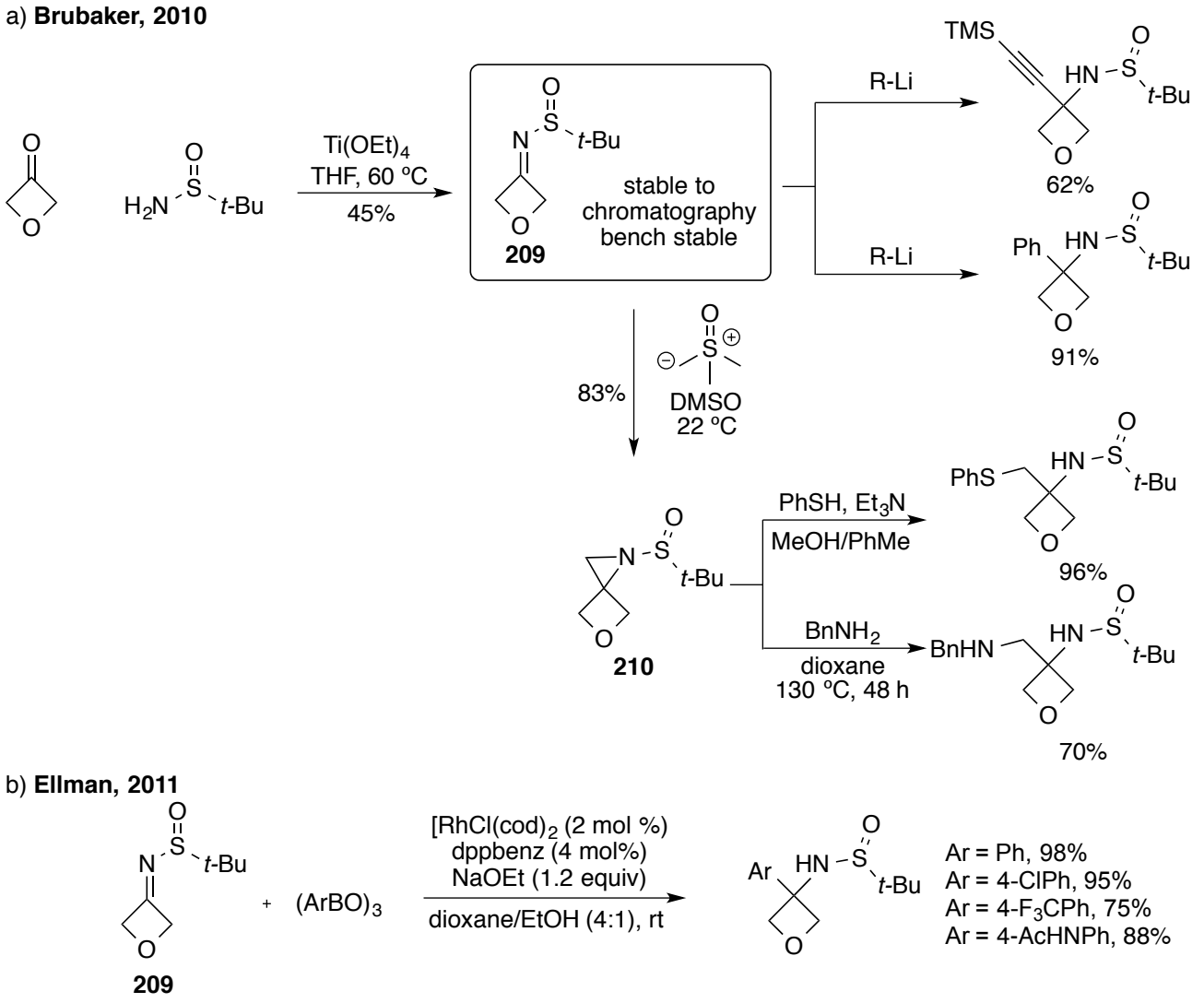


In 2013, scientists at Hoffman-La Roche reported in a patent an example of a four-step synthesis of dehydroxylated oxetane **208** from oxetan-3-ol **206** (Scheme 77c).[343] Near quantitative conversion to the xanthate **207** was realized with subsequent conversion to 3-aryloxetane **208** achieved in a 38% yield by a Barton-McCombie deoxygenation using AIBN and tributylstannane.

To generate 3-aminooxetanes, oxetan-3-one has been widely used in reductive amination sequences (also see Section 5.3).[344,345,346,347,348,349] Brubaker demonstrated the preparation of 3-aminooxetanes through the condensation of oxetan-3-one and *tert*-butylsulfinimine (Bus), followed by the addition of various organometallic reagents to imine **209** (Scheme 78a).[350] 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-amino oxetanes. The Bus group could be successfully removed with 4 N HCl in methanol in a short reaction

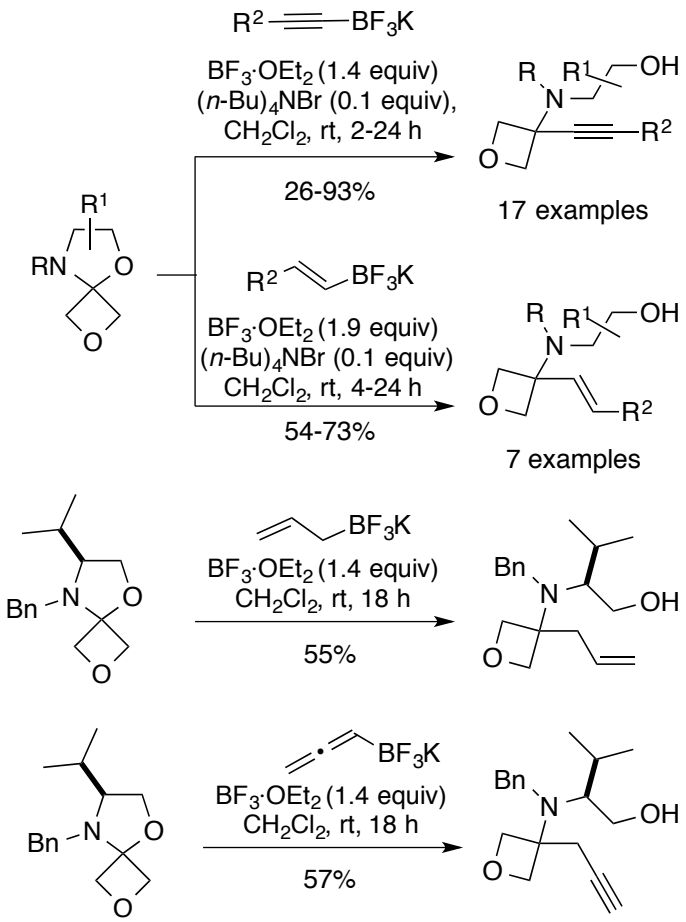
time; longer reaction times gave ring opening with chloride. In a similar approach, Ellman described the Rh-catalyzed addition of aryl boroxines to the oxetane Bus-aldimines (Scheme 78b).[351] The addition was tolerant of various functional groups on the aryl substituent including phenol, ketone and acetamide groups, though interestingly omission of the phosphine ligand was required for a bromo-aryl derivative to minimize side reactions.

Scheme 78. Preparation of 3-Amino Oxetanes by Addition to an Imine



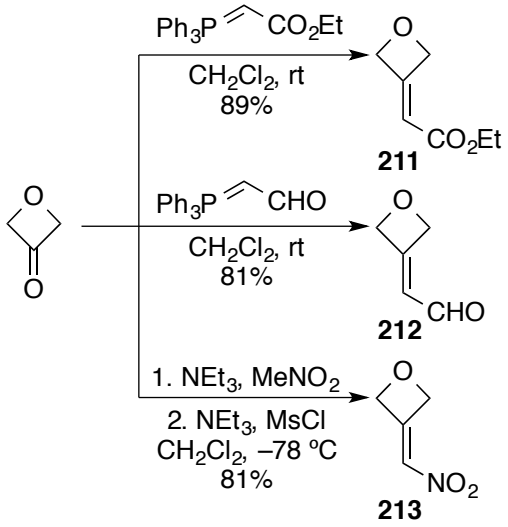
Carreria reported the synthesis of 3-aminooxetanes by nucleophilic addition to *N*,*O*-acetals derived from oxetan-3-one. Alkynyl, vinyl, allyl and allenyl trifluoroborates were added effectively using BF_3•OEt_2 to open the aminal, with tetrabutylammonium bromide included to solubilise the boron reagents.[352]

Scheme 79. Nucleophilic Addition of Carbon Nucleophiles onto Spirocyclic Oxetanes



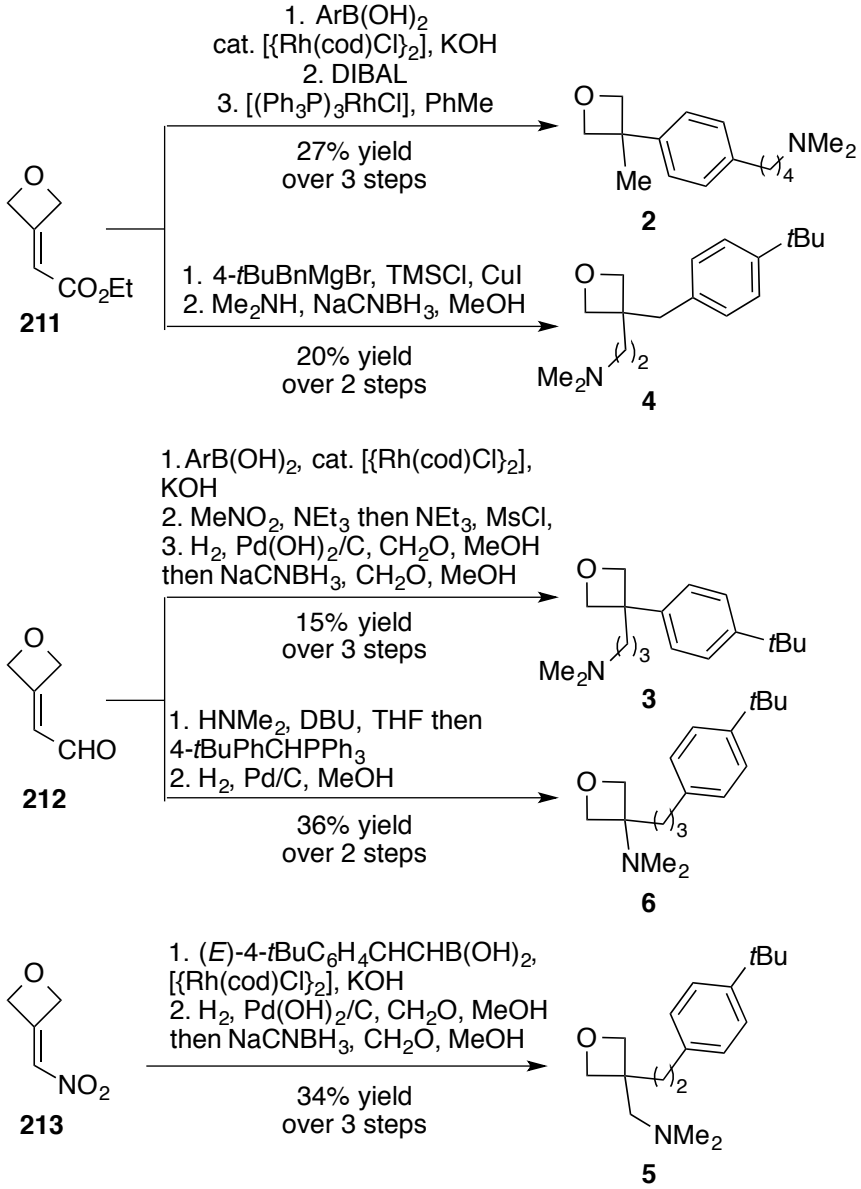
In Carreira's initial studies, oxetan-3-one was used to prepare a series of oxetane Michael acceptors, which have proven to be valuable building blocks in their own right.[63] The synthesis of the α,β-unsaturated ester **211** and aldehyde **212** was achieved by a Wittig reaction with the corresponding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

Scheme 80. Synthesis of Oxetane Michael Acceptors.

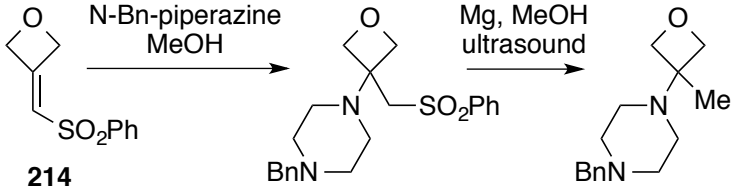


These unsaturated units **211**-**213** underwent conjugate addition with various nucleophiles including amines, organocuprates, aryl boronic acids and vinyl boronic acids allowing the preparation of various 3,3-disubstituted oxetanes (Scheme 81).[63] The physicochemical properties of oxetane-containing compounds **2**-**6** were compared to examine the influence of the oxetane motif (see Section 2). Carreira also prepared the comparable α,β-unsaturated sulfonyl, nitrile and phosphonate oxetane-derivatives.[65] Vinyl sulfone derivative **214** enabled the preparation of 3-functionalized-3-methyl-oxetane 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 through a Julia-Kocienski reaction between oxetan-3-one and fluoromethylsulfones, which was used to prepared fluorine-containing 3,3-disubstituted oxetanes.[353]

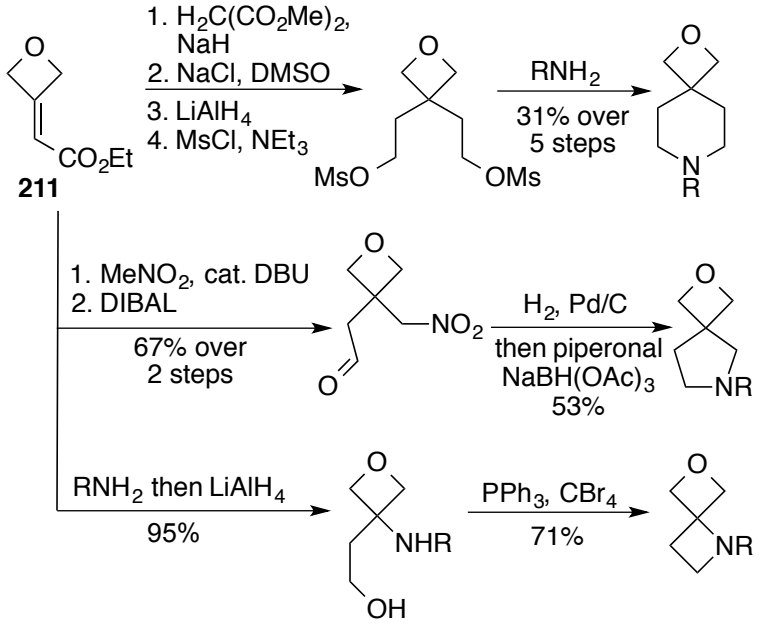
Scheme 81. Synthesis of 3,3-Diaryl Oxetanes via Conjugate Addition to Oxetane Derived α,β-Unsaturated Ester, Aldehyde and Nitroalkene



Scheme 82. Conjugate Addition to Vinyl Sulfone 214 and Reductive Removal

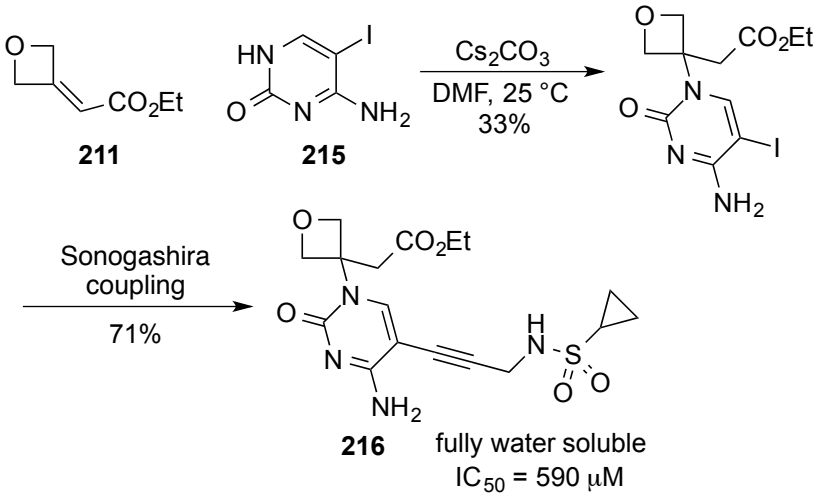


Scheme 83. Synthesis of Oxetane-Containing Spirocyclic Compounds Involving Conjugate Addition (R = piperonyl)



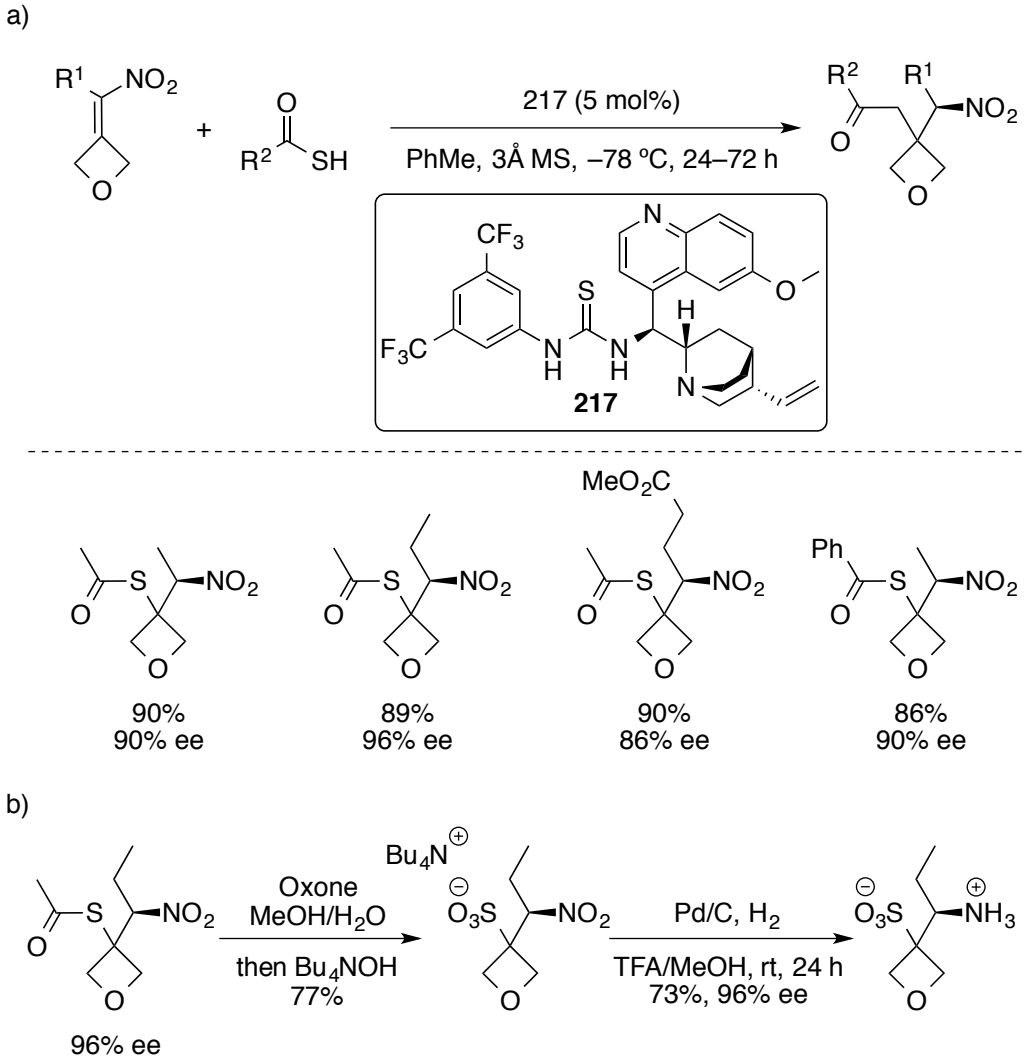
Diederich showed that the incorporation of a pendant oxetane improved the water solubility of compound **216**, an inhibitor of the enzyme IspE (4-diphosphocytidyl-2*C*-methyl-D-erythritol kinase, EC 2.7.1.148), targeting the treatment of diseases such as malaria and tuberculosis (Scheme 84).[354] The key step in the synthesis of **216** was the 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, Carreira's synthesis of oxetanyl-thalidomide (Table 2, Section 2) involved the conjugate addition of an amine to a nitroolefin derived from oxetanone.[80]

Scheme 84. Oxetane-Containing IspE Inhibitor with Improved Aqueous Solubility



In 2014 Ellman reported a catalytic enantioselective addition of thioacids to an oxetane-containing nitroalkene using bifunctional organocatalyst **217** (Scheme 85a).[355] Michael addition into the oxetane-containing nitroalkene 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 using a high yielding, 2-step route with complete retention of ee (Scheme 85b). Very recently, related work on the conjugate addition, and subsequent enantioselective protonation, of pyrazol-5-ones to oxetane-containing trisubstituted nitroalkenes was reported.[356]

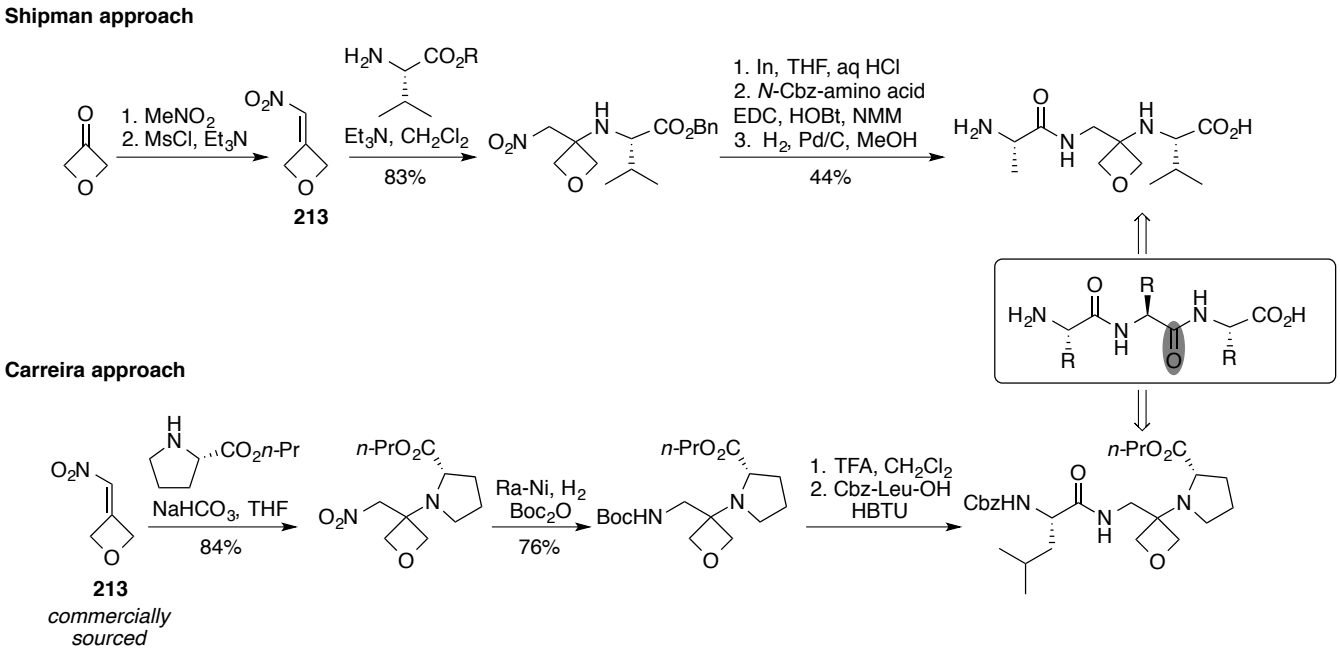
Scheme 85. A Catalytic Enantioselective Synthesis of (a) 1,2-Nitrothioacetates and (b) 1,2-aminosulfonic acids



Carreira[357] and Shipman[358] 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 as 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 recently reported an adaptation of this approach to generate oxetane-containing diketopiperazine

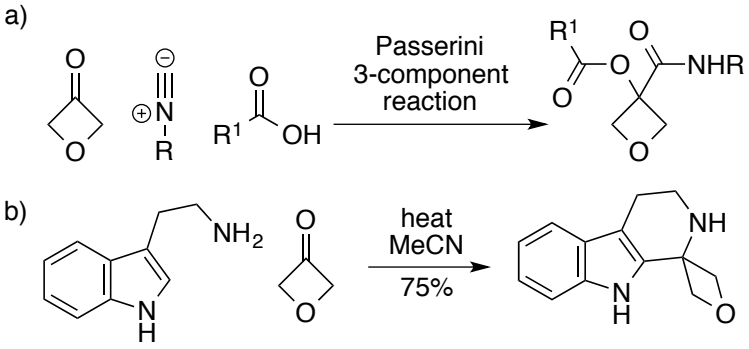
derivatives.[359] Very recently, Jørgensen reported an organocatalyzed cycloaddition to oxetanyl nitroolefins to generate spirocyclohexene-oxetane scaffolds.[360]

Scheme 86. Oxetane Peptidomimetics Formed via Conjugate Addition

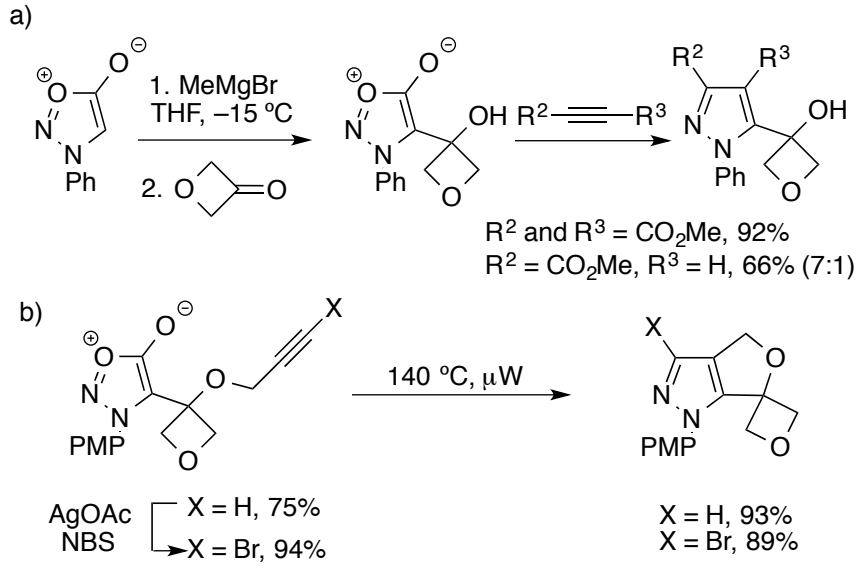


Oxetan-3-one has been used in a number of complexity generating reactions to incorporate oxetanes into interesting structural types. Shipman has used this unit in the Passerini Reaction (Scheme 87a)[361] and also in the Pictet-Spengler reaction (Scheme 87b).[362] Harrity applied his Sydnone cycloadditions to an oxetane-containing motif both in intermolecular and intramolecular cycloadditions to form oxetane-containing pyrazole derivatives (Scheme 88a and b).[363]

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

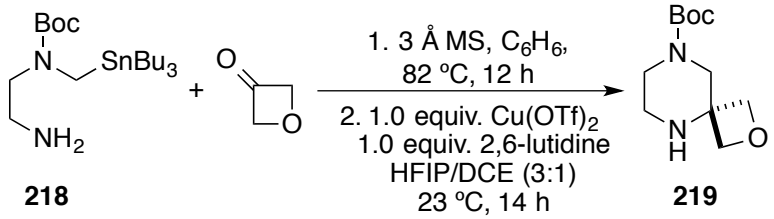


Scheme 88. Inter- and Intramolecular Sydnone Cycloadditions



Bode has developed a powerful one-step protocol for the synthesis of saturated *N*-heterocycles, using stannyl amine reagents in combination with aldehydes (SnAP protocol).[364] 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 the SnAP reagent **218** with oxetan-3-one generated an imine which underwent a Cu-catalyzed radical cyclization to form spirocyclic heterocycle **219**.

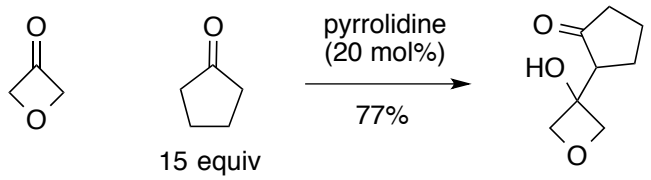
Scheme 89. Synthesis of a Spirocyclic Piperadine-Oxetane Using SnAP Reagents



In 2015, Soós and co-workers showed that oxetan-3-one (as well as other 4-membered cyclic ketones) would undergo selective direct cross-aldol reactions with other ketones, such as cyclopentanone, promoted by pyrrolidine (Scheme 90).[366] The selectivity was attributed to the inherent angle strain of oxetan-3-one, and relief of this strain during the conversion of C(sp^2) to C(sp^3). 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).

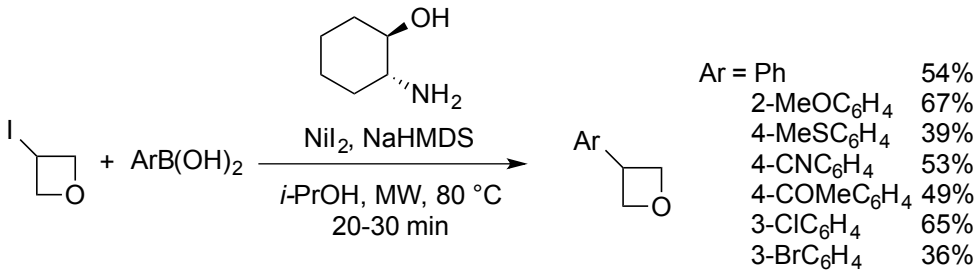
Scheme 90. Strain-Driven Direct Cross-Aldol Reaction with Oxetan-3-one



5.2 Cross-Coupling of Oxetane Building Blocks

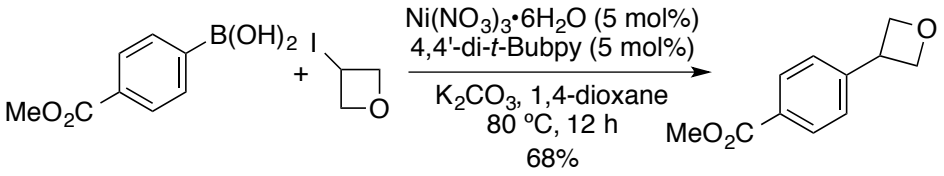
The synthesis of aryloxetanes has been greatly expanded by the use of 3-iodooxetane in transition-metal cross-coupling reactions. In 2008, Duncton (Evotec) demonstrated the use of 3-iodooxetane in cross-coupling reactions with a series of arylboronic acids (Scheme 91).[79] Using conditions developed by Fu for the cross-coupling of alkyl halides,[367] 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.

Scheme 91. Duncton's Ni-Catalyzed Suzuki Coupling of 3-Iodooxetane



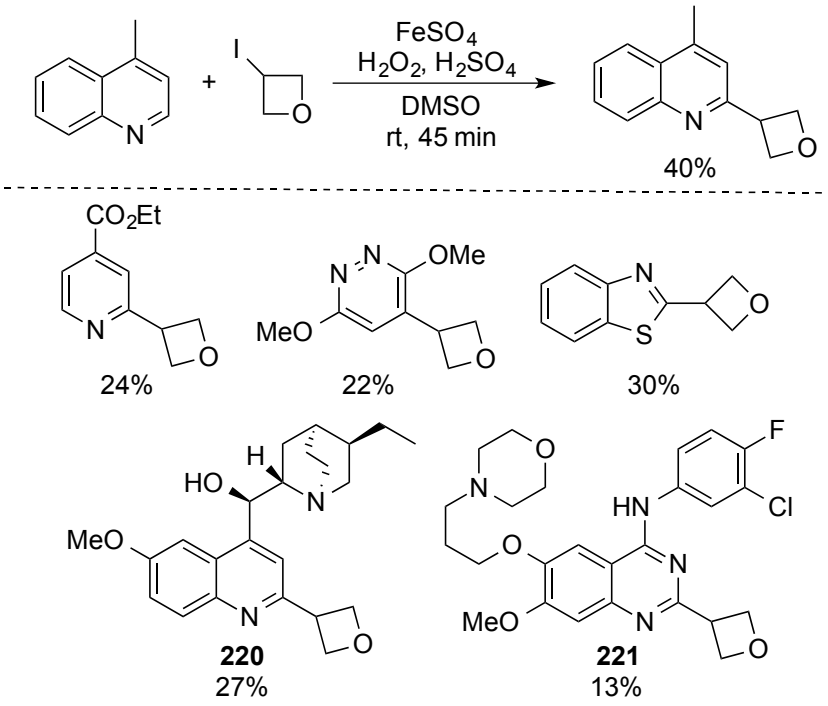
Yang, in 2015, developed a milder Ni-catalyzed Suzuki cross coupling reaction of alkyl halides and arylboronic acids, using K_2CO_3 as the base instead of the more standard Li/KO*t*Bu or Na/KHMDS. In the substrate scope, 3-iodooxetane was found to be a viable substrate, forming the aryloxetane product in 68% yield (Scheme 92).[368]

Scheme 92. Yang's Ni-Catalyzed Suzuki Cross-Coupling Reaction of 3-Iodooxetane and Arylboronic Acids



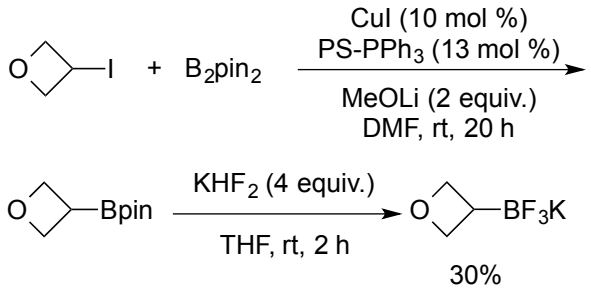
To incorporate an oxetane-3-yl group into heteroaromatic bases Duncton reported a Minisci reaction involving generation of the oxetane radical (Scheme 93).[369] The reaction likely proceeded via the addition of an oxetane radical to the protonated heterocycle, followed by rearomatisation. Although the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

Scheme 93. Fe-Catalyzed Synthesis of Heteroaryloxetanes from 3-Iodooxetane



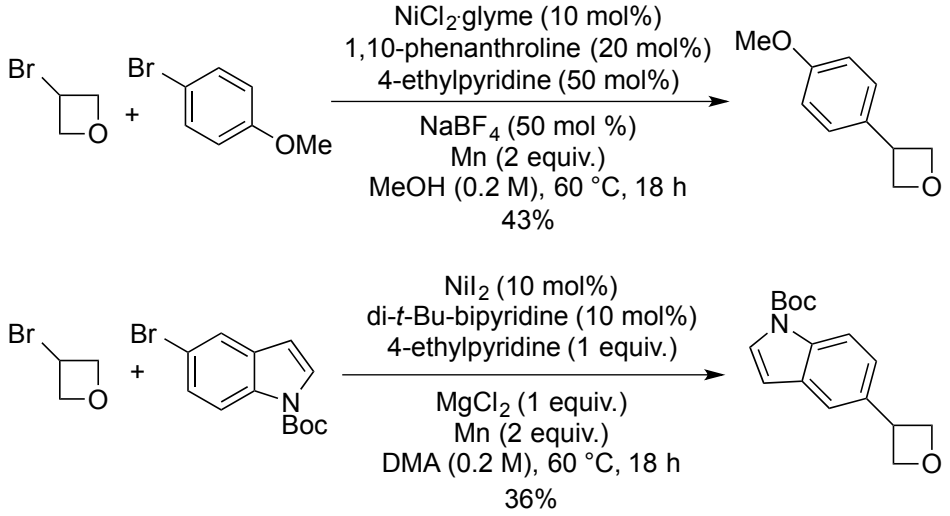
Molander recently extended copper catalyzed borylation methodology to prepare various heterocyclic trifluoroborates, several of which could be applied in a Minisci reaction with heteroaromatics.[370] Several heterocyclic trifluoroborates were prepared from iodo-heterocycles, including 3-iodooxetane (Scheme 94). The oxetane derivative was not demonstrated in the Minisci reaction, indeed, there are no reactions reported to date using oxetane boronates.

Scheme 94. Preparation of an Oxetane Trifluoroborate



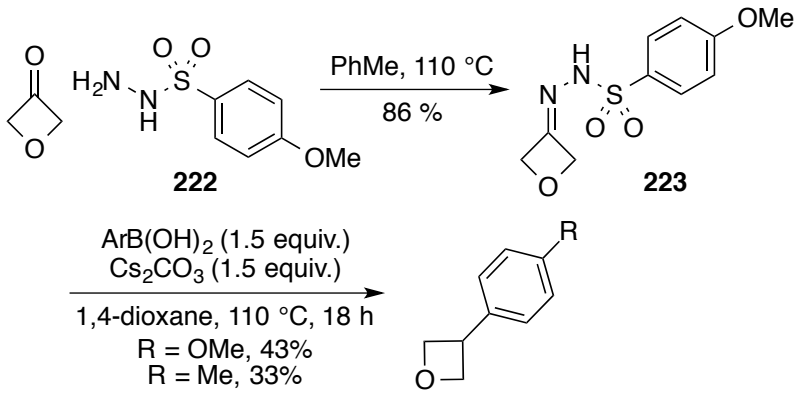
Molander established a Ni-catalyzed, reductive coupling of saturated heterocyclic bromides with aryl and heteroaryl bromides.[371] The reaction was developed by employing a high-throughput experimentation approach to screen Ni sources, ligands, additives and solvents for the coupling of *N*-Boc-4-bromopiperidine with 4-bromoanisole. The scope of the saturated heterocycles included the coupling of 3-bromooxetane with 4-bromoanisole in a yield of 43% (Scheme 95). The reaction conditions were re-optimised 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 a 36% yield.

Scheme 95. Ni-Catalyzed Reductive Coupling of 3-Bromooxetane



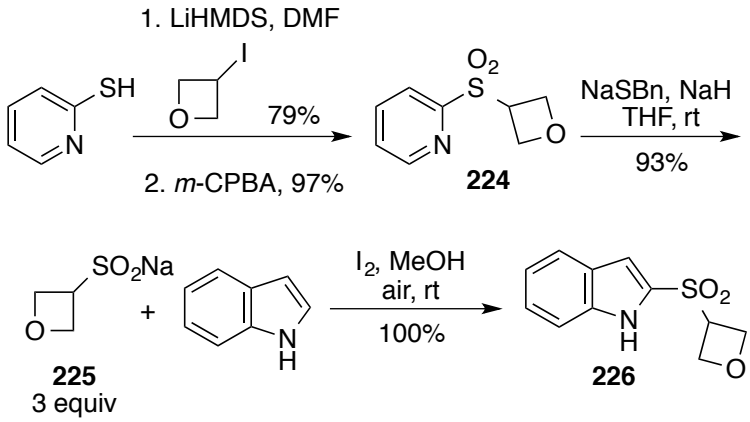
Very recently Buchwald reported a system for Lipshutz-Negishi cross-coupling under aqueous conditions, which included the coupling of 3-bromooxetane in high yields.[372] A new ligand (VPhos) and Pd-precatalyst were developed for the coupling of alkyl bromides, particularly saturated heterocycles, and aromatic and heteroaromatic bromides and chlorides. Ley 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).[373] The reaction was optimised on *N*-Boc-piperidinone-derived tosyl hydrazine with 4-chlorophenylboronic acid. Replacement of the tosyl group of the hydrazone with a *para*-methoxyphenyl sulfonyl group, using **222**, improved the observed yields.

Scheme 96. Metal-Free Coupling of Boronic Acids with Saturated Heterocycles Using Sulfonyl Hydrazones



Harrity prepared oxetane sulfinate salt **225** from 3-iodooxetane in a high yielding 3-step process (Scheme 97).[374] Interestingly the sulfonate salt could be displaced from the pyridylsulfone **224** with a thiolate nucleophile in 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**, using I_2 in MeOH.

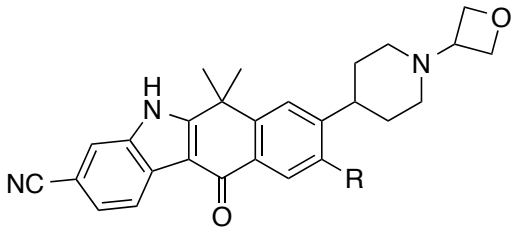
Scheme 97. Preparation and Indole Coupling Reactions of Oxetane Sulfinate Salts



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 and co-workers reported the development of a highly potent and selective anaplastic lymphoma kinase (ALK) inhibitor as a promising therapeutic for cancer.[346] The incorporation of an oxetane group, via a 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). The *N*-oxetan-3-yl-piperidin-4-yl derivative had 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 two-fold increase in potency against KARPAS-299, proposed to be a result of improved ALK selectivity over off-target kinases.[347]



227; R = H
228; R = Et

Figure 16. Highly potent ALK inhibitors.

Stepan explored arylsulfonamides as potential γ-secretase inhibitors towards treatment options for Alzheimer's disease.[82,83] 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). The

incorporation of an oxetane resulted in the greatest improvement in metabolic stability and lipophilicity. Overall, 2,4,4-trisubstituted analog **231** was the most stable γ-secretase inhibitor of the series.

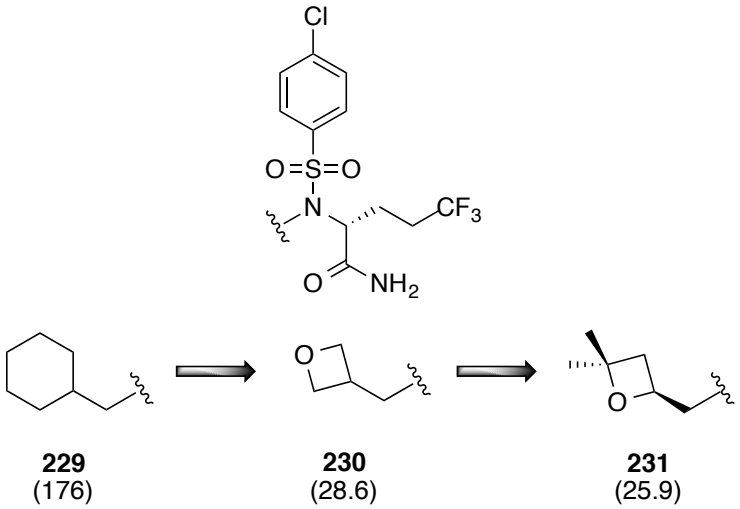


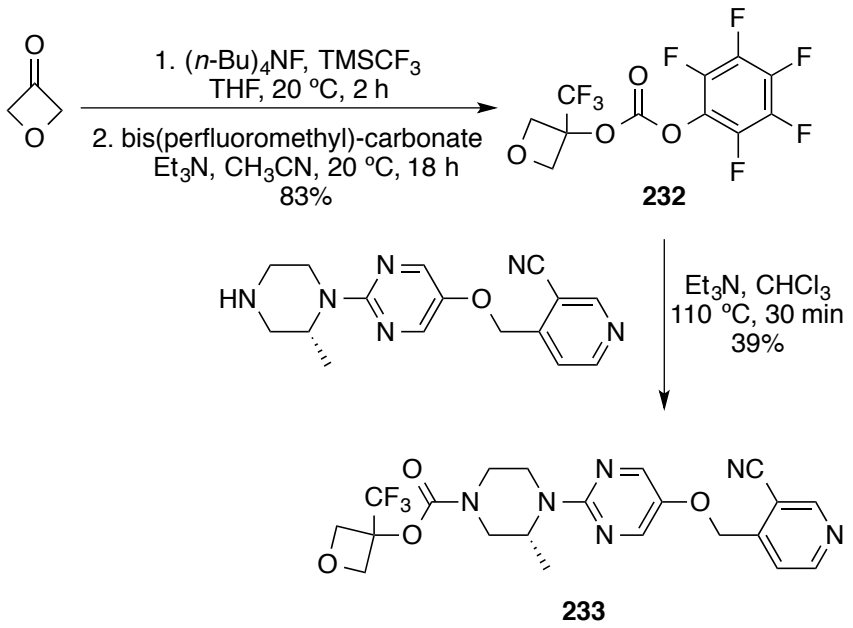
Figure 17. Comparison of metabolic stability of lead compound **229** compared to oxetane-containing analogs. $CL_{int.app}$ (min^{-1} kg^{-1} mL), in parenthesis, is total intrinsic clearance obtained from scaling in vitro HLM half-lives.

Dowling and co-workers at AstraZeneca described a series of 5-anilinopyrazolo[1,5-a]pyrimidine inhibitors of CK2 kinase (Figure 7, Section 2).[81] 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 and co-workers at AstraZeneca developed a series of G-protein coupled receptor (GPCR) 119 agonists as a potential diabetes treatment.[375] Initial development led to the discovery of a *tert*-butyl carbamate-containing compound that, although potent, suffered from non-ideal aqueous solubility (24 μM). 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 μM, 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 whilst maintaining a desirable solubility of 110 μM (Scheme 98). This was incorporated using pentafluorophenyl-carbonate **232**, developed specifically for this transformation after more standard approaches had failed.

Scheme 98. Preparation of Trifluoromethyl-Substituted Oxetane GPCR119 Agonist.



Pei and co-workers at Genentech developed a potent and selective oxetane-containing mammalian target of rapamycin (mTOR) inhibitor as a potential future cancer treatment.[376] 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 whilst 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 substituents, and it was found to still possess the most desirable properties to be brought forward as a clinical candidate.

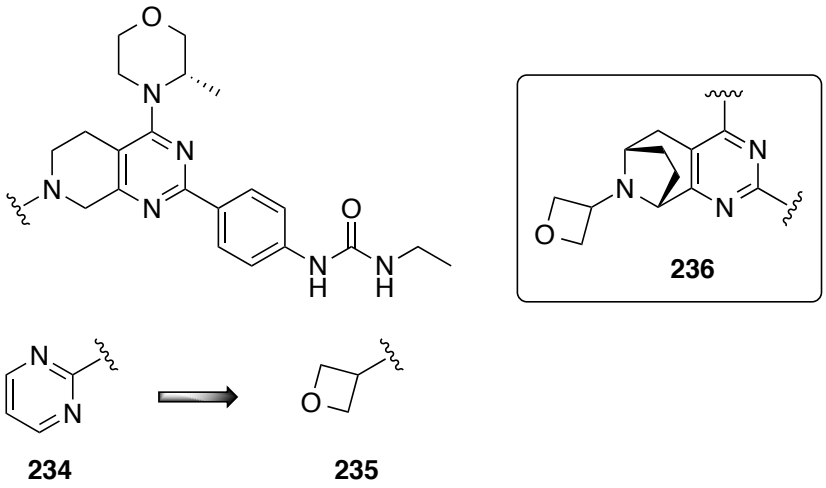


Figure 18. Potent and Selective mTOR Inhibitors.

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

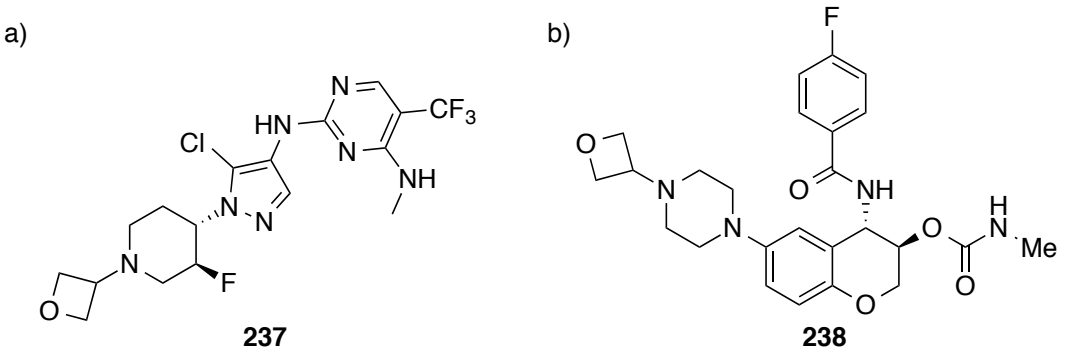


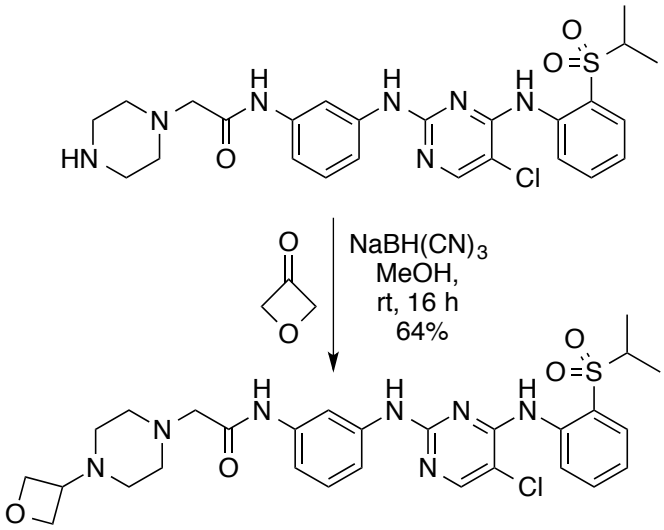
Figure 19. a) Inhibitor of LRRK2. b) Cathespin S Inhibitor.

Jadhav and co-workers at Lilly discovered a series of noncovalent inhibitors of cathespin S, useful as a potential treatment of abdominal aortic aneurysm.[377] Following a medium throughput screen, several hits were identified and one selected for modification to improve its potency and physical properties. A

key aspect of this modification process was replacing the *N*-methyl group on the 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 a clinical candidate **238** (Figure 19b).

Zhang, Geng and co-workers developed 2,4-diarylaminopyrimidine analogs 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.[348] Variation of the substitution of the primary amino group was studied and it was found the 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 active (ALK IC_{50} = 2.7 nM vs. 4.9 nM for the oxetane) and this was chosen for further evaluation.

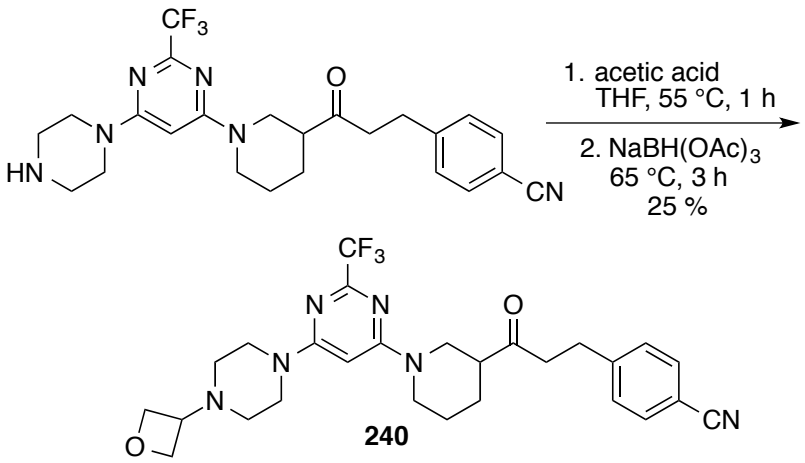
Scheme 99. 2,4-Diarylaminopyrimidine Analogs as Potent Inhibitors Against Wild-Type and Mutant ALK Kinases



239

Phillips and co-workers at Novartis developed GPCR TGR5 agonists, an attractive target for type 2 diabetes treatment and for chronic inflammation.[349] 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 the issue of hERG risk and retained target potency, CYP3A4 inhibition and metabolic stability were not improved; so this example was not taken forward.

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



Schoenfeld and co-workers at Hoffmann-La Roche developed a series of hepatitis C virus inhibitors.[378] An advanced lead structure was developed containing a *tert*-butyl group, which was succeptible 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 Mitsonobu conditions.

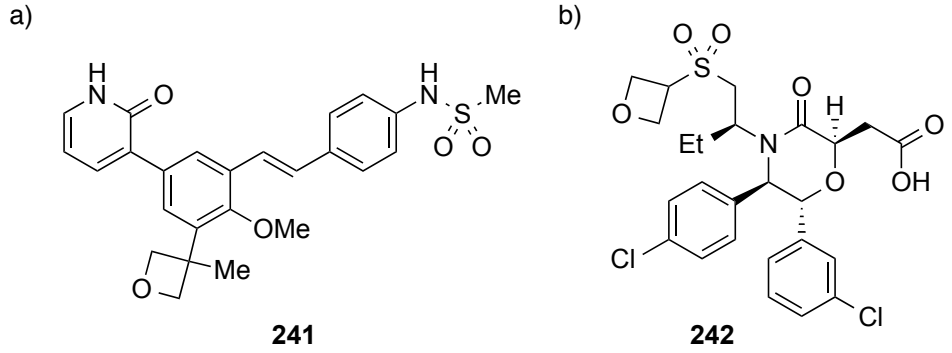


Figure 20. a) Oxetane-Containing Hepatitis C Virus Inhibitors. b) 3-Sulfonyl Oxetane Inhibitor of MDM2.

Gonzalez (Amgen) utilized a 3-sulfonyl oxetane during variation of the *N*-alkyl substituent of a series of morpholinone inhibitors of the MDM2-p53 interaction.[379] Disruption of MDM2 binding to p53 can reactivate the p53 pathway in tumour cells to allow cell cycle arrest and apoptosis. The 3-

sulfonyloxetane 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 were developed by Austin and co-workers at Satori Pharmaceuticals as a potential treatment of Alzheimer's disease.[380] 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 SAR study,[381] *N*-oxetanyl substituted morpholine derivatives were utilized to examine the effects of varying other key parts of the structure.

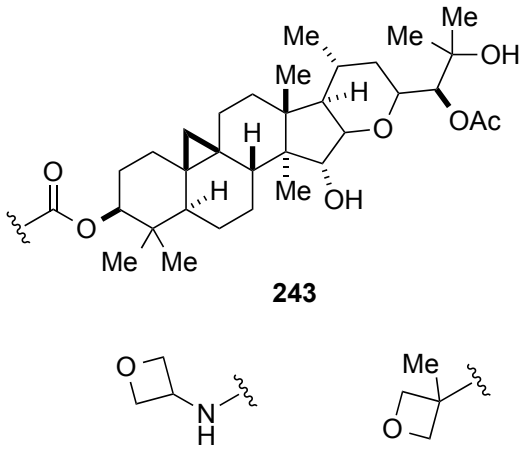


Figure 21. γ-Secretase Modulators with Improved Metabolic Stability.

Procopiou and co-workers at GlaxoSmithKline reported the development of a series of indazole arylsulfonamides as CC-chemokine receptor 4 (CCR4) antagonists.[382] A modified ligand lipophilicity index (LLE_{AT}), which combined lipophilicity, potency, size and made comparisons to conventional ligand efficiency, was used as a metric to compare analogs. 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 analogs but **245** was similar to the acetamide, attributed to the greater exposure of the oxygen in **244**.

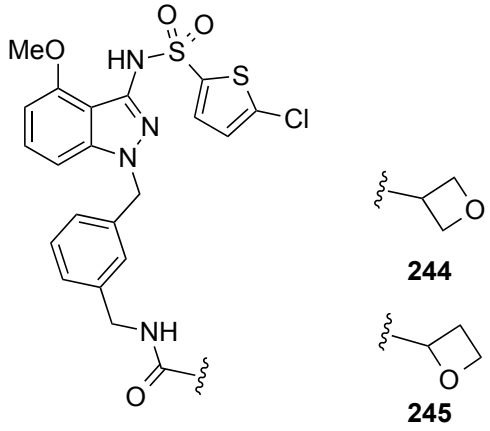


Figure 22. Oxetane-Containing Indazole CCR4 Antagonists.

Dineen (Amgen) identified a potent inhibitor of β-site amyloid precursor protein cleaving enzyme (BACE1).[383] A previously reported amino-oxazoline xanthene scaffold **246** was modified to improve BACE1 potency and prevent off-targert 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 analog (Figure 23). To further reduce the hERG activity 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.

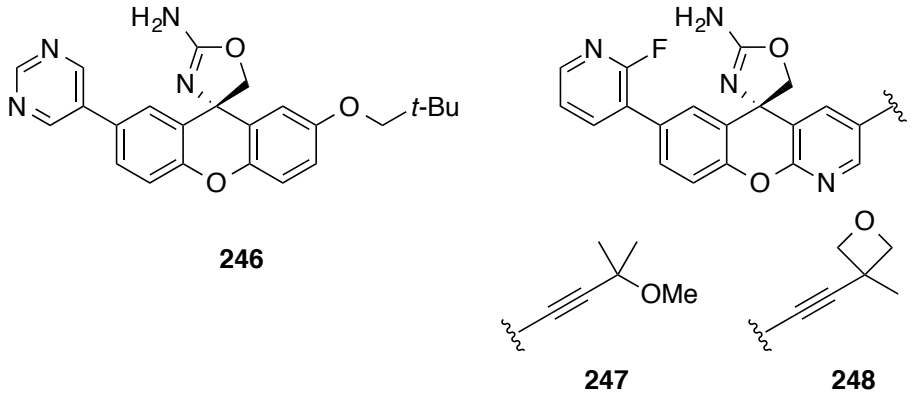


Figure 23. 4-Aza-Xanthene BACE1 Inhibitors Containing a Pendent Oxetane.

Plancher and co-workers at Hoffmann-La Roche developed a series of 5-hydroxyindole based histamine-3 receptor inverse agonists as a potential treatment for obesity.[384] 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 hH_3R binding (K_i = 23 nM) although it suffered from poor microsomal clearance.

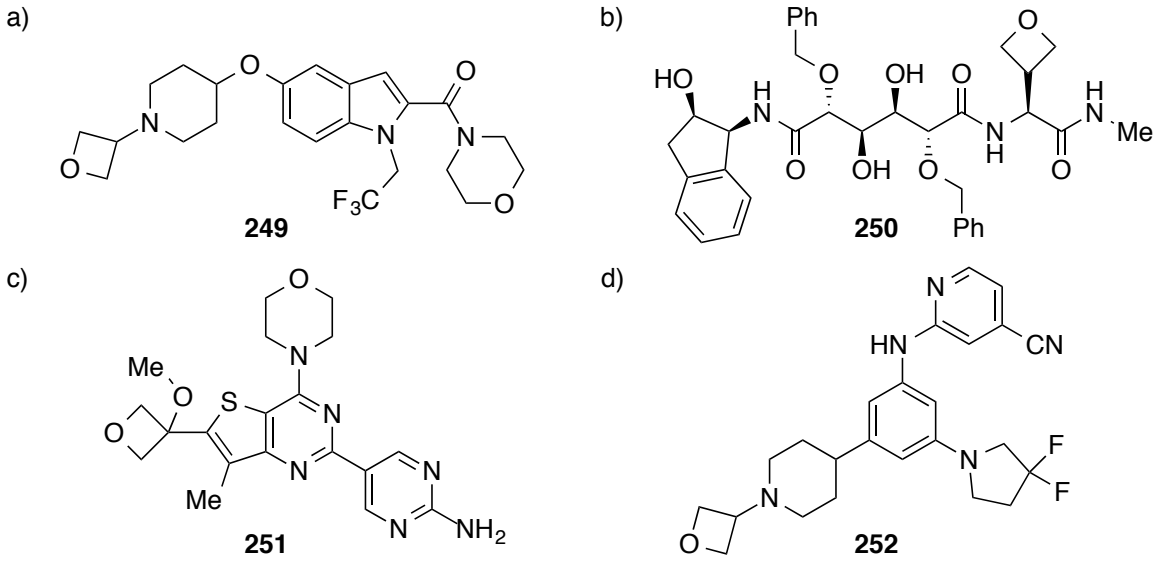


Figure 24. a) Oxetane Modulating the Basicity of H_3R Agonists. b) HIV-1 Protease Inhibitor. c) Brain-Penetrant 3-Methoxy-Substituted Oxetane PI3K Inhibitor. d) Potent and Selective DLK Kinase Inhibitor.

Samuelsson and co-workers described a series of HIV-1 protease inhibitors with a number of different substituents containing hydrogen bond acceptors.[385] 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 log*P*, 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 and co-workers 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.[387] 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 multi-parameter optimization (CNS MPO) was utilized. The 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 and successfully inhibited tumor growth beyond the BBB and was taken forward for further study towards clinical application.

Lewcock, Siu and co-workers have recently developed a series of inhibitors of dual leucine zipper kinase (DLK, MAP3K12), prominent in the regulation of neuronal degradation.[388] Following the discovery of an initial hit through a 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 analogs. An oxetane was successfully used to reduce the basicity of a key piperidine to limit efflux, important for a brain-penetrant, whilst 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 have examined the synthesis of oxetane-containing compounds which appeared in WO or US patents for use in medicinal chemistry or drug discovery programs. Here, oxetane-containing molecules from these patents are collated to include the structure, the source of the oxetane building block used, the bioactivity including any available data, along with the patent 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 was available.

One particular patent warrants further discussion. The original patent, filed by Hoffmann-La Roche, described the preparation of benzothiazepines and analogs 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 IC_{50} values in comparison to other non-oxetane-containing examples. This new-class of RSV inhibitors displayed EC_{50} values as low as 0.2 nM. Compound **255** (Scheme 101) was shown to have a less potent EC_{50} value 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 the 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 amino-

oxetane fragment at the 4-position, followed by the benzothiazepine. Deprotection of the carbamate under acid conditions furnished 5.82 kg of **255** (Scheme 101).

Scheme 101. Large-Scale Preparation of Benzothiazepine RSV Inhibitors

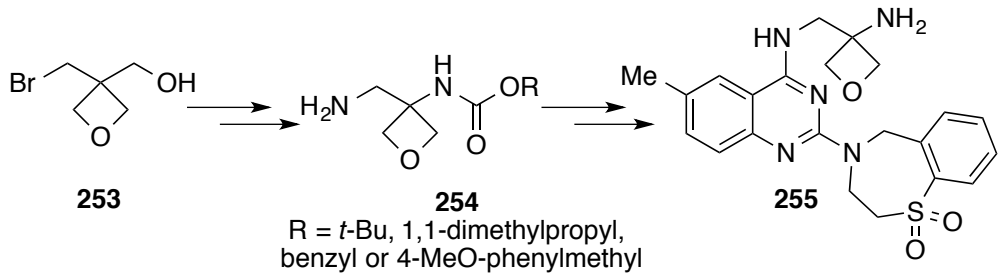
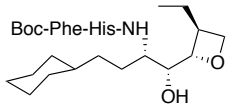
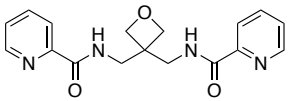
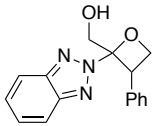
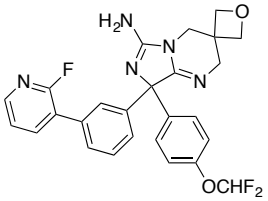
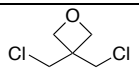
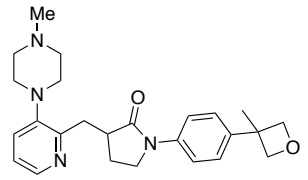
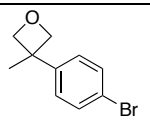
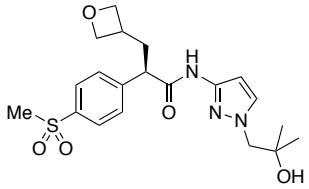
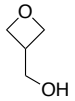
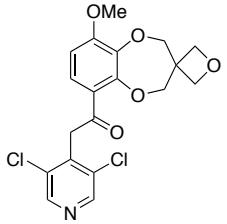
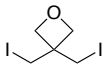
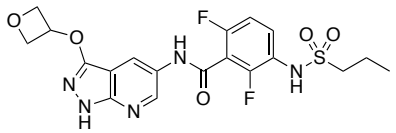
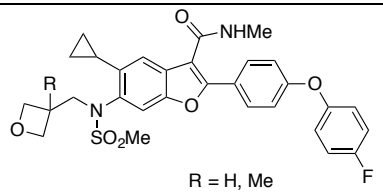
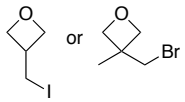
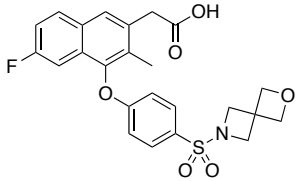
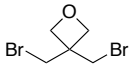
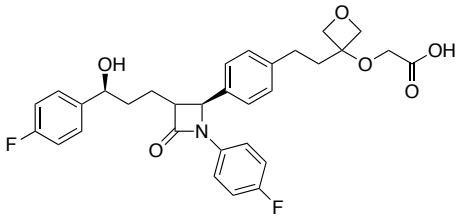
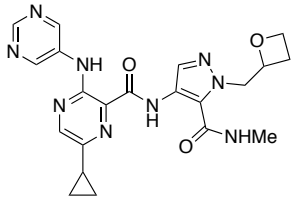
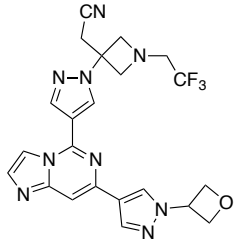
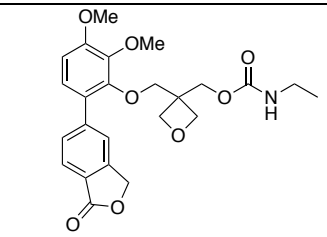
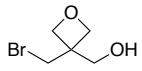
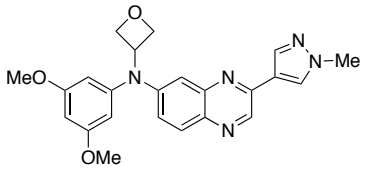
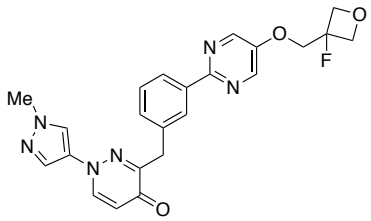
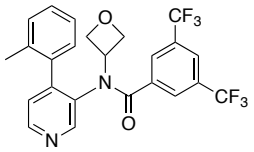
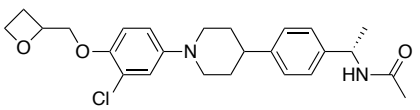
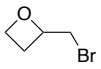


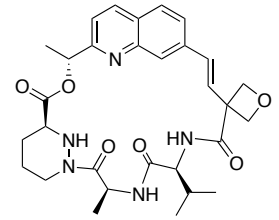
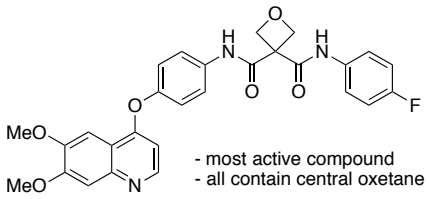
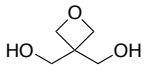
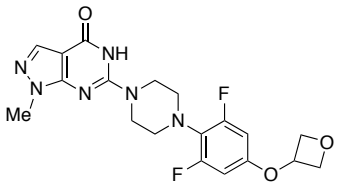
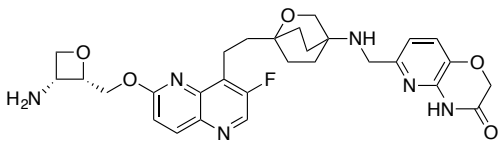
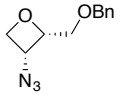
Table 18. Oxetanes Prepared in Patents During Drug Discovery Research

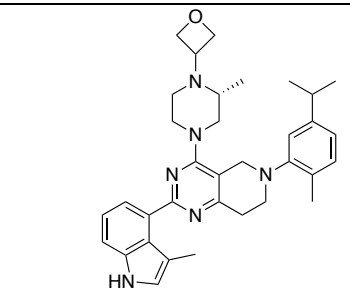
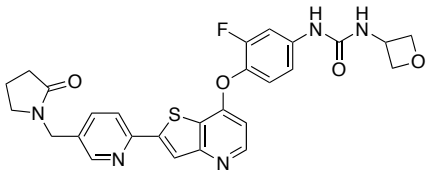
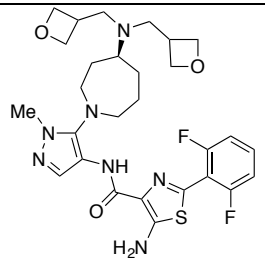
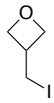
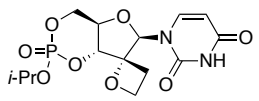
Oxetane	Oxetane Source	Potential Therapeutic Use/ Biological Data	Patent No.	Ref
	Cyclization; C-O bond via OTs displacement	Human renal renin, IC_{50} = 0.19 nM	WO9222313A1 *Abbott Laboratories, USA*.	[391]
	n.d.	Hematopoietic synergistic activity in stromal cells	WO9717964A1 *Smithkline Beecham Corporation, USA*.	[392]
	 From 2-methyleneoxetane[393]	Nucleoside analog related disorders	WO2005051944A1 *University of Connecticut, USA*.	[394]
	 C-O bond cyclization from chlorohydrin	β-secretase inhibitors	US20050282826A1 *Wyeth, John, and Brother Ltd., USA*.	[395]

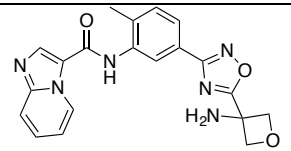
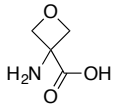
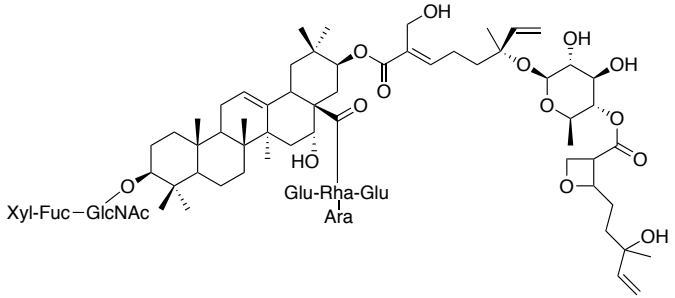
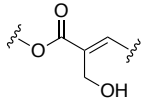
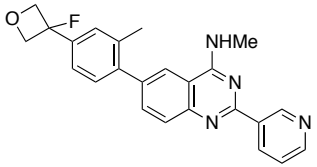
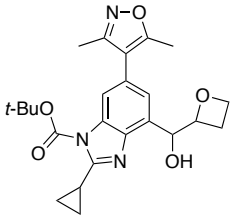
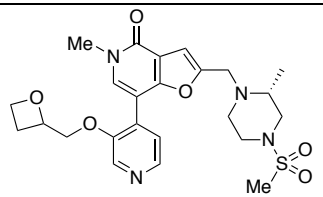
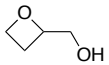
	 From corresponding diol by Mitsonobu	Antagonists, agonists of serotonin 1 (5-HTi) receptors, specifically the 5-HT_{1B}	WO2006106416A1 *Pfizer Inc., USA.*	[396]
		Glucokinase activators	US20080021032A1 *Hoffmann-La Roche Inc., USA.*	[397]
		Phoshodiesterase inhibitors (PDE4) IC_{50} = 52 nM	WO2008104175A2 *Leo Pharma A/S, Den.*	[398]
		Raf kinase inhibitor	WO2009111279A1 *Array BioPharma Inc., USA; Genentech, Inc.*	[399]
 R = H, Me		Anti-hepatitis C viral activity (NS5B poylmerase) IC_{50} = 0.013 μM (R = H)	WO2009101022A1 *F. Hoffmann-La Roche AG, Switz.*	[400]

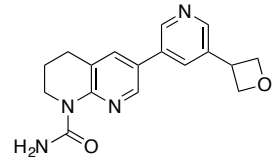
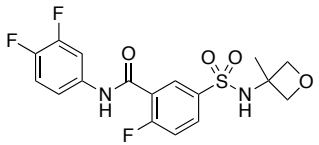
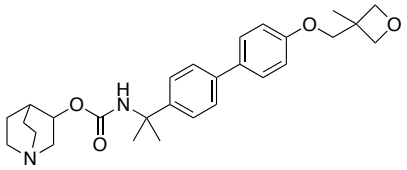
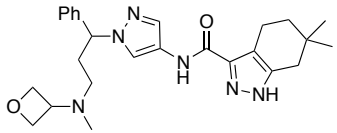
		IC_{50} = 0.134 μM (R = Me)		
		Human CRTH2 IC_{50} = 0.0018 μM	WO2010055004A1 *F. Hoffmann-La Roche AG, Switz.*	[401]
		Hypocholesterolemic activity, 87% inhibition of cholesterol absorption in mice at 1 mg/kg	WO2010100255A1 *Lipideon Biotechnology AG, Switz.*	[402]
		phosphodiesterase (PDE10A) inhibitor	WO2011154327A1 *F. Hoffmann-La Roche AG, Switz.*	[403]
	 via mesylate	JAK kinase inhibitor (Tyk2) IC_{50} < 10 nM	WO2011130146A1 *Array BioPharma Inc., USA.*	[404]

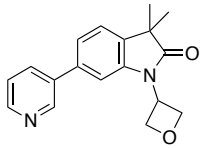
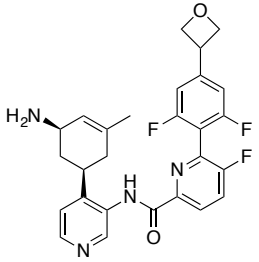
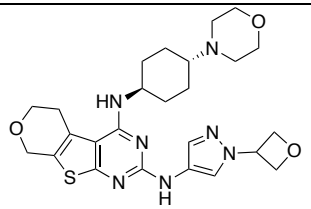
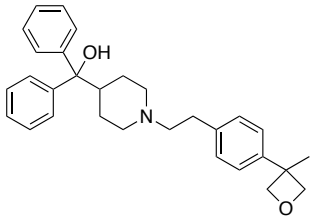
		phosphodiesterase (PDE4) inhibitor IC_{50} < 10 nM	WO2011134468A1 *LEO Pharma A/S, Den.*	[405]
		FGFR1 kinase inhibitors pIC_{50} = 7.97	WO2011135376A1 *Astex Therapeutics Limited, UK.*	[406]
	 Cyclization: C-O bond from bromohydrin	Tyrosine kinase MET inhibitor IC_{50} < 100 nM	WO2011084402A1 *Merck Sharp & Dohme Corp., USA.*	[407]
		GPBAR1 agonist EC_{50} = 1.20 μM	WO2012117000A1 *F. Hoffmann-La Roche AG, Switz.*	[408]
		Acetyl-CoA carboxylase inhibitor (ACC2) IC_{50} = 1.1 nM	WO2012001107A1 *Boehringer Ingelheim International GmbH,*	[409]

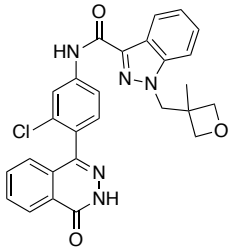
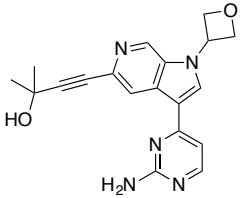
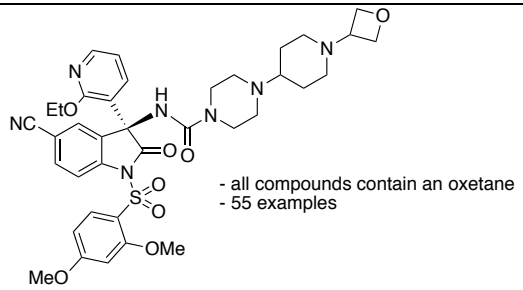
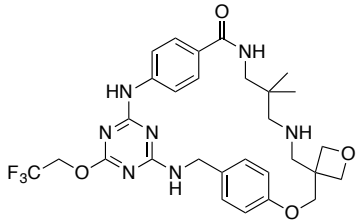
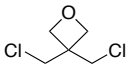
			Germany.	
		Viral replication inhibitor	WO2013185103A1 *Gilead Sciences, Inc., USA; Selcia Limited*.	[410]
 - most active compound - all contain central oxetane		Protein kinase activity modulator Human c-Met kinase assay $IC_{50} < 0.1$ μM	WO2013032797A2 *New Hope R & D Bioscience, Inc., USA*.	[411]
		Tankyrase inhibitor (TNKS1) $IC_{50} = 0.017$ μM	WO2013182546A1 *F. Hoffmann-La Roche AG, Switz.; Hoffmann-La Roche Inc*.	[412]
	 Cyclization: C-O bond from OTs	Antibacterial activity (*S. aureus* Smith) MIC = 0.25 μg/mL	WO2013003383A1 *Kyorin Pharmaceutical Co.,*	[413]

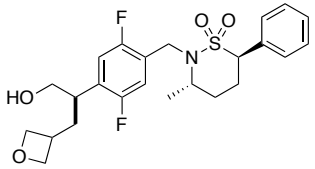
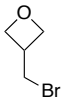
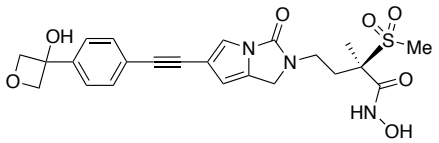
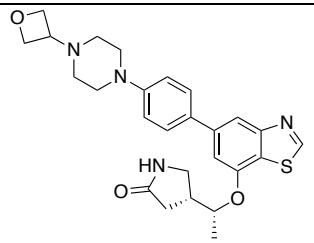
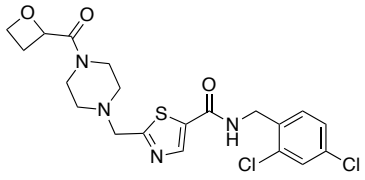
			Ltd., Japan; Merck Sharp & Dohme Corp., USA.	
		C5A Receptor modulators IC_{50} = 16 nM	WO2013016197A1 *Novartis AG, Switz.*	[414]
		PTK inhibitor (VEGFR/KDR) IC_{50} = 0.035 μM	WO2013044360A1 *MethylGene Inc., Can.*	[415]
		Pim kinase inhibitor PIM1 LC3K K_i = 0.962 nM	US20130079321A1 *Genentech, Inc., USA.*	[416]
	Mesylation and cyclization of corresponding diol	HCV antiviral agent EC_{50} = 0.13 μM	WO2013174962A1 *Janssen R&D Ireland, Ire.*	[417]

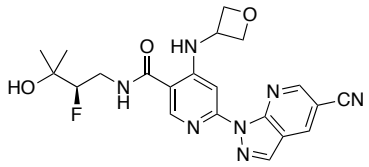
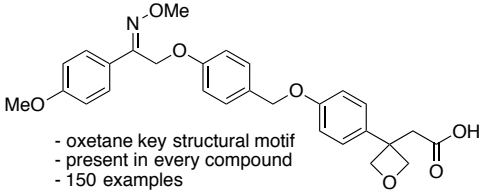
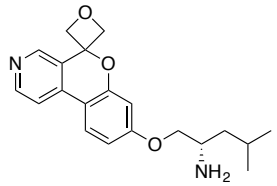
		C-kit kinase inhibitor	WO2013033116A1 *IRM LLC, Bermuda.*	[418]
	 via avicin D (above) using phosphate buffer	Oxetane analog of avicin D, antitumor agents, increased potency compared to natural product	WO2013126730A1 *Research Development Foundation, USA.*	[419]
		Striatal-enriched tyrosine phosphatase inhibitor	WO2013003586A1 *Otsuka Pharmaceutical Co., Ltd., Japan.*	[420]
		Bromodomain inhibitors (BRD4)	WO2014182929A1 *Gilead Sciences, Inc., USA.*	[421]
		Bromodomain inhibitors BRD4 BD1 assay $pIC_{50} \geq 6.0$	WO2014140077A1 *Glaxosmithkline*	[422]

		Aldosterone synthase inhibitor IC_{50} = 14.3 nM	US20140323468A1 *Boehringer Ingelheim International GmbH, Germany*.	[423]
		HBV antiviral agent	WO2014106019A2 *Philadelphia Health & Ed. Corp., D/B/A Drexel and 2 others*.	[424]
		Glucosylceramide synthase inhibitors IC_{50} = 7.2 nM	WO2014043068A1 *Genzyme Corporation, USA*.	[425]
		ITK Kinase inhibitors K_i = 0.6 nM	WO2014023258A1 *F.Hoffmann-La Roche AG, Switz.; Genentech, Inc*.	[426]

		L-687,414-Induced hyperlocomotion inhibitor (CNS diseases)	WO2014202493A1 *F. Hoffmann-La Roche AG, Switz.*	[427]
		Pim kinase inhibitor (Pim 1) IC_{50} = 0.02 nM	WO2014033631A1 *Novartis AG, Switz.*	[428]
		Fms-like tyrosine kinase 3 inhibitor (FLT-3) $IC_{50} \leq 1$ μM	WO2014194242A2 *Nimbus Iris, Inc., USA.*	[429]
		Antiinfective activity MIC = >256 μg/mL	WO2014052836A2 *University of Rochester, University of Kansas, USA.*	[430]

		Rho-kinase inhibitor (ROCK1) IC_{50} = 0.1–100 nM	WO2014113620A2 *Bristol-Myers Squibb Company, USA*.	[431]
		NIK inhibitor (MSD MBP) IC_{50} = 15 nM	WO2014174021A1 *Janssen Pharmaceutica NV, Belg*.	[432]
		Vasopressin-related diseases (V1b receptor) K_i = < 1 nM	WO2014140186A1 *Abbvie Deutschland GmbH & Co. KG, Germany*.	[433]
		HCV entry inhibitor (H77C) EC_{50} = 0.796 nM	WO2014123894A1 *Bristol-Myers Squibb Company, USA*.	[434]

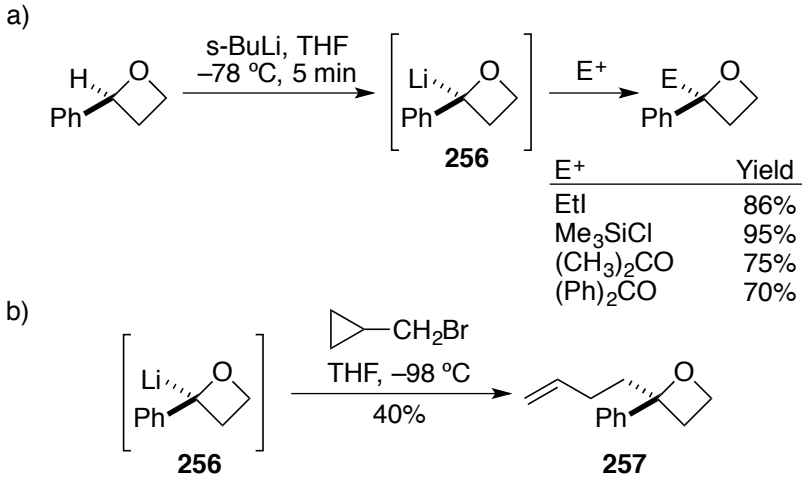
		RORc modulator IC_{50} = 0.004 μM	WO2015104356A1 *F. Hoffmann-La Roche AG, Switz.; Genentech, Inc.*	[435]
		Antibacterial activity MIC *E.Coli* = 0.5 mg/L MIC *P. aeruginosa* = 1 mg/L MIC *K. Pneumoniae* = 1 mg/L	WO2015132228A1 *Actelion Pharmaceuticals Ltd., Switz.*	[436]
		Spleen tyrosine kinase (Syk) inhibitor IC_{50} = 0.6086 nM	WO2015017610A1 *Gilead Sciences, Inc., USA*	[437]
	n.d.	Soluble epoxide hydrolase (sEH) IC_{50} = 9.67 nM	WO2015082474A1 *Sanofi, Fr.*	[438]

		Interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitor IC_{50} = 3.7 nM	WO2015103453A1 *Bristol-Myers Squibb Company, USA*	[439]
		G-protein coupled receptor (GPR40) EC_{50} = >5 but <200 nM	WO2015028960A1 *Piramal Enterprises Limited, India.*	[440]
		AAK1 kinase inhibitor	WO2015038112A1 *Bristol-Myers Squibb Company, USA.*	[441]

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

Recently a small number of examples of the functionalisation of intact oxetane rings at the 2-position have emerged, involving deprotonation of oxetane derivatives. Capriati reported the synthesis of 2-substituted phenyloxetanes by the formation of 2-lithio-2-phenyloxetane **256** which was chemically stable at –78 °C for up to 30 min (Scheme 102a).[442] 2-Phenyloxetane was regioselectively deprotonated using *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 non-polar (hexane/TMEDA) solvents, the lithiated intermediate being configurationally unstable. The reaction of the lithiated intermediate with cyclopropylmethyl bromide gave the butenyl-coupled product **257** which was cited as support for an SET mechanism, also being the cause of racemization (Scheme 102b).

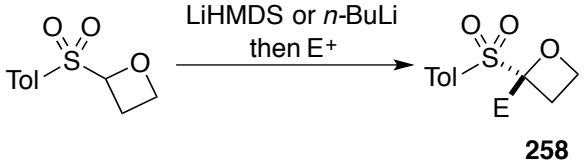
Scheme 102. Formation and Reactivity of 2-Lithio-2-phenyloxetane.



Bull reported the regioselective lithiation of 2-tolylsulfonyloxetane followed by reaction with electrophiles to generate 2-substituted-2-sulfonyloxetanes **258** (Scheme 103).[246] Depending on the nature of the electrophile, *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, which was particularly prominent when *s*BuLi was employed.

Scheme 103. Functionalization of 2-Aryl Sulfonyl Oxetanes via Lithation of the Oxetane Ring

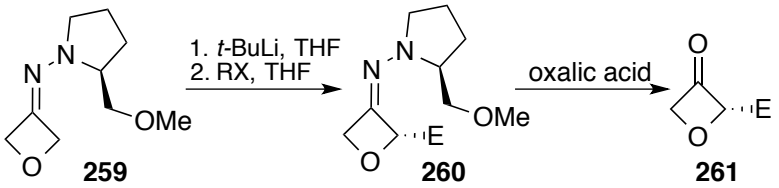


258

E^+	Yield
MeI	93
EtI	85
allylBr	91
3-F-$(C_6H_4)CH_2Br$	90
$(CH_3)_2CHCHO$	86

Shipman reported the enantioselective synthesis of 2-substituted oxetan-3-ones by α-lithiation and alkylation of the SAMP/RAMP hydrazones **259** derived from oxetan-3-one (Table 19).[443,444] Deprotonation of hydrazone **259** with *t*BuLi to form the aza-enolate, followed by electrophilic trapping, accessed 2-alkylated oxetanes **260** in good yields and diastereoselectivities. Using ozone or oxalic acid, the alkylated hydrazones **260** were converted to the corresponding enantioenriched oxetan-3-ones **261** with ee's of up to 84%. The synthesis of a 2,2-disubstituted oxetan-3-one was achieved in 90% ee using 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.

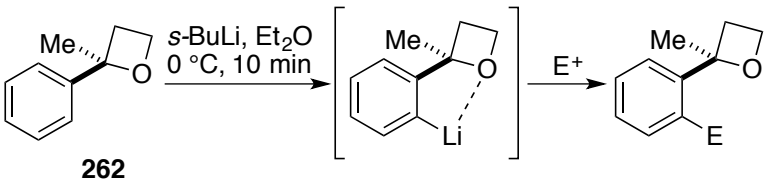
Table 19. Enantioselective Synthesis of 2-Substituted Oxetan-3-ones



Entry	Electrophile (RX)	Yield **260** (%)	Yield **261** (%)	ee (%)
1	BnBr	73	79	74
2	$BrCH_2CH{=}CHPh$	57	77	84
3	$CH_3(CH_2)_7I$	60	85	83
4	$ICH_2CH_2CH_2OTBS$	68	60	84
5	PhCHO	62	92 (1:1 dr)	(*S*,*R*) = 54 (*S*,*S*) = 2

Oxetanes have recently been shown to be powerful directing groups for *ortho*-lithiation on aromatic rings. Capriati first developed this feature of the oxetane ring in 2012 using 2-methyl-2-phenyloxetane **262**, without a benzylic proton, for the regioselective synthesis of functionalized 2-aryloxetanes (Scheme 104).[445] Treatment of oxetane **262** with *s*BuLi in Et_2O resulted in lithiation of the *ortho* position of the aryl ring, which was reacted with a variety of electrophiles including aldehydes, ketones, Me_3SiCl and Bu_3SnCl 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 metallation.

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

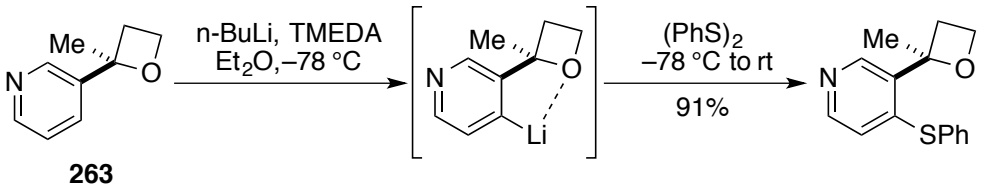


262

E^+	Yield
MeI	98
Me_3SiCl	90
$PhCON(CH_3)_2$	70
CH_3COCH_3	80

Rouquet reported the regioselective *ortho* functionalization of 3-oxetanyl pyridines.[446] Treating 3-(2-methyloxetan-2-yl)pyridine **263** with 1.4 equiv of *n*BuLi in the presence of TMEDA at –78 °C in Et_2O resulted in lithation at the pyridine C4 position (Scheme 105). A wide range of electrophiles was employed to generate the 4-functionalized pyridines, including for example diphenyl disulfide. The reaction was carried out on a gram scale, using MTBE as the solvent and I_2 as the electrophile, to afford the 4-iodopyridine derivative in 67%.

Scheme 105. *Ortho*-Metallation on Pyridine Directed by an Oxetane

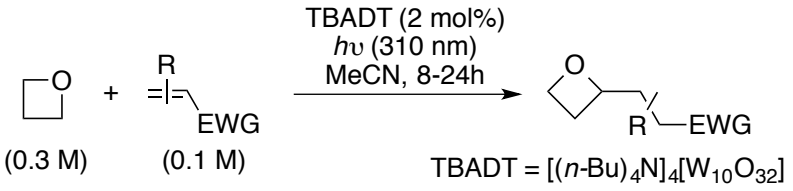


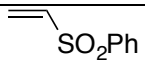
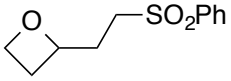
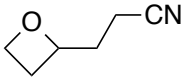
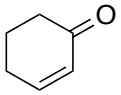
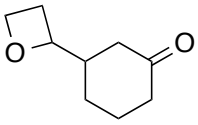
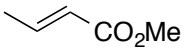
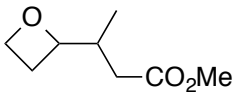
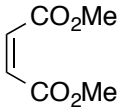
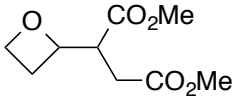
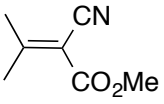
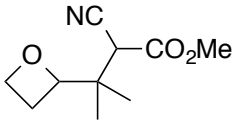
263

There have been two recent reports of a radical functionalisation at the 2-position of oxetane itself, maintaining the ring intact.[447,448,449] Ravelli reported the functionalisation of oxetane through C–H activation by a decatungstate photocatalyst TBADT, $[(n\text{-}Bu)_4N]_4[W_{10}O_{32}]$, and addition to an electron poor olefin (Table 20).[447] Using 3 equiv relative to the olefin, oxetane was irradiated in the presence of TBADT (2 mol%) in acetonitrile to generate the oxetane α-oxy radical. Substituted oxetanes were generated using 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]

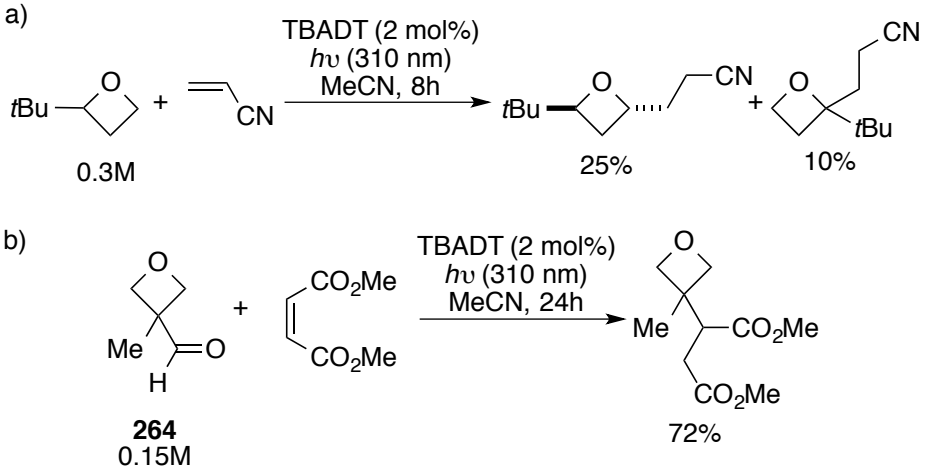
Table 20. Photocatalytic Synthesis of Oxetane Derivatives



Entry	Olefin	Product	Yield (%)
1			70
2			51
3			62
4			60
5			75
6			88

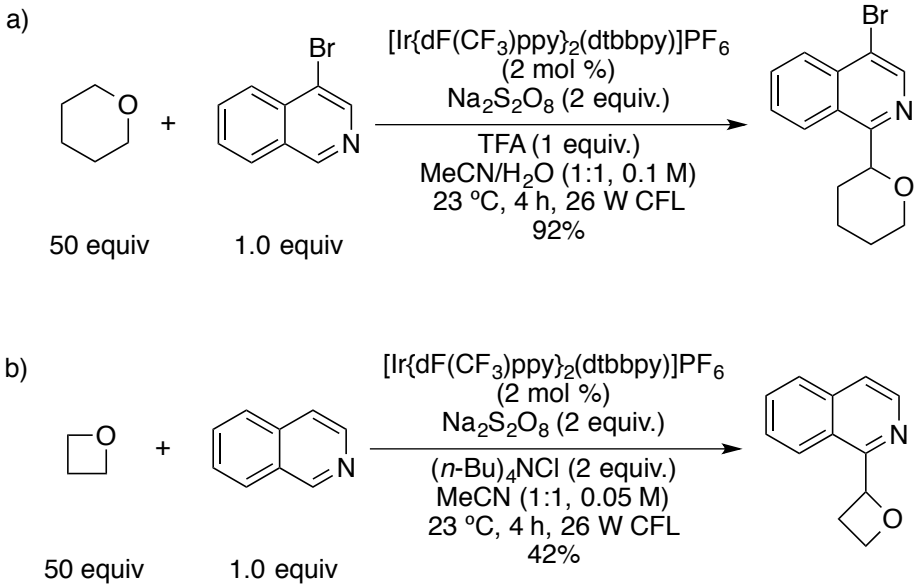
When a 2-substituted oxetane was used, in the presence of a non-hindered olefin, a mixture of the 2,2-disubstitued and 2,4-disubstituted regioisomers was formed. When a bulky substituent (e.g. *t*Bu) was present at C2 of the oxetane, reaction at the secondary radical was preferred (Scheme 106a). This was suggested to be due to a decreased reaction rate allowing back-hydrogen transfer to occur. Functionalization at the 3-position could be achieved by employing oxetanecarbaldehyde **264** (Scheme 106b).[447]

Scheme 106. Regioselectivity of the Alkylation of Oxetane Using a Decatungstate Photocatalyst



MacMillan and co-workers recently developed a visible-light-promoted photoredox catalytic method for the direct α-arylation of dialkylethers with electron-deficient heteroarenes.[448] Using 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 dialkylether component included a number of THFs, 1,4-dioxane, 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 the addition of $(n\text{Bu})_4\text{NCl}$ to solubilize the persulfate anion, led to successful coupling of oxetane and isoquinoline, albeit in a yield of 42% (Scheme 107b).

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

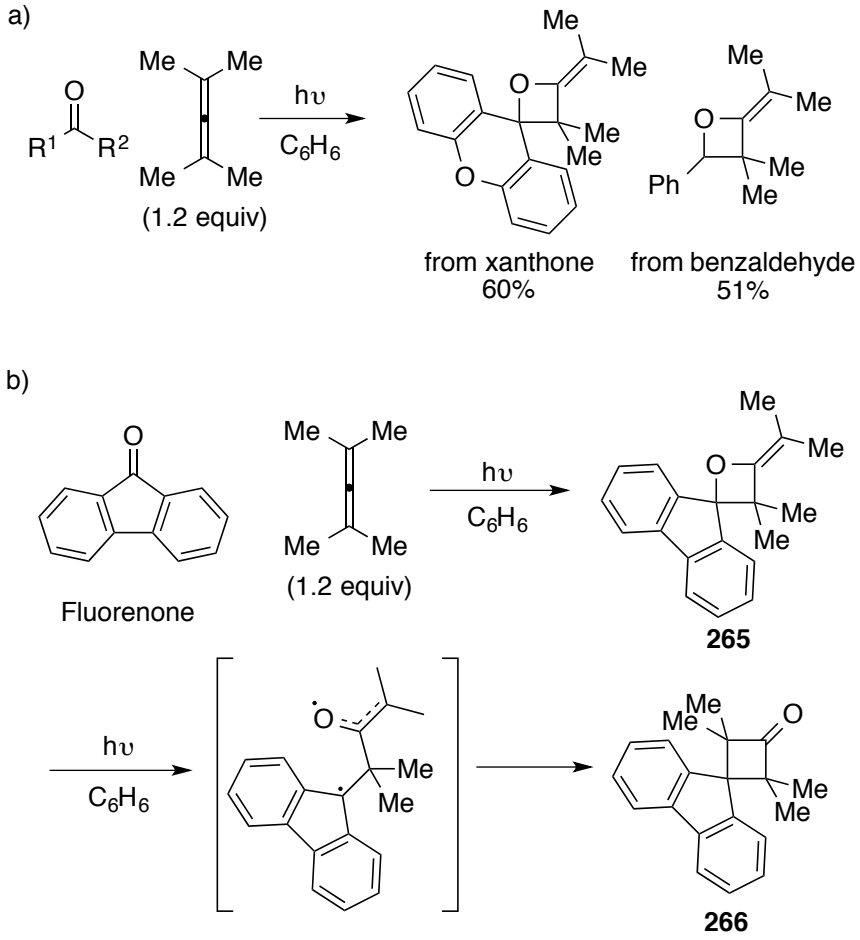


7 SYNTHESIS AND REACTIVITY OF 2-METHYLENEOXETANES

7.1 Synthesis of 2-Methyleneoxetanes

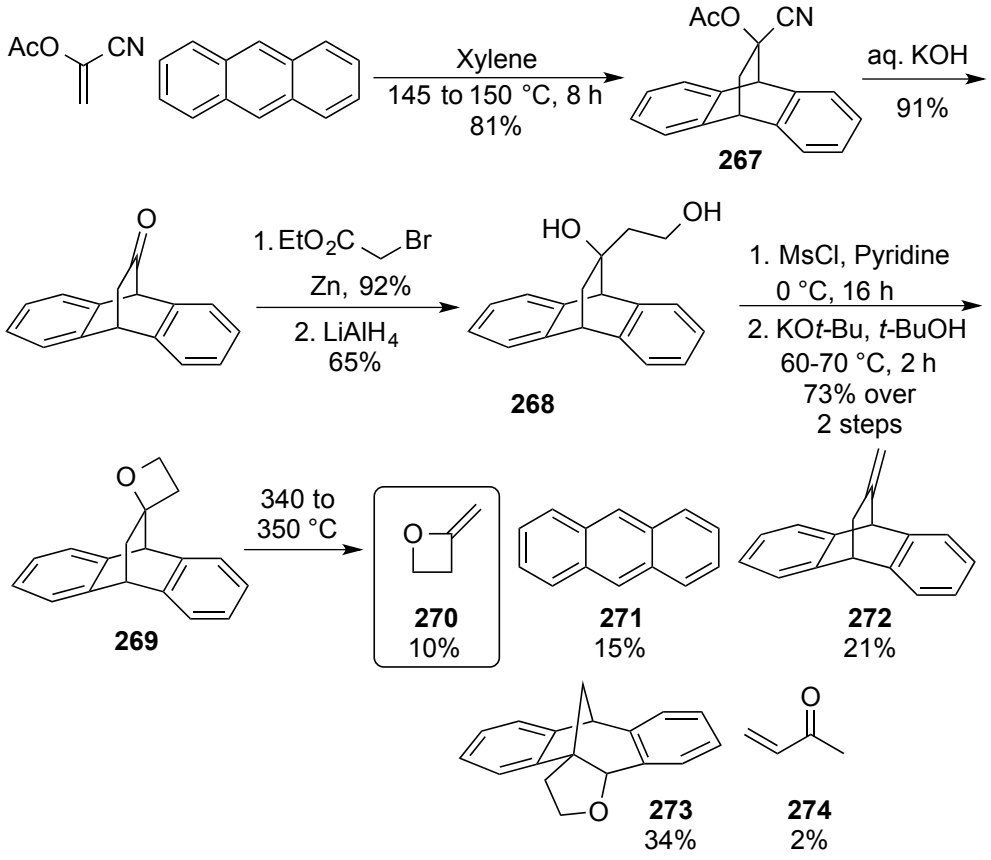
2-Methyleneoxetanes, oxetanes that bear an exocyclic C=C double bond at the 2-position, have been known since the late 1960s. The first examples of 2-methyleneoxetanes were synthesized by the Paternò–Büchi reaction. In 1966, Glick showed that excited state carbonyl derivatives added to allenes using a high pressure mercury arc lamp.[450] 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 extended the Paternò–Büchi reaction with allenes and carbonyl compounds to include xanthone and benzaldehyde (Scheme 108a).[451,452] 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).[451,452]

Scheme 108. 2-Methyleneoxetanes from Xanthone, Benzaldehyde and Fluorenone



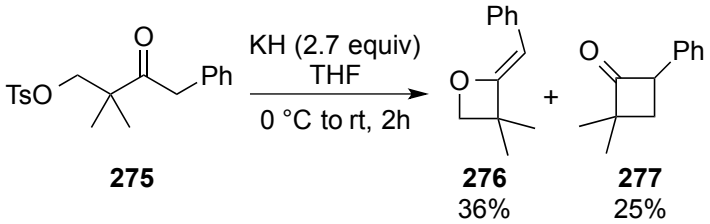
In the 1970s, Hudrlik prepared the parent 2-methyleneoxetane **270** through a retro-Diels–Alder reaction (Scheme 109).[453,454] A lengthy synthesis commenced with a Diels-Alder reaction between anthracene and α-acetoxyacrylonitrile to afford **267**, followed by several transformations to afford diol **268**. The primary alcohol was activated with MsCl and the crude reaction material was cyclized using Williamson etherification conditions (KO*t*Bu/*t*BuOH) 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]

Scheme 109. First Synthesis of 2-Methyleneoxetane 270



Hudrlik also demonstrated that 2-methyleneoxetanes could be synthesized through an intramolecular *O*-alkylation of enolates (Scheme 110).[455] 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 through crude; so the yields for the final products are estimated. The *gem*-dimethyl group was essential to facilitate cyclization.

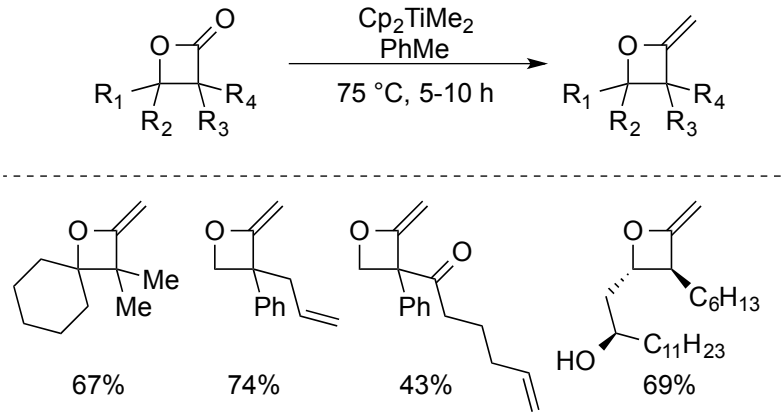
Scheme 110. Synthesis of 2-Methyleneoxetanes via an Intramolecular *O*-Alkylation of an Enolate



With no further investigations reported for over 20 years, in 1996 Howell reported a new approach to 2-methyleneoxetanes through the methylenation of β-lactones (Scheme 111).[456] Good yields were achieved with the Petasis reagent to generate varied substituted methyleneoxetanes, whereas with the

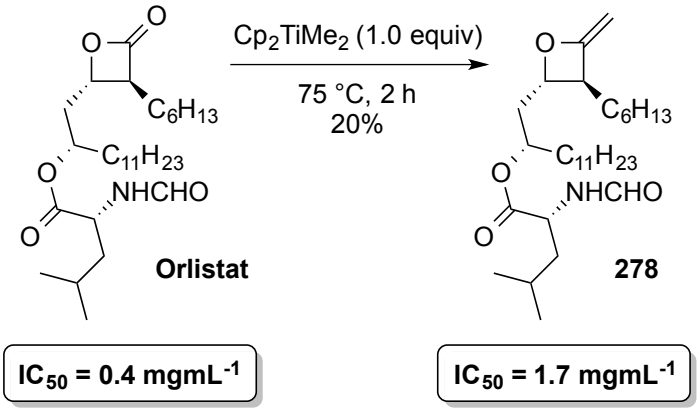
more Lewis acidic Tebbe reagent the product could not be isolated. Howell has used this method extensively for the preparation of 2-methyleneoxetanes and in numerous studies on their reactivity (See Section 7.2).

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



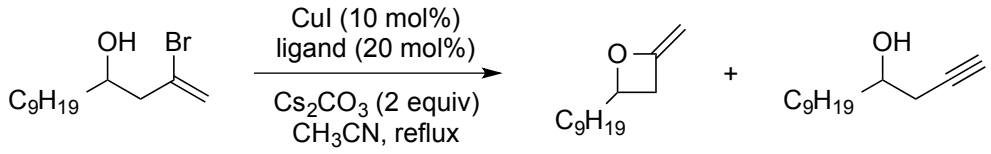
A 2-methyleneoxetane analog of Orlistat (**278**), a pancreatic lipase inhibitor, was prepared in 20% yield using the Petasis reagent to react at the β-lactone (Scheme 112).[457,458,459] This analog was then directly compared against Orlistat in an assay against porcine pancreatic lipase (PPL) with tributyrin as the substrate.[459,460] Comparative IC_{50} values showed that analog **278** displayed activity against PPL, albeit lower than Orlistat (IC_{50} = 1.7 mg mL^{-1} vs IC_{50} = 0.4 mg mL^{-1}), and preliminary kinetic studies suggested irreversible inhibition. Despite the lower activity of the methyleneoxetane analog this was a significant result as the carbonyl group of Orlistat was believed to be integral to both interaction and reaction with pancreatic lipase.

Scheme 112. Synthesis of 2-Methyleneoxetane Analog of Orlistat



In an alternative approach, Li reported the synthesis of 2-methyleneoxetanes by a Cu-catalyzed intramolecular *O*-vinylation.[461] 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** was observed (Scheme 113). Only alkyne **281** was observed in the absence of a ligand, formed by direct elimination of HBr.

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

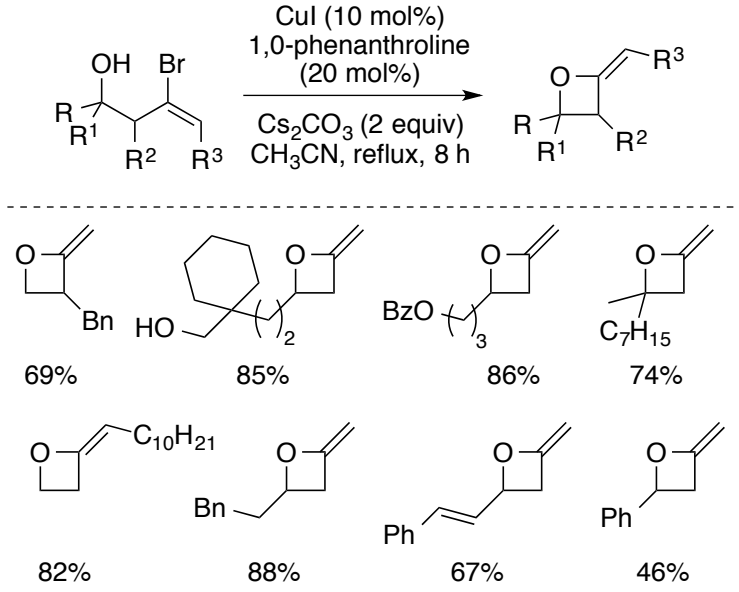


279 **280** **281**

ligand:	**280**	**281**
n.a.	0%	85%
1,10-phenanthroline	98%	0%

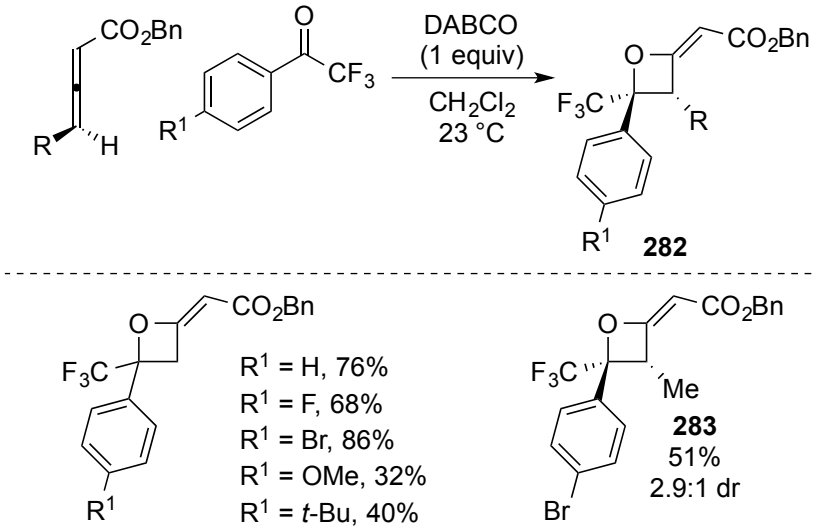
Primary, secondary and tertiary alcohols were all good substrates under these cyclization conditions (Scheme 114), with the order of reactivity of secondary alcohols being: aliphatic > allylic > benzylic. The configuration of a substituted C=C double bond was retained in the cyclization, but the presence of the additional substituent required higher temperatures. γ-Chlorohomoallylic alcohol analogs were unreactive under the reaction conditions. The reaction was successful for other ring sizes, and interestingly, competition experiments established that the 4-*exo* ring closure was preferred over ring closure to form 5 or 6 membered rings. This was proposed to be due to pre-coordination of the Cu-catalyst to the alkoxide prior to oxidative addition, leading to the formation of a favorable 5-membered ring structure containing Cu, following oxidative addition. Interestingly, the equivalent Pd-catalyzed reactions favor the 5-*exo*-ring closure.[461]

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



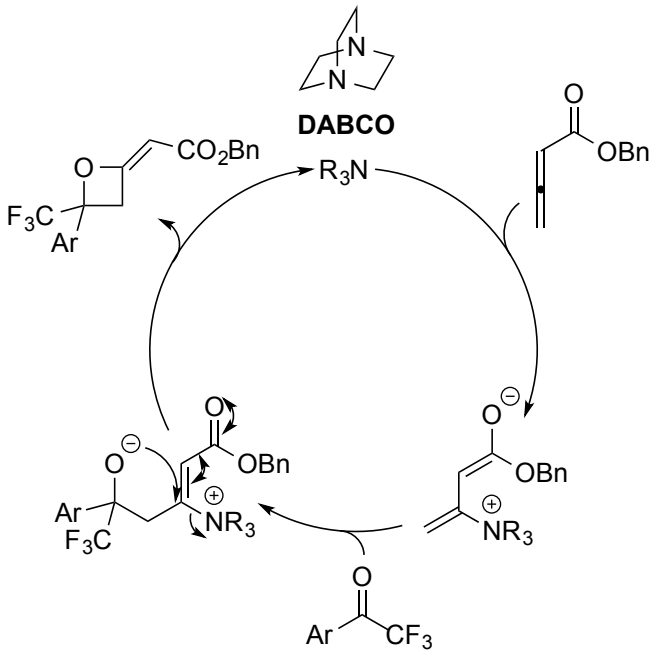
In 2011 Miller and Saunders showed that formal cycloadditions of allenoates and 2,2,2-trifluoroacetophenones could be achieved to form either dihydrofurans or 2-alkylideneoxetanes when Lewis basic catalysts were used.[462] While phosphines catalyzed the [3+2] cycloaddition to give the dihydrofurans, 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 a Lewis Base-Catalyzed Formal [2+2] Cycloaddition



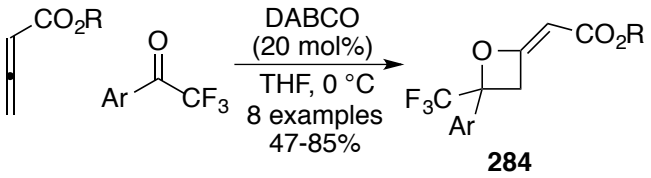
The reaction was successful with various aryl substituents: 4-halo-substituted aromatics were well tolerated, but low yields were obtained with electron rich aryl substituents. Ketones that did not possess a trifluoromethyl group were unreactive. Substitution at the γ-position of the allenic esters was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

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



At around the same time, Ye reported a similar reaction using catalytic quantities of DABCO (20 mol%) in THF at 0 °C to form 2-alkylideneoxetanes **284** (Table 21).[463] Again, electron rich ketones gave lower yields, and some sterically bulky ester groups (Cy and *t*-Bu) were tolerated on the allenoate.

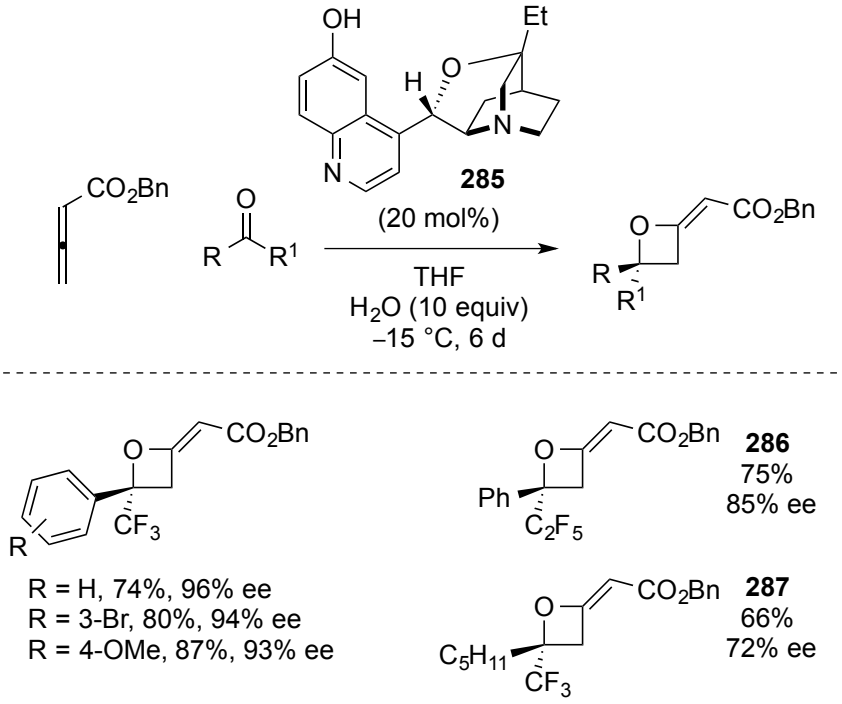
Table 21. Selected Examples of 2-Alkylideneoxetanes Synthesized Using Catalytic Amounts of DABCO



Entry	R =	Ar =	Yield (%)
1	Et	3-MeC_6H_4	73
2	Et	2-thienyl	47
3	Cy	Ph	79
4	*t*Bu	Ph	60

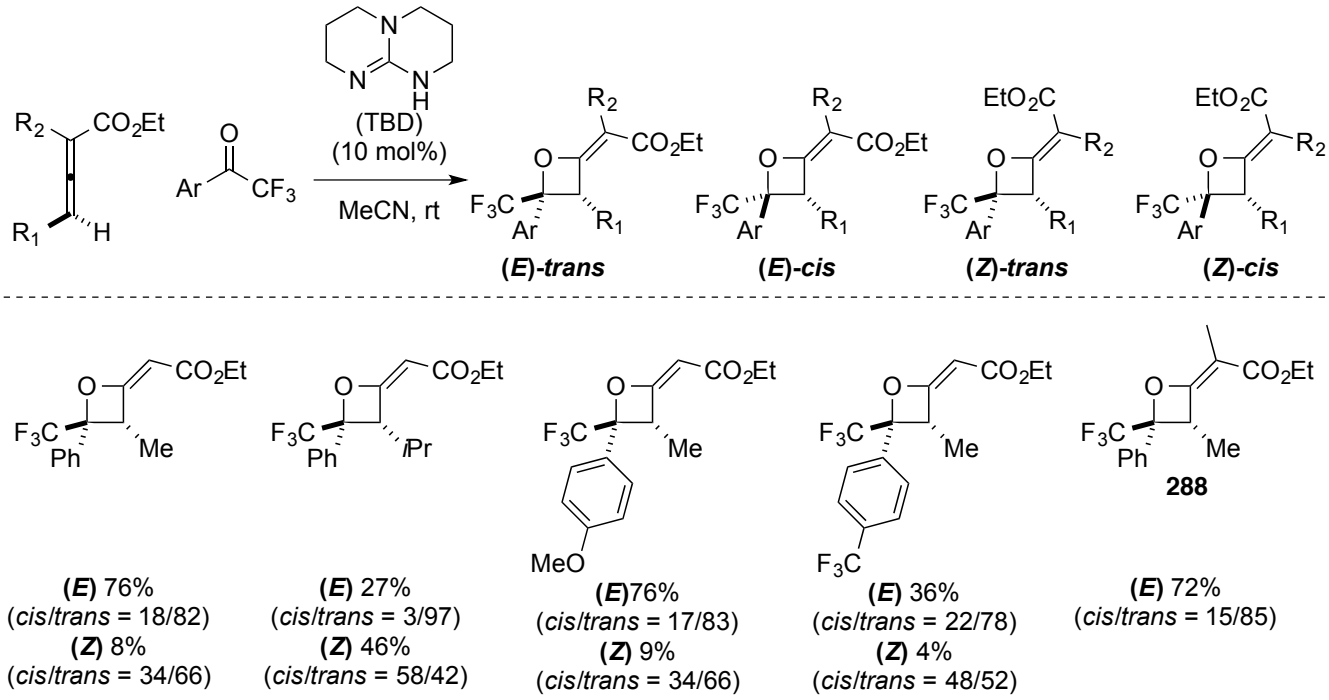
In 2012, an asymmetric version of this Lewis base-catalyzed formal [2+2] cycloaddition was reported (Scheme 117).[464] The optimized conditions used 20 mol% of β-isocupreidine **285** as catalyst, 10 equiv water as an additive in THF at –15 °C for 6 days. High yields and good to excellent ee were obtained with a variety of substrates including both electron-rich and electron-deficient aromatics. As well as trifluoromethylarylketones, the reaction worked similarly with a pentafluoroethyl ketone (**286**) and with a pentyl trifluoromethyl ketone (**287**). The proposed role of water was to stabilize the transition state for γ-addition of the extended enolate to the ketone through the formation of a 6-membered hydrogen bonded ring with the hydroxy group of the catalyst.

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



A formal [2+2] cycloaddition was developed by Selig to form more substituted 2-alkylideneoxetanes through the incorporation of additional substituents on the allenoate.[465] Using 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), a highly active nitrogen Lewis base,[466] for allenoate activation a variety of γ-substituted allenoates 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 allenoate 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**).

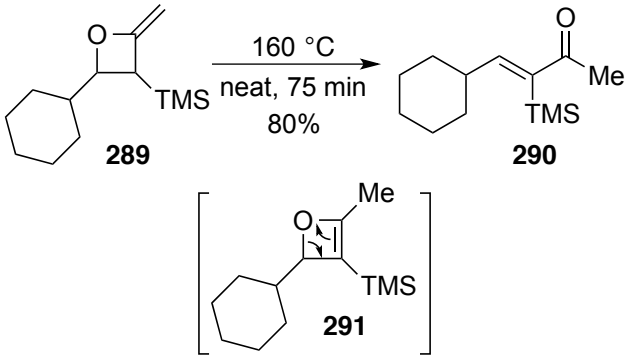
Scheme 118: Use of TBD as the Lewis Base Catalyst for the Synthesis of Highly Substituted 2-Alkylideneoxetanes



7.2 Reactivity of 2-Methyleneoxetanes

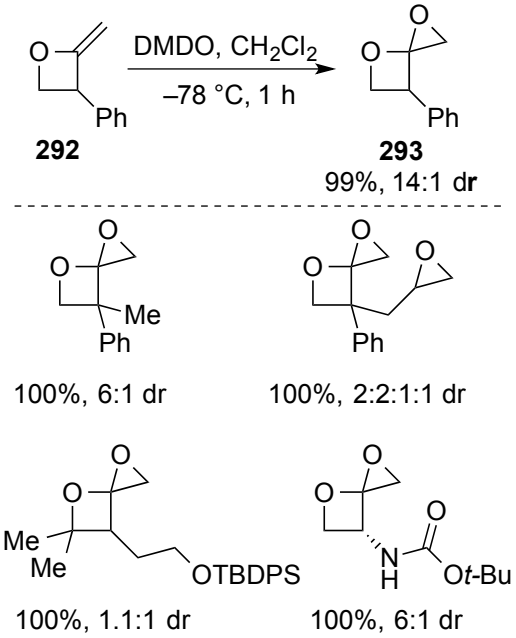
The reactivity of 2-methyleneoxetanes can be separated into two types: i) ring opening of the oxetane, and ii) functionalization of the C=C double bond. Ring opening reactions include conversion to homopropargylic alcohols through elimination,[467] nucleophilic attack with carbon or heteroatom nucleophiles at C4 to generate ketones,[468,469] and reductive ring opening of 4-aryl derivatives using 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 **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**.

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



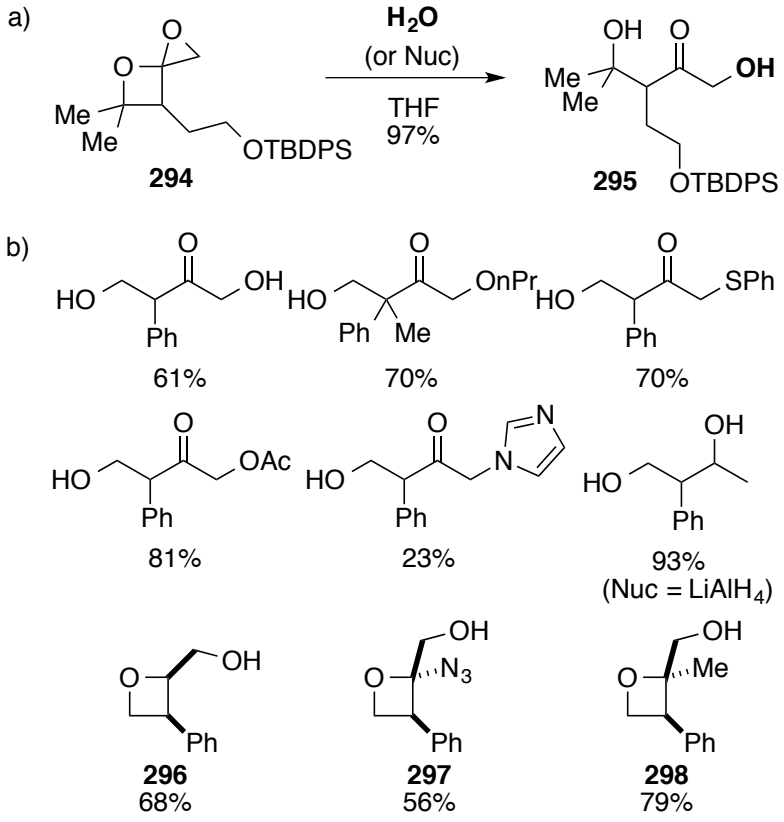
The first example of the functionalization of the exocyclic C=C double bond of a 2-methyleneoxetanes, such as **292**, was reported in 1998 through epoxidation to form 1,5-dioxaspiro[3.2]hexanes (eg **293**, Scheme 120).[393] Using anhydrous, acetone free, dimethyldioxirane (DMDO) to provide neutral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

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



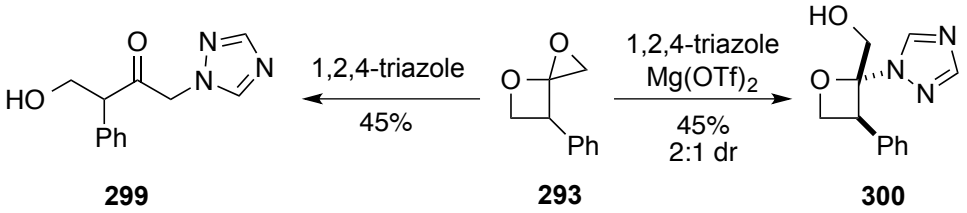
The internal acetal of these spirocycles, such as **294**, underwent hydrolysis in the absence of acid to afford ketones such as **295** in very high yields (Scheme 121a).[393] This reactivity was then reported for a variety of nucleophiles: oxygen nucleophiles gave good yields of the hydroxy ketones, 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 $LiAlH_4$ (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 $TMSN_3$ (**297**) and $AlMe_3$ (**298**).

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



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 analog 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 therefore investigated other Lewis acids, and the addition of $Mg(OTf)_2$ with 1,2,4-triazole, which originally gave oxetane ring opening (**299**), gave 2,2-disubstituted oxetane formation (**300**, Scheme 122).

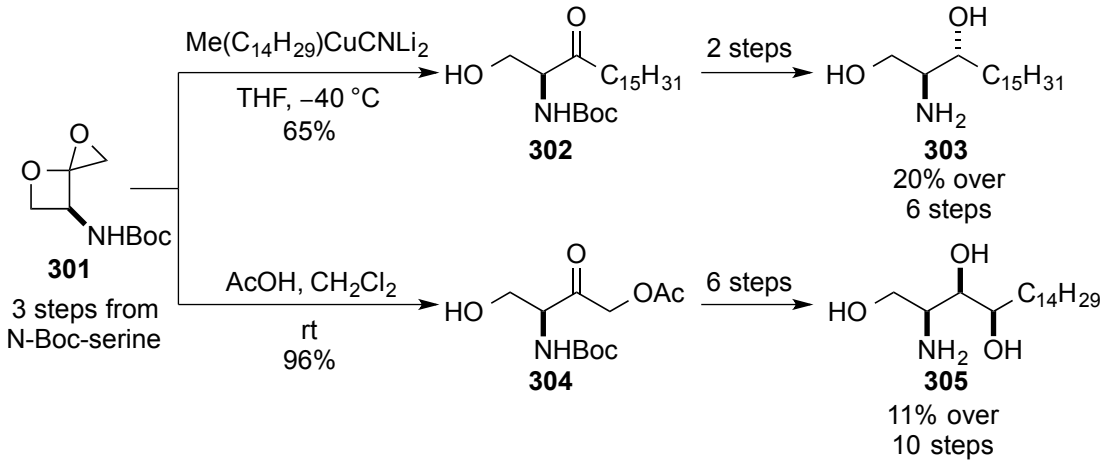
Scheme 122. Synthesis of 2,2-Disubstituted Oxetane 300 Using $Mg(OTf)_2$ and 1,2,4-Triazole



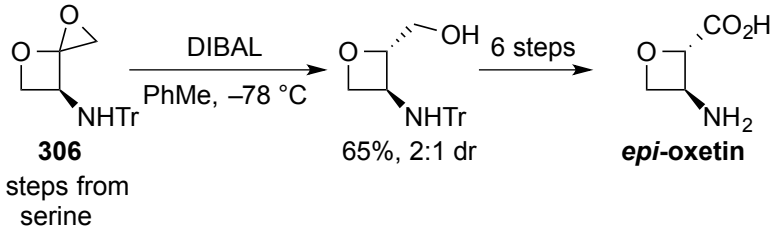
299 **293** **300**

The tandem ring opening of 1,5-dioxaspiro[3.2]hexanes was utilized in the synthesis of the challenging sphingoid base of glycosphingolipids.[476] 1,5-Dioxaspiro[3.2]hexane **301** was prepared in 3 steps from *N*-Boc-protected L-serine (Scheme 123). Addition of a higher order cuprate led to the formation of ketone **302** through nucleophilic attack at the least hindered epoxide carbon, which was converted to D-*erythro*-dihydrosphingosine **303** in 2 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 6 steps. A similar strategy was used in the synthesis *epi*-oxetin, involving a DIBAL opening of epoxide **306** (Scheme 124).[477]

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

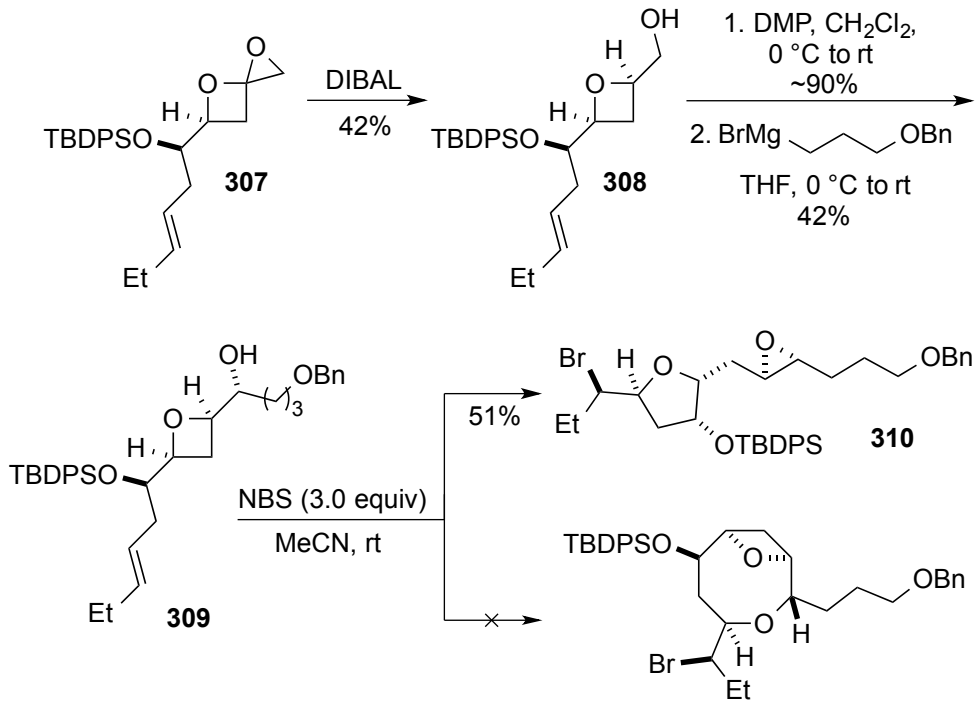


Scheme 124. Howell's Synthesis of *epi*-Oxetin Through DIBAL Opening of a 1,5-Dioxaspiro[3.2]hexane



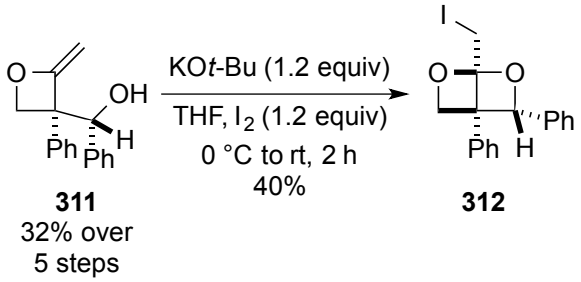
In 2012, ring opening spirocyclic epoxide **307** was used to generate hydroxymethyloxetane **308** as a possible intermediate in the synthesis of Laureatin.[478] However, treatment of derivative **309** with NBS instead mediated a rearrangement forming epoxytetrahydrofuran **310** in a 51% yield (Scheme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

Scheme 125. Unexpected Rearrangement of Oxetane 309 Affording Epoxytetrahydrofuran



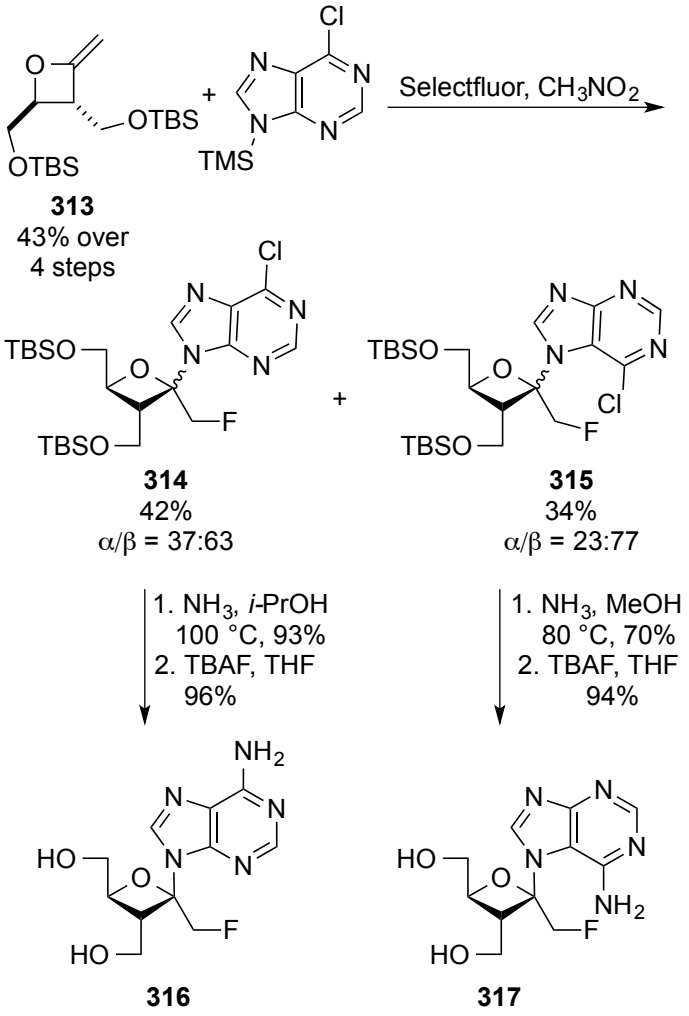
Howell also examined the reactivity of the enol ether of the 2-methyleneoxetanes with halo-electrophiles, intending to trap the intermediate oxonium ion. Treatment of oxetane **311** with KO*t*Bu followed by the addition of I_2 gave the first example of a [2.2.0] fused ketal **312** in 40% yield (Scheme 126).[479]

Scheme 126. Synthesis a [2.2.0]-Fused Ketal



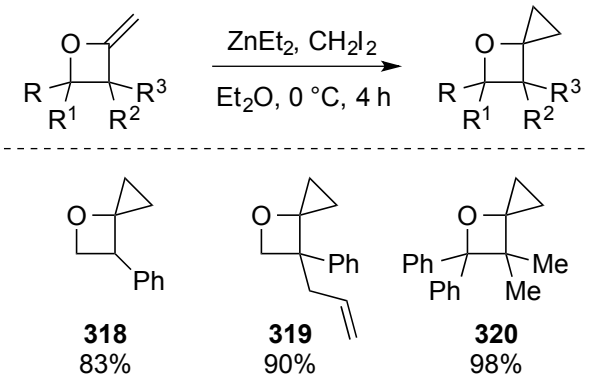
A similar strategy was used to access oxetane-containing *psico*-nucleosides, ie with a hydroxymethyl group adjacent to the base, related to the natural product oxetanocin A. This was achieved through the electrophilic addition of F^+ followed by nucleophilic attack of the nucleobase (Scheme 127).[480] From 2-methyleneoxetane **313**, selectfluor gave a good yield for the 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]

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

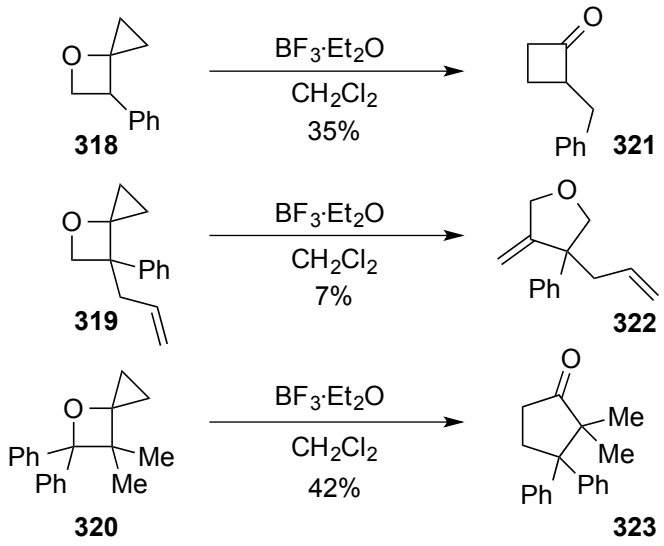


The cyclopropanation of the exocyclic C=C double bond of 2-methyleneoxetanes was achieved to form 4-oxaspiro[2.3]hexanes (Scheme 128).[481] Using $ZnEt_2$ and CH_2CI_2 in the Furukawa modification of the Simmons-Smith reaction[482] gave a good yield of the spirocyclic cyclopropanes, providing the reaction temperature was not raised above 0 ºC, across a variety of substituted oxetanes. Howell showed that 4-oxaspiro[2.3]hexanes underwent rearrangement when treated with $BF_3{\cdot}OEt_2$ (Scheme 129).[481] For example, treatment of oxetanes **318–320** with $BF_3{\cdot}Et_2O$ led to 3 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 opening and hydride shifts with the pathway influenced by the substitution on the oxetane ring.

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

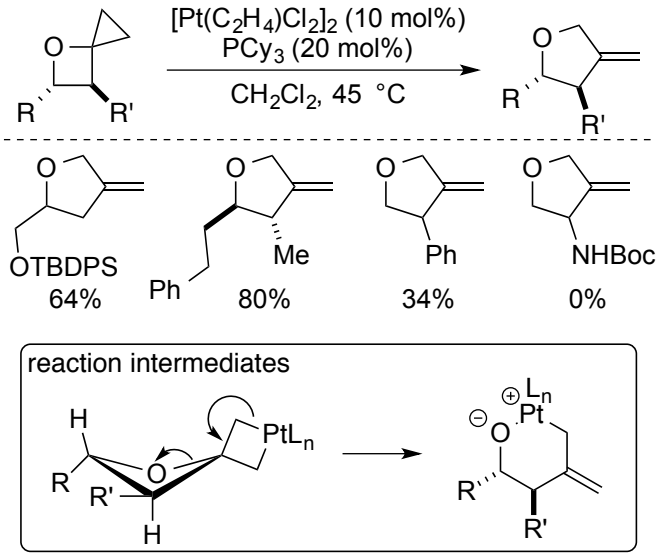


Scheme 129. Rearrangement of 4-Oxaspiro Hexanes Catalyzed by $BF_3{\cdot}Et_2O$



Oxaspirohexanes that were synthesized from 2-methyleneoxetanes also underwent rearrangement catalyzed by Zeise's Pt(II) dimer.[483] Mono-substituted 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



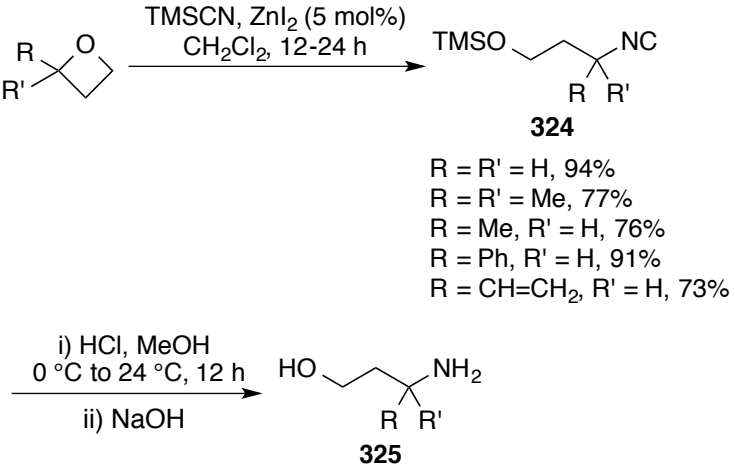
8. RING OPENING AND RING EXPANSION REACTIONS OF OXETANES

In an apparent contradication with the stability required of the oxetane ring in many medicinal chemistry applications, the strain present in the ring (106 kJ 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 Howell, on aspects of using oxetanes in the preparation of other heterocycles,[7] and by Sun, on enantioselective oxetane ring opening desymmetrisation reactions.[8] The 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

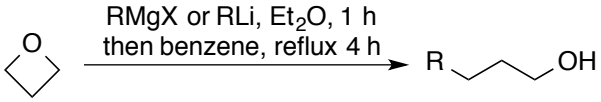
Under acidic conditions the oxetane ring can be opened with simple nucleophiles, including hydrolysis to give 1,3-glycols.[484,485] Various nucleophiles have been employed, including amines,[486,487,488,489] $KPPh_2$,[490] lithiated alkynes,[491,492,493] TMSCN,[494,495] allyl silanes,[496] $LiAlH_4$,[497] and aza-enolates.[498] Lithium enolates have been used to open mono- or di-substituted oxetanes in the presence of $BF_3{\cdot}OEt_2$.[499] Gassman reported the treatment of 2-substituted and 2,2-disubstituted oxetanes with TMSCN in the presence of zinc iodide to afford γ-hydroxy isonitriles **324** in yields of 73–94%, by ring opening at the more substituted position (Scheme 131).[495] The isonitriles were converted into the corresponding γ-amino alcohols **325** in 65–81%, following deprotection and hydrolysis.

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



Organometallic reagents alone can open oxetane at higher temperatures. In 1916, oxetane was treated with *n*-propyl magnesium bromide under reflux in ether/benzene, which resulted in the formation of *n*-hexanol in a 49% yield.[500] This prompted the seminal work by Searles on the reaction of oxetane with organometallic compounds.[501] 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

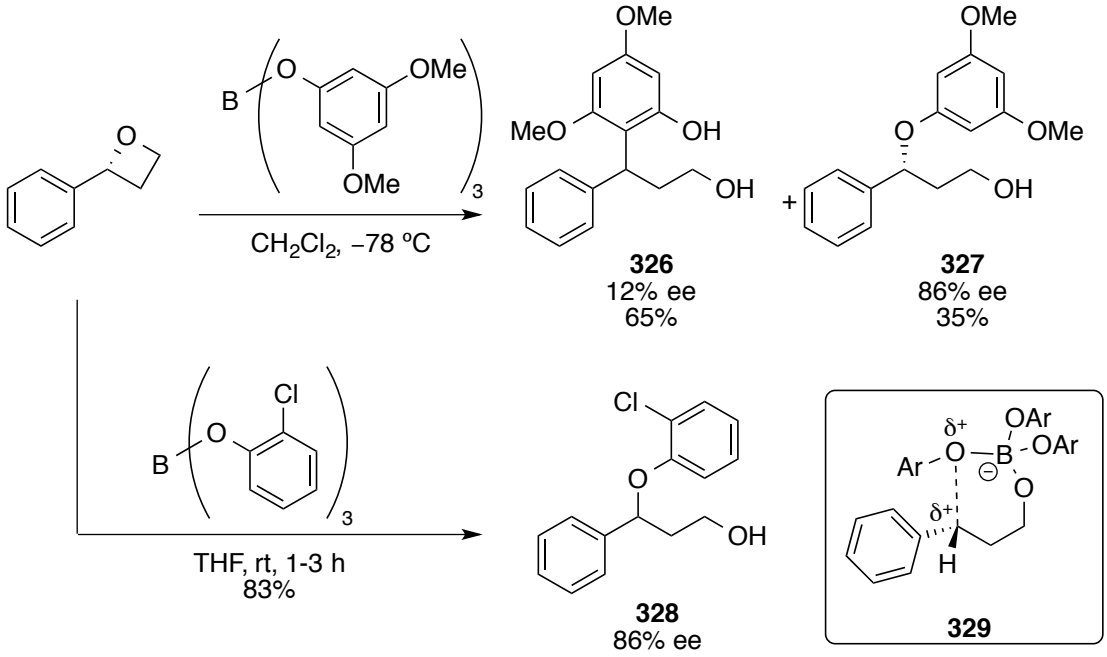


Entry	Grignard Reagent	Yield (%)
1	PhMgBr	84
2	CyMgBr	28
3	1-naphthylMgBr	80
4	*i*-PrMgCl	28
5	BnMgCl	83
6	PhLi	85
7	*n*-BuLi	28

Huynh reported milder, room temperature reaction conditions for the opening of oxetane using Grignard reagents in the presence of CuI (10 mol%) for 20 h.[504] 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]

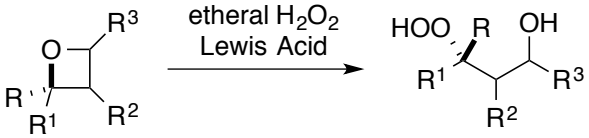
In 2008 Pineschi developed a regioselective ring opening of 2-aryl oxetanes with aryl borates under mild, neutral conditions.[506] The use of enantiomerically pure 2-phenyloxetane led to the formation of enantioenriched β-aryloxyalcohols such as **327** or **328** with little reduction in ee. This was proposed to occur via the intramolecular delivery of the aryloxy group in a six-membered transition state (**329**, Scheme 132), resulting in retention of configuration at the reacting centre. 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 of up 86% and up to 86% ee (e.g. **328**, Scheme 132).

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

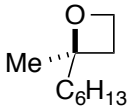
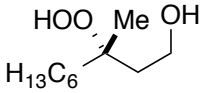
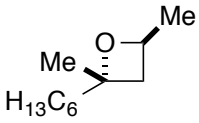
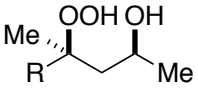
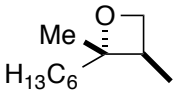
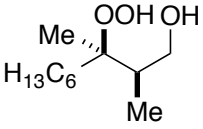


In 2002, Dussault reported the regioselective Lewis acid-catalyzed ring opening of oxetanes to afford enantiomerically enriched 1,3-hydroperoxyalcohols and 1,3-peroxyalcohols which could be converted into enantiomerically enriched 1,2,4-trioxepanes.[113] Enantioenriched oxetanes were treated with ethereal H_2O_2 in the presence of Lewis acids to form hydroperoxyalcohols. No reaction was observed when $MgCl_2$, $ZnCl_2$ or $BF_3{\cdot}OEt_2$ was employed, and the use of TFA, CSA, $BF_3{\cdot}OEt_2$ or H_2SO_4 resulted in significant amounts of 1,3-diol being formed. However, treating the oxetanes with ethereal H_2O_2 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-peroxyalkanols in yields of 39–51%.

Table 23. Opening of Substituted Oxetanes with Hydrogen Peroxide to Access Hydroperoxyalcohols

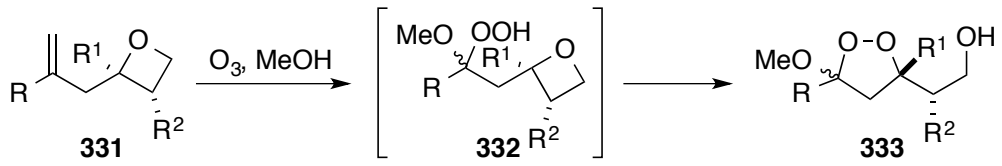


330

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

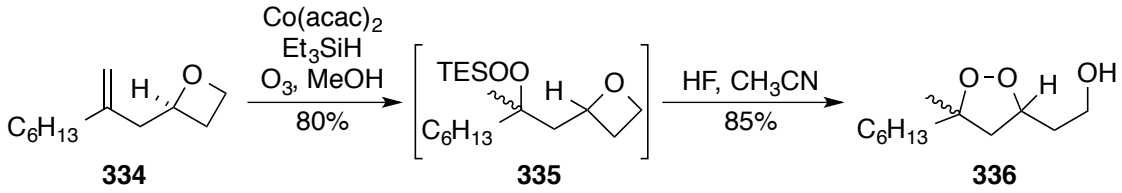
Dussault reported the corresponding intramolecular reaction in 2005.[507] Oxetanes **331** were treated with O_3 in methanol to give intermediate **332**, which underwent a 5-*exo* cyclization to afford 1,2-dioxolanes **333** as a 1:1 mixture of *cis*- and *trans*-isomers (Table 24). Interestingly, cyclization onto a mono-substituted 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). Deprotection with HF followed by 5-*exo* cyclization afforded 1,2-dioxolane **336**.[507]

Table 24. Intramolecular Opening of Substituted Oxetanes.



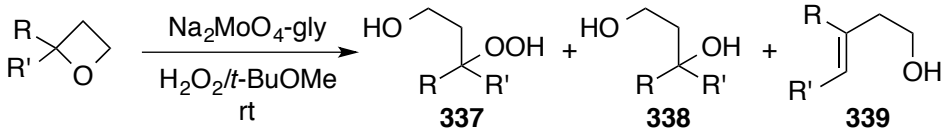
Entry	R	R^1	R^2	Yield (%)
1	Me	Me	H	57
2	C_6H_{13}	Me	H	73
3	C_6H_{13}	H	H	77
4	C_6H_{13}	Me	Me	72

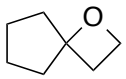
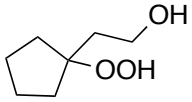
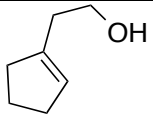
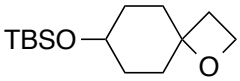
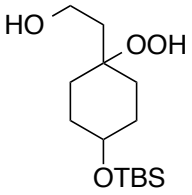
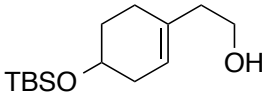
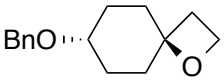
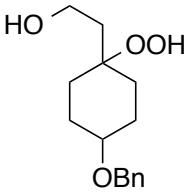
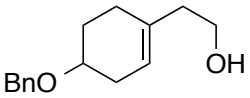
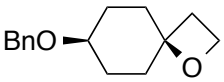
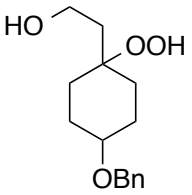
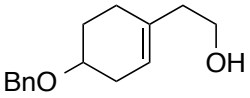
Scheme 133. Intramolecular Opening of Substituted Oxetanes with Alkyl Hydroperoxides.



Wu and Han reported the perhydrolysis of tertiary and secondary oxetanes in the presence of a molybdenum species, Na_2MoO_4-gly, in H_2O_2/*t*-BuOMe.[508] 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 3-4). Secondary oxetanes were less reactive than tertiary oxetanes under the reaction conditions; therefore a more acidic catalyst, PMA (phosphomolydbic acid), was required.[508]

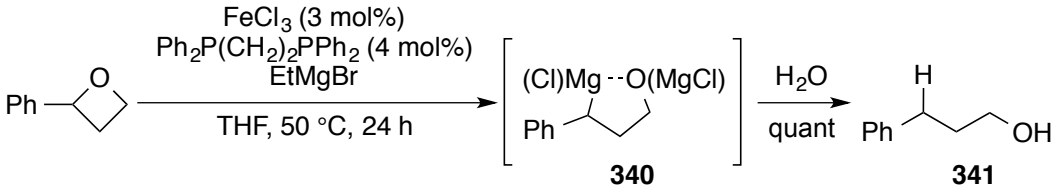
Table 25: Perhydrolysis of Oxetanes in the Presence of a Molybedenum Species.



Entry	Oxetane	Product **337**	Yield (%)	Product **339**	Yield (%)
1			48		13
2		 54%	54		13
3			33 (*cis*) 23 (*trans*)		14
4			8 (*cis*) 34 (*trans*)		12

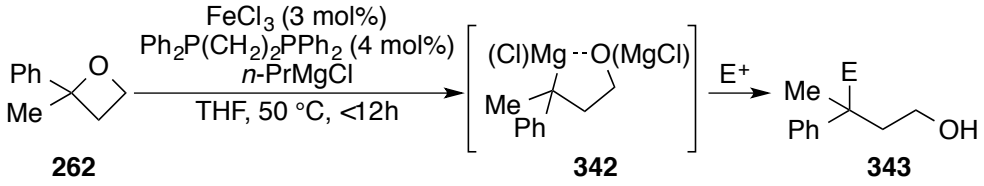
In 2014, Okamoto reported the ring opening of 2-substituted oxetanes by Fe-catalyzed reductive magnesiation at the 2-position to afford substituted 3-oxidopropylmagnesium compounds such as **340** in excellent yields.[509] 2-Phenyloxetane was treated with a Grignard reagent in THF in the presence of $FeCl_3$ 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 using 2-alkyl, 2,2-diphenyloxetane and 2,2-phenylmethyloxetane substrates, but no reaction occurred when a 3,3-disubstituted oxetane was investigated.

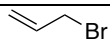
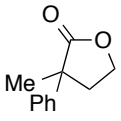
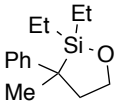
Scheme 134. Fe-Catalyzed Reductive Magnesiation of 2-Phenyl Oxetane



The 3-oxidopropylmagnesium intermediates **342** were also successfully quenched with electrophiles (Table 26). Okamoto 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.[509]

Table 26. Electrophilic Trapping of Oxidopropylmagnesium Compounds



Entry	E^+	Yield **343** (%)
1		91
2	*n*-BuBr (CuCN 10 mol%)	81
3	Me_3SiCl	98
4	PhCHO + $Ti(OiPr)_4$	91
5	CO_2	 61
6	Et_2SiCl_2	 94

In 2013, Okamoto 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 Me_3SiCl and Mg powder to form a low-valent titanium alkoxide which, in the presence of 1,4-

cyclohexadiene, reduced oxetanes to alcohols in good yields. 3,3-Disubstituted oxetanes; 2-mono-aryl and 2-mono-alkyl oxetanes; 2,2-disubstituted oxetanes and spiro compounds were all successfully reduced to the corresponding alcohols (Table 27). Okamoto proposed that the oxetane coordinated to an intermediate Ti-complex, then underwent a single electron transfer to generate a titanoxy 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 the formation of the less substituted alcohols as the major products.[510]

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

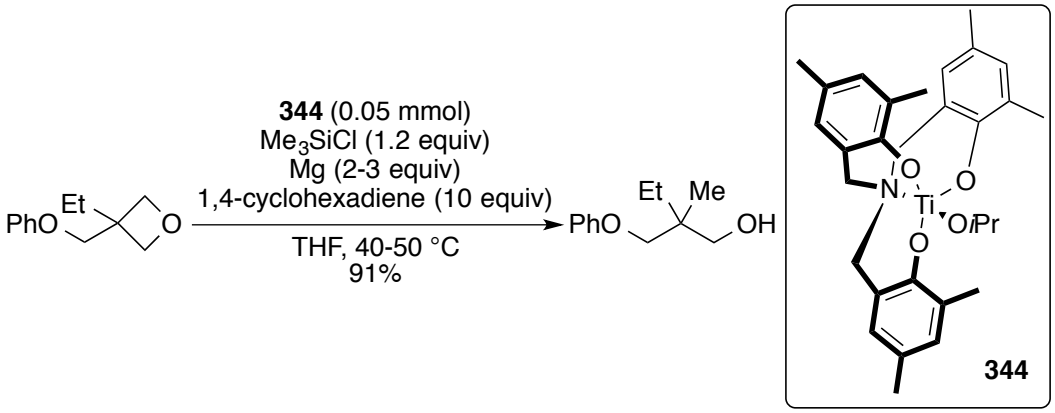
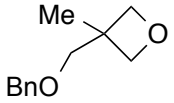
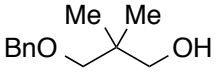
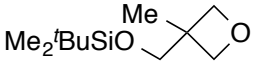
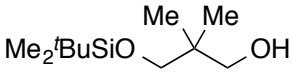
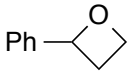
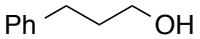
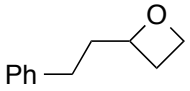
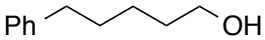
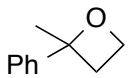
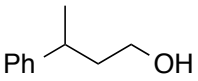
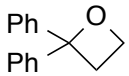
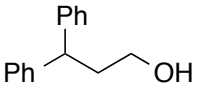
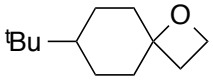
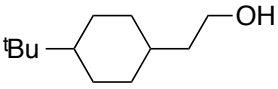
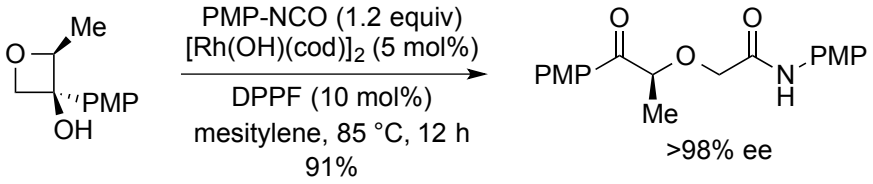


Table 27. Radical Ring Opening of Oxetanes by Treatment with a Low-Valent Titanium Complex 344

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

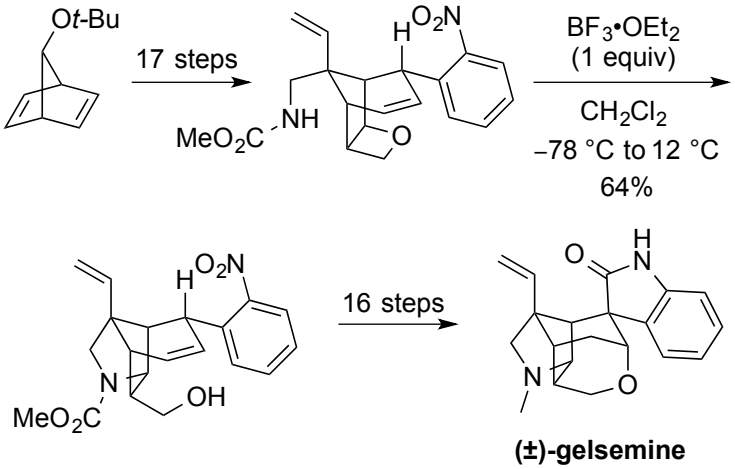
Murakami and co-workers, in 2013, showed that cyclobutanols underwent ring opening and addition to isocyanates with a Rh-catalyst. Conventionally, carbamates would be formed when cyclobutanols are reacted with isocyanates, but this combination of Rh-catalyst and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) ligand directed isocyanate addition through the *C*-atom, generating amide derivatives.[511] 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 integrity of an enantioenriched oxetanol (>98% ee; >20:1 dr) was retained in ring-opened amide (>98% ee).

Scheme 136. Rh-Catalyzed *C*-Carbamoylation of Oxetanols and Isocyanates.



Intramolecular ring opening. The use of intramolecular nucleophiles can be effective in generating new ring systems. In the total synthesis of (±)-gelsemine, Danishefsky utilized a Lewis acid-mediated intramolecular oxetane ring opening strategy with a nitrogen nucleophile (Scheme 137).[512,513]

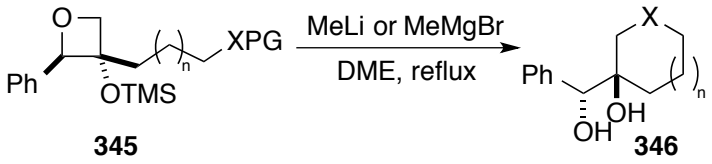
Scheme 137. Oxetane Ring Opening in Danishefsky's Total Synthesis of (±)-Gelsemine.



In 1996, Bach reported intramolecular ring opening reactions of oxetanes **345** to give diastereomerically pure sulfur, nitrogen and oxygen heterocycles **346** (Table 28).[514] A Paternò-Büchi reaction of silyl enol ethers followed by Mitsunobu reaction generated oxygen, sulfur or nitrogen containing precursors.[514,515] Cyclization to 6 and 7 membered heterocycles was achieved by treatment with organometallic reagents and heating. A tetrahydropyran was synthesized in a 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 7-membered oxepane derivative could not be generated under the same conditions with only deprotection being observed (Entry 2). Replacing DME with high boiling (162 ºC) diglyme allowed the oxepane derivative to be synthesized in a 32% yield as a mixture of diastereomers.[515] The thiotetrahydropyran and thiooxepane derivatives could be delivered as single diastereoisomers using 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.

Table 28. Scope of Bach's Ring Opening Reaction.

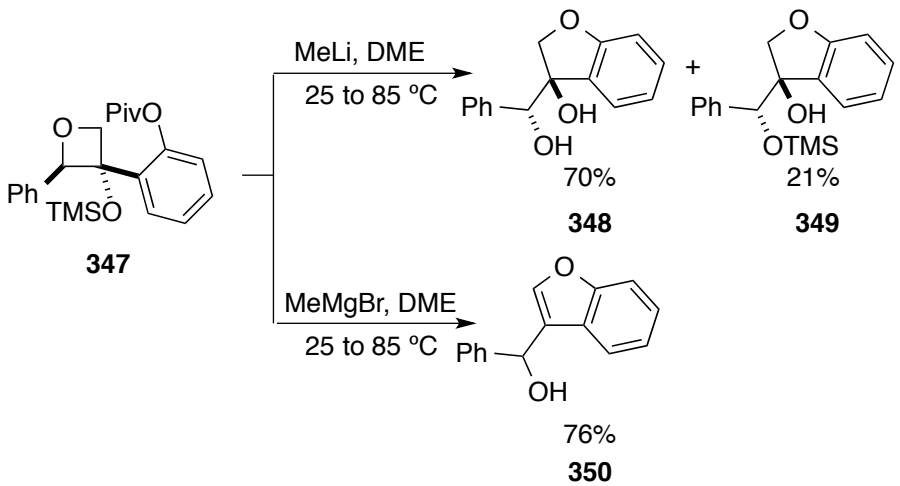


345 **346**

Entry	n	X	PG	Reagent	Time	Yield
1	1	O	Piv	MeLi	6	54
2	2	O	Piv	MeLi	5	-
3	1	S	Ac	MeLi	4	91
4	2	S	Ac	MeMgBr	5	54
5	1	NTs	H	MeMgBr	5	52

Similarly, oxetane **347**, prepared in 3 steps from 2-hydroxyacetophenone by Paternò-Büchi reaction, could be cyclized using either 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.

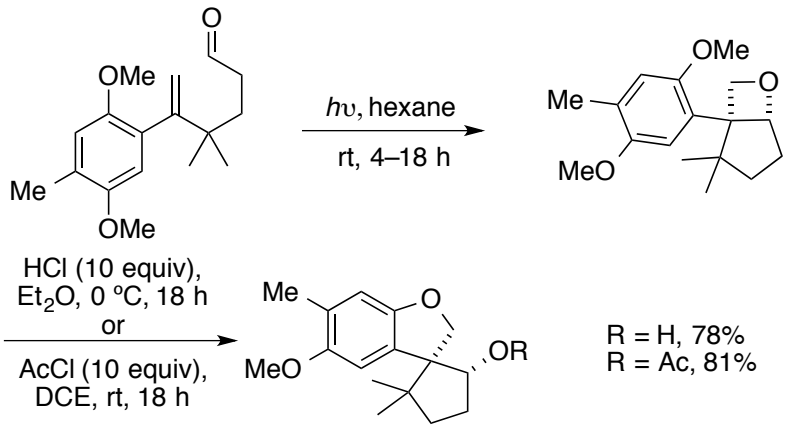
Scheme 138. Intramolecular Cyclization to Dihydrobenzofuran or Benzofuran Derivatives



347 **348** **349** **350**

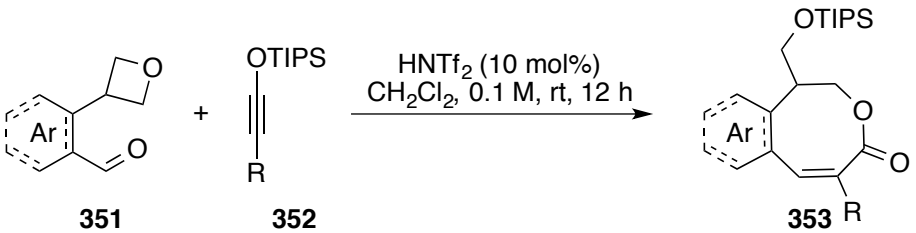
Grainger examined the ring opening of oxetanes to yield dihydrobenzofurans.[516] A Paternò-Büchi reaction formed the oxetane moiety, and then acid-promoted intramolecular cyclization occured with a proximal aryl-methoxy group acting as the nucleophile (Scheme 139). The use of ten equiv of HCl gave the bis-spirocyclic hydroxy products in yields between 34 and 78%. Acetyl chloride could also be used as a promotor to give acetate derivatives.

Scheme 139. **Synthesis of *bis*-Spirocycles through a Paternò-Büchi Reaction and Acid Promoted Intramolecular Cyclization**

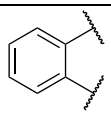
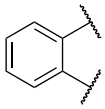
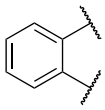
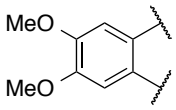
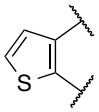


In 2012, Sun reported the synthesis of 8-membered lactones via a [6+2] cyclization process between oxetane-containing benzaldehydes and ynol silyl ethers.[517] When oxetane **351** was treated with siloxy alkynes **352** in the presence of trifluoromethanesulfonimide as a Lewis acid, 8-membered lactones **353** were formed (Table 29). Nucleophilic attack on the aldehyde moiety of oxetane **351** resulted in an intramolecular oxetane ring opening process. 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 for an epoxide, a similar intermolecular reaction was not observed. Instead an intermolecular homocyclization between the oxirane and the aldehyde moiety occurred.

Table 29. Intramolecular Ring Opening of Oxetane Resulting in the Formation of 8-Membered Lactones



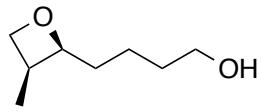
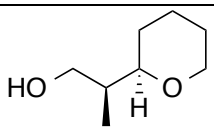
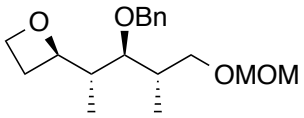
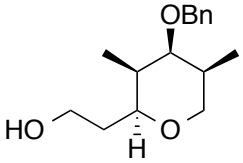
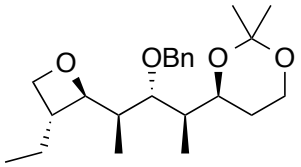
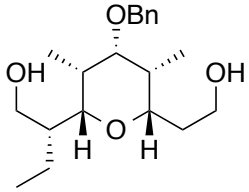
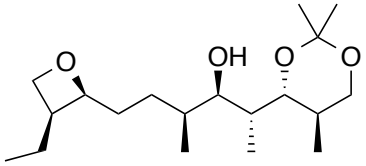
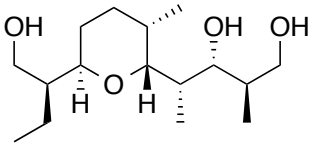
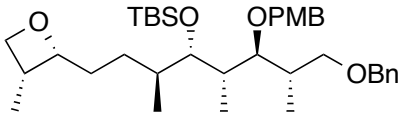
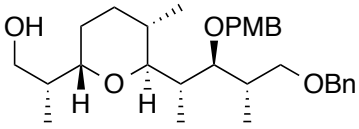
351 **352** **353**

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

Yadav utilized an acid catalyzed oxetane ring opening approach to form a key substituted tetrahydropyran (THP) skeleton in the synthesis of the C1–C17 fragment of the polyether natural product salinomycin.[518] Using a model substrate, the desired regioselective ring opening was achieved with both Lewis and Bronsted acids using MeOH as the solvent; however, the methyl ether product was favored over the THP. Switching to an aprotic solvent (CH_2Cl_2) led to selective formation of the THP, and the use of a 15:1 ratio of CH_2Cl_2:*i*PrOH resulted in significantly faster reaction times using either camphorsulfonic acid or *p*-toluenesulfonic acid (Entry 1, Table 30). The reaction was viable for the 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]

Table 30. Acid catalyzed THP Formation by Intramolecular Oxetane Ring Opening; Natural Product Fragments

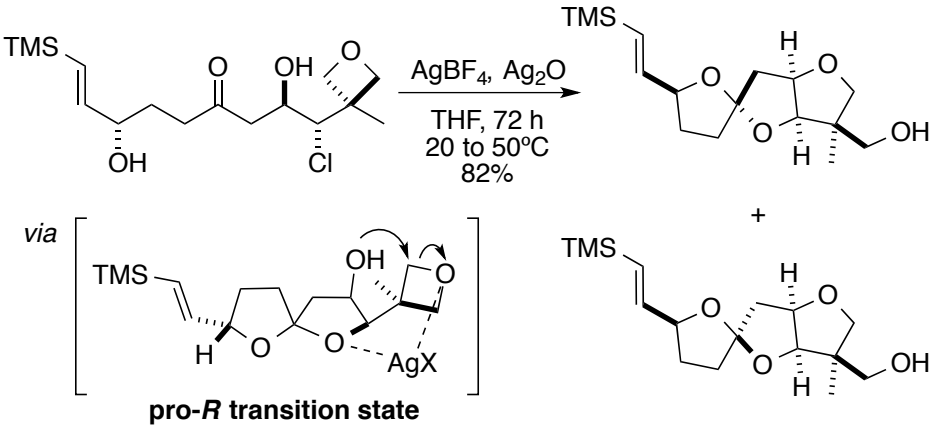
Entry[a]	Substrate	Product[a]	Yield (%)
1			94
2[b]			70
3			80
4			92
5[c]			83

[a] Conditions: CSA (1 equiv), CH_2Cl_2/*i*-PrOH (15:1), 0 ºC to rt, 2h to 2h 30. [b] Reaction run for 48 h. [c] Reaction run overnight.

In 2015, Britton reported a total synthesis of the marine fungus-derived natural product ascospiroketal, targeted due to potential biological activity.[520,521] An Ag(I)-promoted oxetane ring opening was used to install the desired tricyclic structure. A brief screen of Ag(I) salts found a

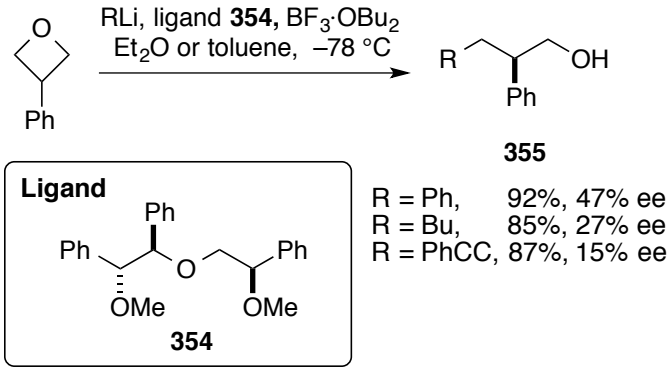
combination of $AgBF_4$ and Ag_2O gave the best yield of 82% with complete diastereoselectivity (Scheme 140). The complete diastereoselectivity was attributed to the ability of the pro-*R* oxetane transition structure to form a bidentate chelation between the oxygen of the oxetane ring and the oxygen 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 epimiserized using $ZnCl_2$ and MgO.

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



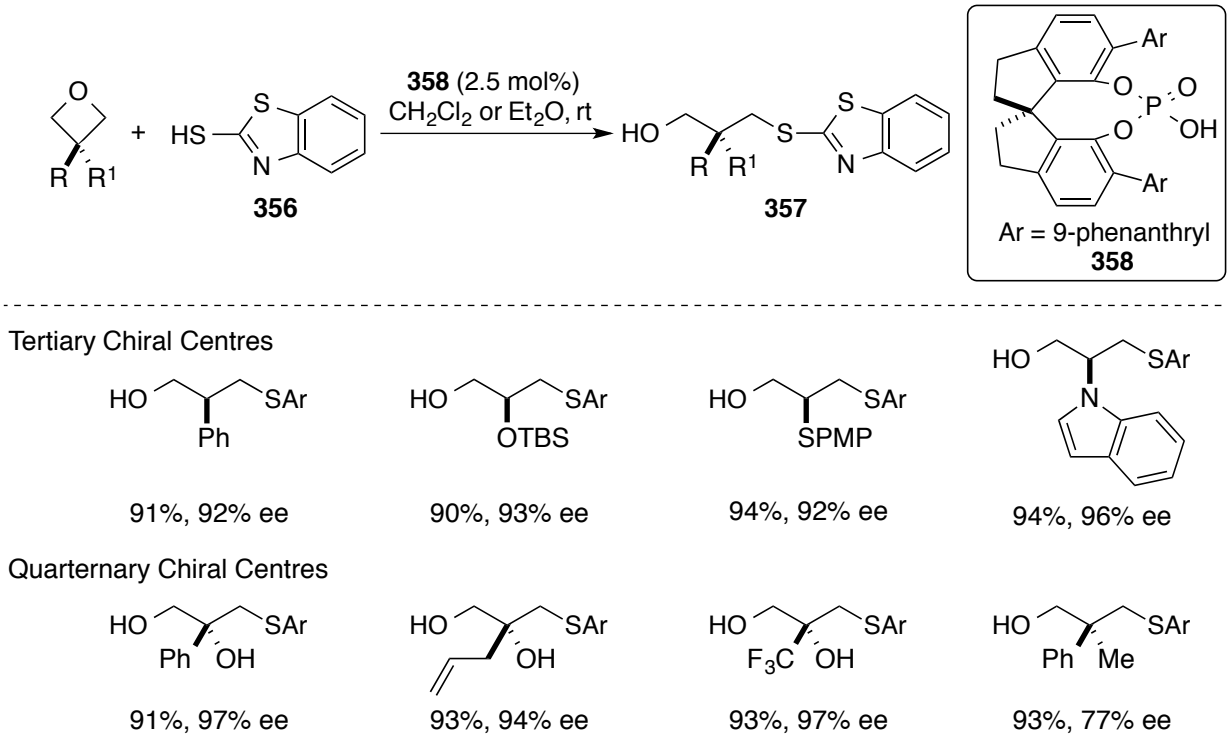
Enantioselective ring opening. Tomioka reported the first example of enantioselective desymmetrization of 3-substituted oxetanes, in 1997, by treatment with organolithium reagents.[522] 3-Phenyloxetane was treated with PhLi, stoichiometric $BF_3{\cdot}OBu_2$ and an external chiral tridentate ligand **354** at –78 ºC to afford chiral alcohol **355** in a yield of 92% and ee of 47% (Scheme 141). *n*-Butyllithium and lithum phenylacetylide also successfully gave the corresponding alcohols in good yields, however with low ee's of 27% and 15% respectively.

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



The catalytic enantioselective ring opening of 3-substituted oxetanes using 2-mercaptobenzothiazoles **356** as nucleophiles with chiral phosphoric acid catalyst **358** was reported in 2013 by Sun (Scheme 142).[8,289] Substituted and unsubstituted mercaptobenzothiazoles were 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.

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



In 2009, Jacobsen reported the intramolecular enantioselective ring opening of 3-substituted and 3,3-disubstituted oxetanes catalyzed by Co-salen complex **359** or **360** (Scheme 143).[523] Bimetallic catalyst **360** (n=1) showed enhanced reactivity compared to monomeric catalyst **359**, likely due to cooperative interaction between (salen)Co motifs. THFs and tetrahydropyrans were formed in high yields of 89-93% and excellent ee*'s* (96-99%) when oligomeric catalyst **360** was employed (Table 31). Alkyl and phenyl substitution at the 3-position of the 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.

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

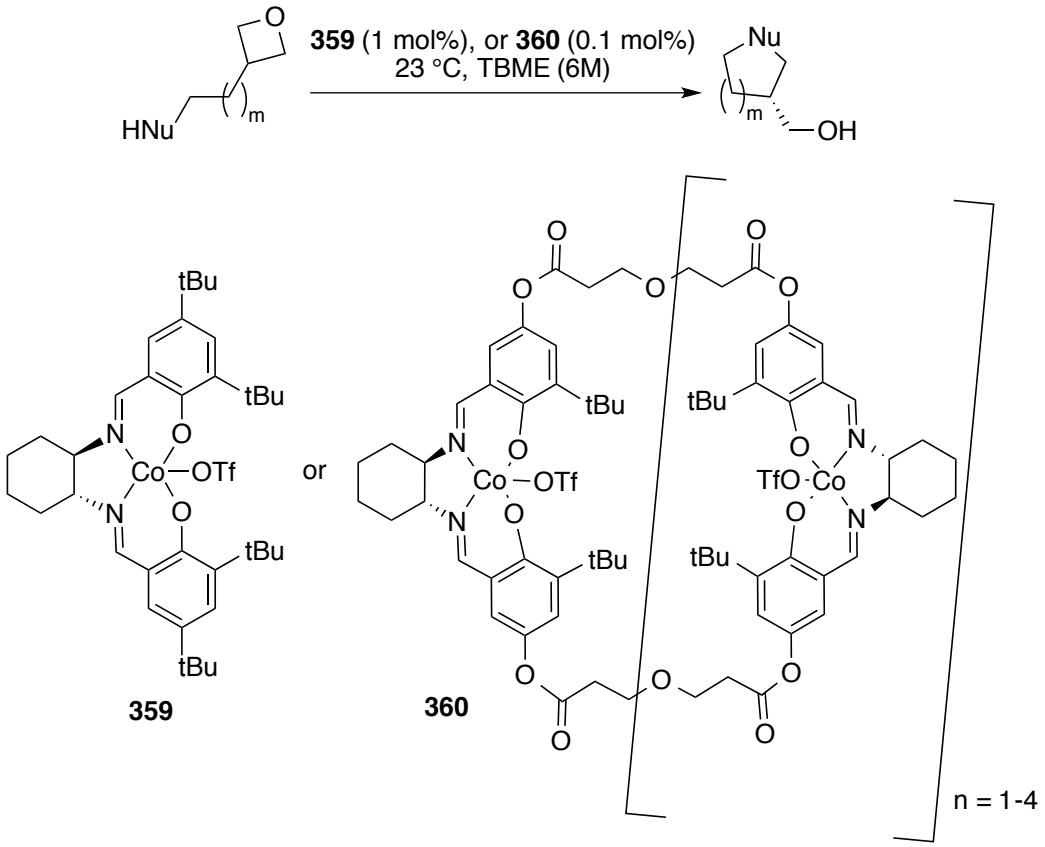
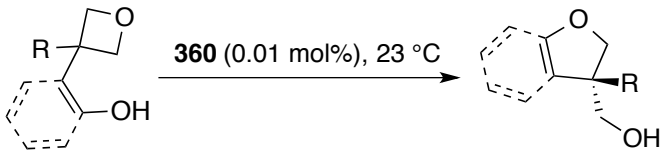
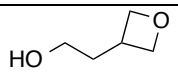
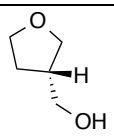
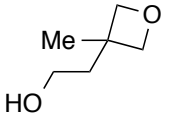
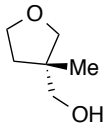
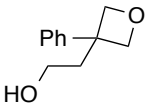
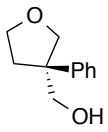
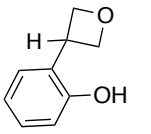
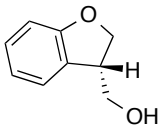
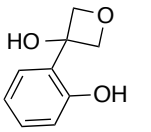
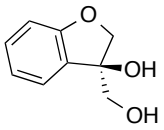
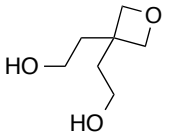
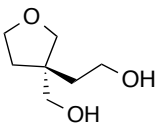


Table 31. Scope of the Enantioselective Intramolecular Ring Opening Reaction of 3-Substituted and 3,3-Disubstituted Oxetanes

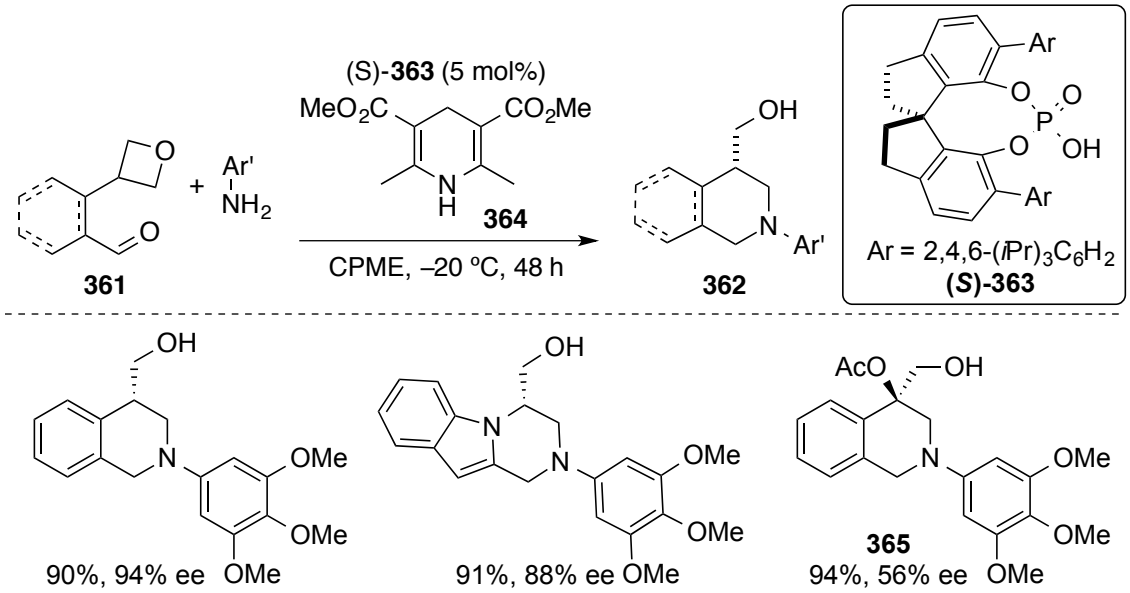


Entry	Substrate	Product	Yield (%)	ee (%)
1			93	96
2			88	96
3			98	99
4			89	98
5			94	88
6			98	99

Sun has recently reported several examples of intramolecular enantioselective oxetane ring opening.[8] 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

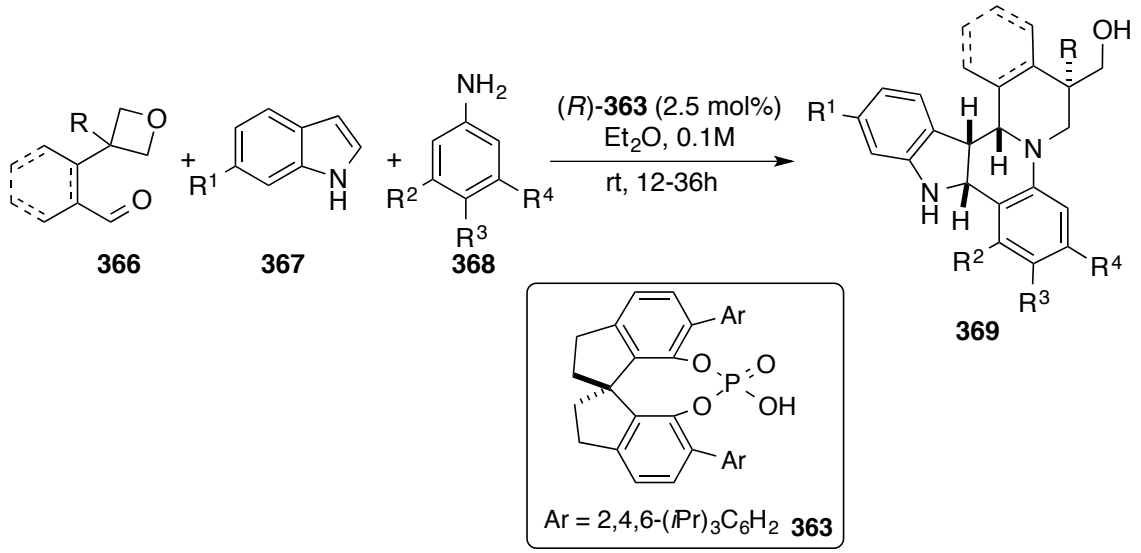
electron-withdrawing aryl aldehydes. With 3,3-disubstituted oxetanes the product with a quaternary centre (**365**) was formed with an excellent yield of 94% but moderate enantioselectivity (56% ee).

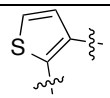
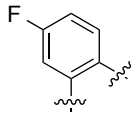
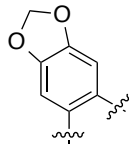
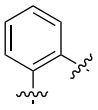
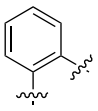
Scheme 144. Asymmetric Ring Opening of 3-Substituted Oxetanes Using Aromatic Amines and Chiral Phosphoric Acid Catalyst



By a similar principle, Sun 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.[525] 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).

Table 32. Cataytic Asymmetric Multicomponent Aza-Diels Alder Reaction

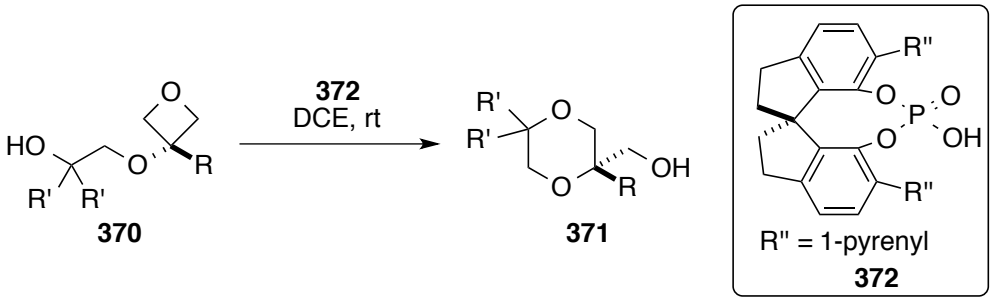


Entry	Ar	R	R^1	R^2	R^3	R^4	Yield **369** (%)	ee (%)	dr
1		H	Br	OMe	H	OMe	68	92	80/20
2		H	Br	OMe	H	OMe	93	78	>95/5
3		H	Br	OMe	H	OMe	67	88	>95/5
4		H	H	OMe	OMe	OMe	45	65	>95/5
5		OAc	H	OMe	H	OMe	67	63	>90/10

Sun described the enantioselective synthesis of 1,4-dioxanes via the intramolecular desymmetrization of oxetanes in 2016.[526] 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 efficiency or enantioselectivity. When the oxygen atom in the side chain was replaced with a carbon atom (**373**), other oxa-heterocycles **374** were synthesized in yields of 89–94% and ee's of 68–91% (Scheme 145). Very recently, the same group reported an enantioselective opening of 3-substituted oxetanes using 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.

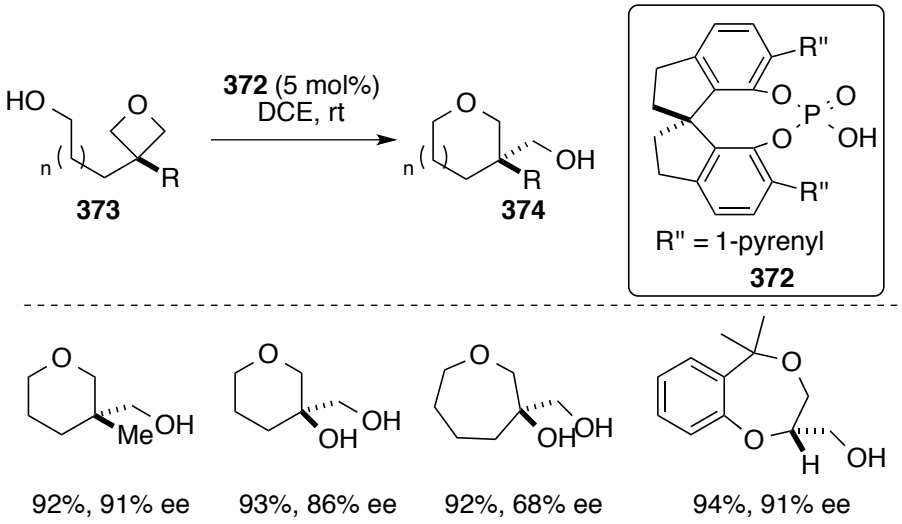
Table 33. Enantioselective Synthesis of 1,4-Dioxanes via Oxetane Desymmetrization



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

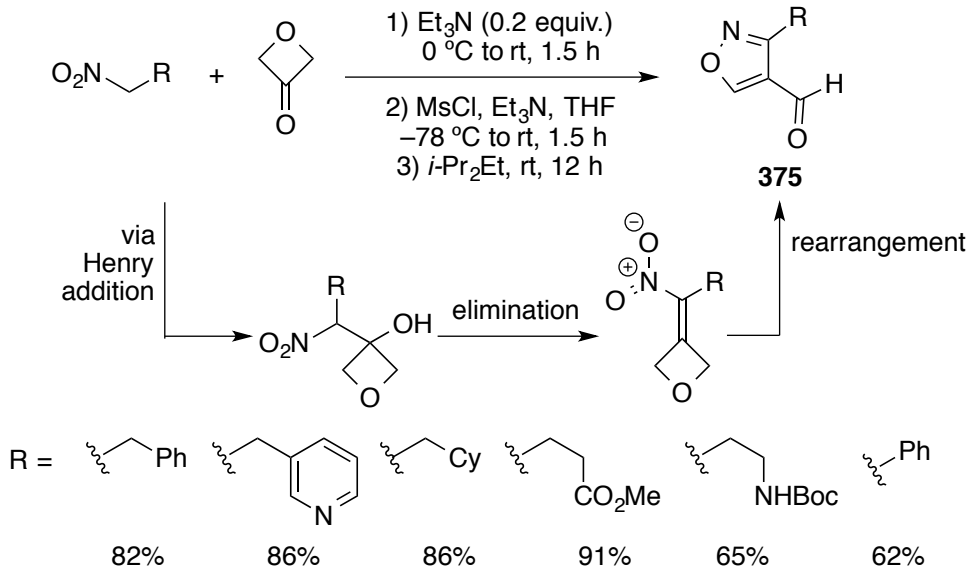
[a] Reaction run at 60 °C.

Scheme 145. Enantioselective Synthesis of Alternative Oxa-Heterocycles



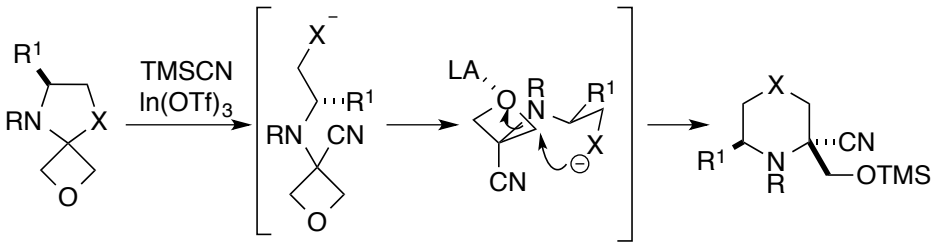
Ring opening of oxetan-3-one derivatives. The last 5 years has seen reports of the conversion of oxetan-3-one to a variety of heterocycles. Carreira developed a formation of isoxazoles via a base mediated rearrangement of 3-(nitromethylene)oxetanes.[528] The use of *i*Pr_2EtN in THF resulted in clean 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-benzyl-isoxazole-4-carboxaldehyde. The scope of the isoxazole-4-carboxaldehyde products at the 3-postion 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.

Scheme 146. Cascade Formation of Isoxazoles by Rearrangement of Oxetanes



Carreira 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).[529] This involved a Strecker reaction with TMSCN to introduce the nitrile, then activation of the oxetane by the Lewis acid to promote intramolecular cyclization, which proceeded in excellent yields and dr.[529]

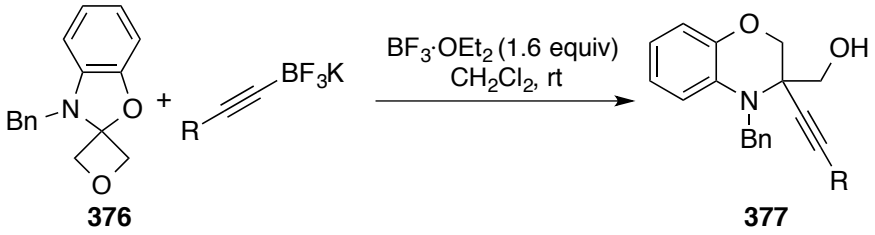
Table 34. Conversion of Oxetan-3-one into Saturated Nitrogen Heterocycles via the Formation of Intermediate Spirocycles



Entry	X	R	R^1	Yield (%)	dr
1	O	H	*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

The reaction of trifluoroborate nucleophiles with similar N,O-acetals, promoted by $BF_3{\cdot}OEt_2$, 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, aminals **376** were converted to benzomorpholines **377** by employing an excess of $BF_3{\cdot}OEt_2$ with substituted alkynyl potassium trifluoroborates (Table 35).

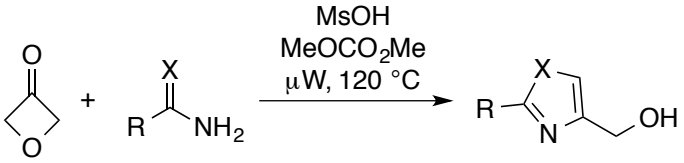
Table 35. One-Pot Ring Expansion of Spirocyclic Oxetanes



Entry	R	Yield **377** (%)
1	(*p*-Cl)(C_6H_4)	85
2	Ph	69
3	H	81
4	TMS	75
5	Cy	64
6	$(CH_2)_3Cl$	82

Orr and co-workers 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).[530] A range of aromatic substituents as well as tertiary and secondary alkyl groups were tolerated under the reaction conditions. The mechanism was proposed to involve first the opening of oxetan-3-one, followed by condensation.

Table 36. Microwave mediated synthesis of oxazoles and thiazoles.



X = O, S

X = O **378**
X = S **379**

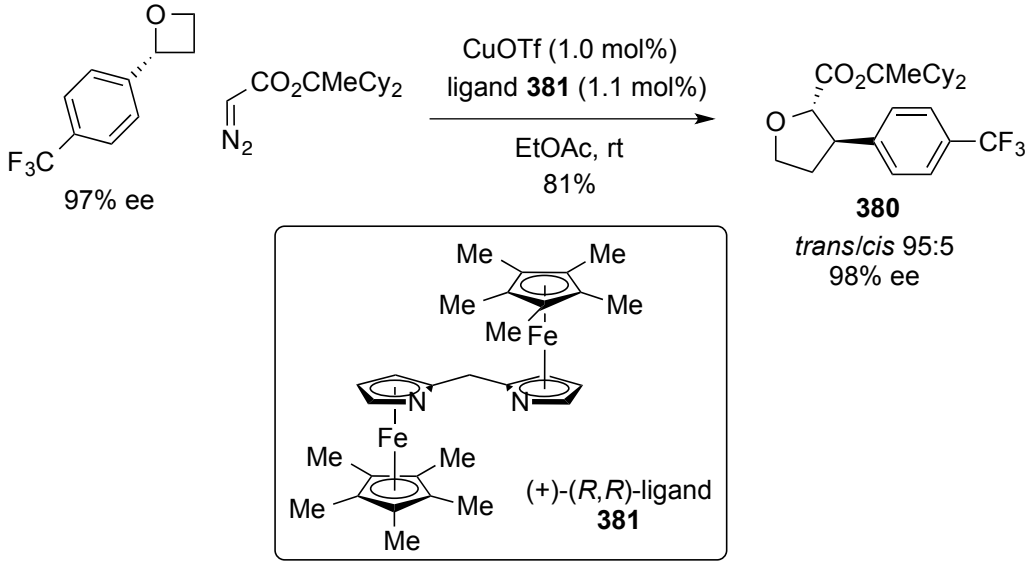
Entry	R	yield **378** (%) X = O	yield **379** (%) X = S
1	Ph	36	64
2	cyclohexyl	17	63
3	*t*Bu	14	40
4	(3-F_3C)Ph	24	36
5	(4-MeO)Ph	15	50

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, ylide formation with protonation or rearrangement.[531,532] In the 1960s, Nozaki found that, when treated with a diazo compound in the presence of a chiral copper chelate, 2-phenyloxetane would undergo ring expansion to give a mixture of *cis*/*trans* THF derivatives.[533,534] In 1994, Ito reported the asymmetric ring expansion of oxetanes to THFs.[535] 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*butyl THF-2-carboxylates, *(R)*-2-phenyloxetane preferentially afforded the *trans* isomer whilst reaction with *(S)*-2-phenyloxetane afforded the *cis* isomer preferentially.[536,537,538,539]

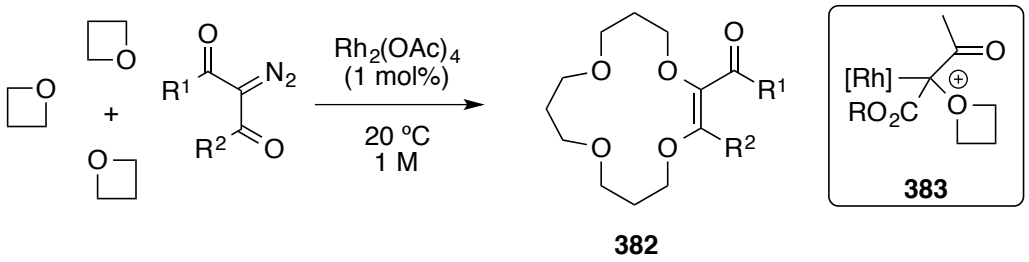
In 2001, Fu and Lo published conditions for the asymmetric ring expansion of oxetanes to THFs using diazoesters in the presence of a Cu(I)/bisazaferrocene catalyst, giving excellent diastereo- and enantiocontrol over the newly generated stereocentre (Scheme 147).[111] Both the *cis*- and *trans*-diastereoisomers could be synthesized simply by swapping the enantiomer of the bisazaferrocene ligand (*R*,*R*–**381:** 98% ee *trans*–**380**, *S*,*S*–**381**: 95% ee *cis*–**380**).

Scheme 147: Asymmetric Ring Expansion of 2-Aryl Oxetanes using a Cu(I)/bis(azaferrocene) Catalyst



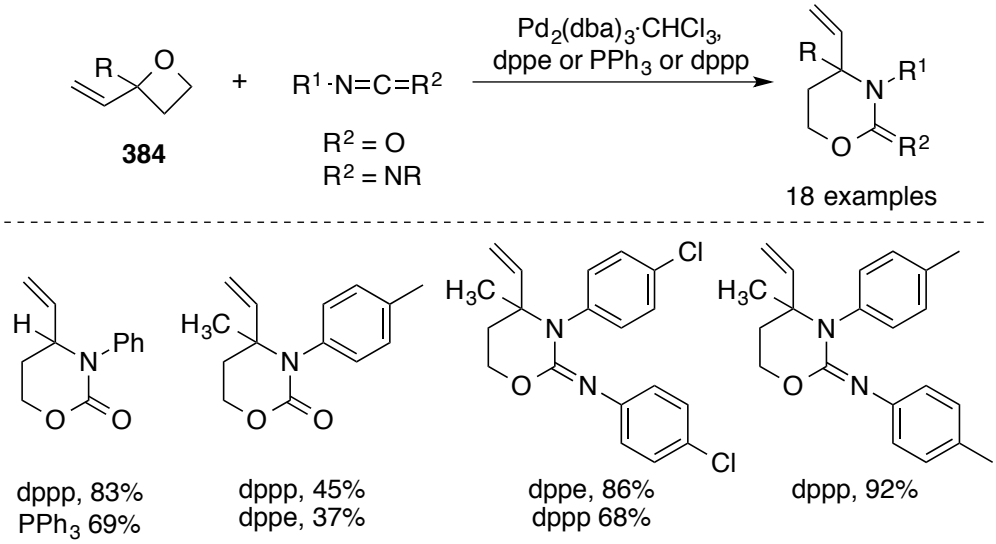
Lacour and co-workers described the formation of a number of interesting functionalized 15-membered macrocycles via a Rh-catalyzed condensation of a single α-diazo-β-keto ester with three oxetane molecules (Scheme 148).[540] The reaction proceeded under mild conditions at 20 ºC, a catalyst loading of just 1 mol% $Rh_2(OAc)_4$ and oxetane as the solvent, forming the macrocycle in yields of up to 84%. Different ester substituents were well tolerated (R^1 = Me, Et, *t*Bu, allyl; R^2 = Me), as were different ketone substituents (R^2 = Et, Pr, Ph, *i*Pr; R^1 = Et), giving excellent yields (55–84%) of the macrocylic 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 the 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.

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



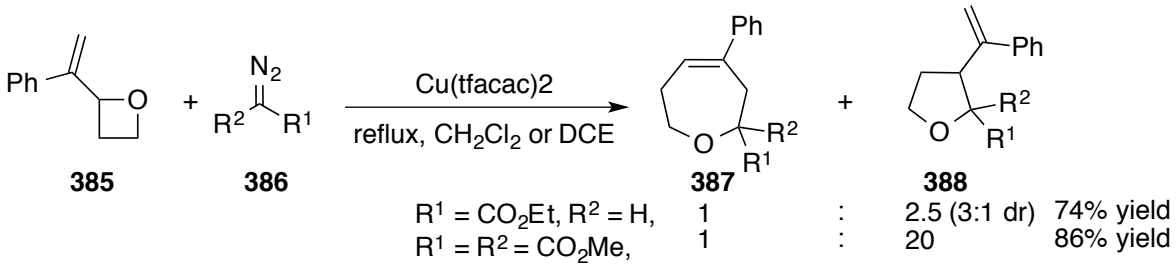
In 1999, Larksarp and Alper reported the cycloaddition of vinyl oxetanes with heterocumulenes as a method to access 1,3-oxazines.[541] 2-Vinyloxetane **384** was reacted with an isocyanate or a carbodiimide in the presence of a palladium(0) catalyst and a phosphine ligand (Scheme 149). Alper proposed that the reaction proceeded via a π-allyl palladium intermediate, formed by addition of the vinyl oxetane to the palladium complex, followed by reaction with the isocyanate or carbodiimide. The reaction yields were lower when using isocyanates, 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.

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



Njardarson has reported the ring expansion of vinyl substituted oxetanes **385** in the presence of diazo compounds **386** and catalytic $Cu(tfacac)_2$.[542] 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 the formation of both products.

Scheme 150. Ring Expansion of Vinyl Oxetanes to 3,6-Dihydro-2H-pyrans

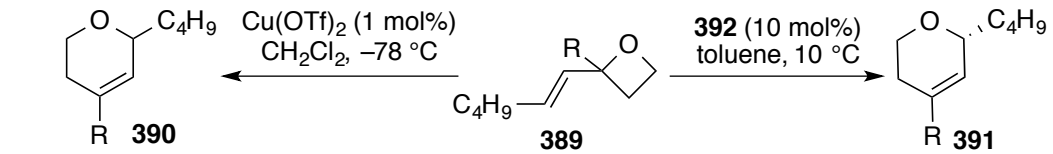


385 **386** **387** **388**

$R^1 = CO_2Et$, $R^2 = H$,	1	:	2.5 (3:1 dr)	74% yield
$R^1 = R^2 = CO_2Me$,	1	:	20	86% yield

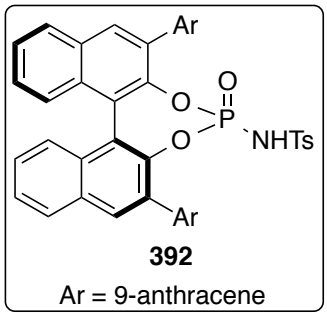
In subsequent studies, Njardarson reported the ring expansion of vinyl oxetanes **389** to 3,6-dihydro-2*H*-pyrans **390** in the presence of 1 mol% of $Cu(OTf)_2$ or 10 mol% of triflic acid.[543,544,545,546] Njardarson proposed that $Cu(OTf)_2$ coordinated to the oxetane oxygen atom prompting ring opening, 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 Vinyl Oxetanes to 3,6-Dihydro-2H-pyrans



$R = CH{=}CHC_4H_9$	78%
R = H	83%
R = Me	93%
$R = HCCHC_4H_9$	92%

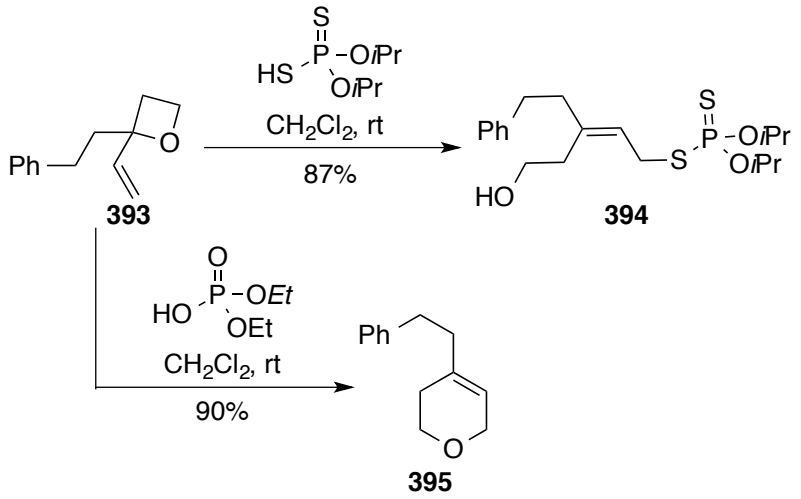
$R = CHCHC_4H_9$
41%, 90% ee



392
Ar = 9-anthracene

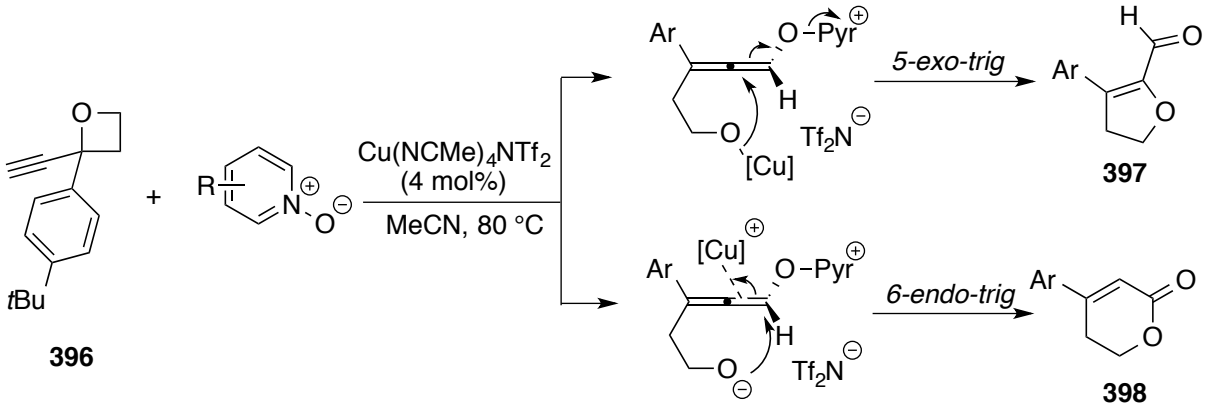
Treating vinyl oxetane **393** with diisopropyl dithiophosphate resulted in a nucleophilic ring opening to form **394** with *Z*-selectivity, whilst a less nucleophilic reagent, diethyl phosphoric acid, resulted in ring expansion to form the six-membered ring **395** (Scheme 152).[547] Sterics played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

Scheme 152. Z-Selective Ring Opening and Ring Expansion of Vinyl Oxetanes



Alkynyl oxetanes have been used in metal-catalyzed oxidative cyclization reactions. Gagosz showed that when alkynyl oxetane **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).[548] Careful 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 alkynyl oxetanes 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.

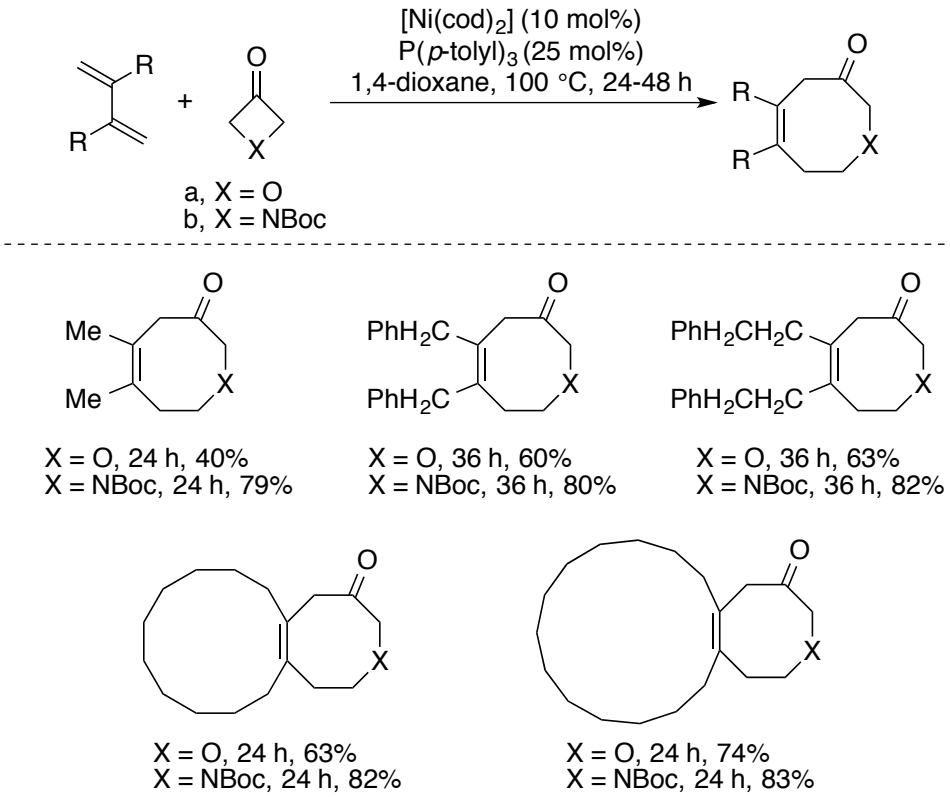
Table 37. Cu(I)-Catalyzed Ring Opening of Alkynyl Oxetane 396 to Lactone and Dihydrofuran



Entry	R	Ratio (**397:398**)	Yield (%)
1	H	1.9:1	84
2	3-Br	1:0	85
3	4-OMe	0:1	74

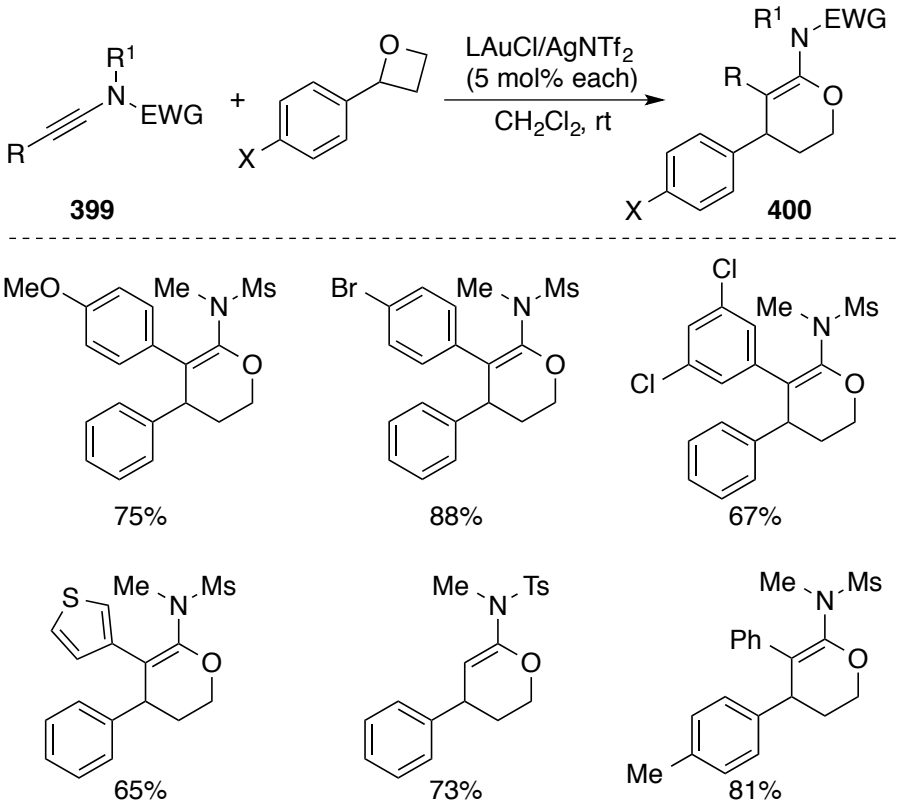
Formation of 8-membered heterocycles via a Ni-catalyzed reaction of oxetane-3-ones with 1,3-dienes was reported by Louie in 2013.[549] Oxetan-3-one was treated with 1,3-dienes in the presence of $Ni(cod)_2$ and P(*p*-tolyl)$_3$ to afford medium sized rings (Scheme 153). The methodology was also successful in the reaction of azetidin-3-ones with 1,3-dienes to form 8-membered *N*-heterocycle. Dienes with benzyl and homobenzyl substituents were well tolerated under the reaction conditions, as were macrocyclic dienes.

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



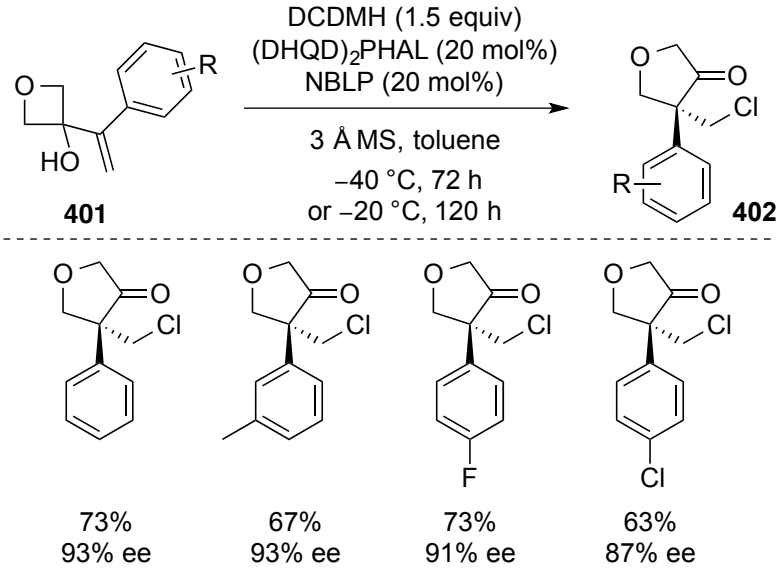
In 2014, Liu reported the [4+2] cycloaddition of ynamides **399** with 2-aryloxetanes in the presence of an Ag and Au-complex to afford six-membered 6-amino-3,4-dihydro-2*H*-pyrans **400** (Scheme 154).[550] Excellent regioselectively was observed due to the electrophilicity of the Au–π–ynamides, which react with the oxetane nucleophiles.[550] A variety of aryl oxetanes and arylynamides were successfully employed in the cycloaddition reaction.

Scheme 154. Au and Ag Catalyzed [4+2] Cycloaddition of Ynamides with Oxetanes (L = (*ortho*-biphenyl)(*t*-Bu)$_2$P)



In 2014, Yin and You reported an enantioselective chlorination/ring-expansion cascade of cyclobutanols, accessing chiral 2-alkyl-2-aryl cycloalkanones with excellent ee's using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and (DHQD)$_2$PHAL as a catalyst and *N*-Boc-L-phenylglycine (NBLP) as a ligand.[551] 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.

Scheme 155: Asymmetric Chlorination/Ring-Expansion of Oxetanols.



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 present important opportunities to tune physicochemical properties and increase the stability of a molecule, as well as providing IP 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 non-racemic oxetanes. These synthetic challenges continue to limit the full exploitation of this ring system.

The Williamson etherification remains the most common approach for oxetane synthesis, with the 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 using 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 which 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 has 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 if extended 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 using 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 application in more complex ketone-chemistry and multi-component 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 the reductive coupling of an oxetane halide with an aryl halide component. Furthermore, only mono-substituted 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 using 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 oxetanes 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 the 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 the incorporation of this motif. Most commonly, 3-substitued oxetane derivatives are observed in these potential medicinal compounds, being derived from simple building blocks; 3-amino and 3-mono- or 3,3-di-substituted 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 analogs, 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 the 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 on 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; the replacement of the carbonyl of thalidomide with an oxetane to prevent racemization providing 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, e.g. 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 5 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 offers similar potential. The opening of enantioenriched oxetanes provides valuable chiral building blocks, but nucleophilic opening remains under explored.

On the other hand, the enantioselective opening of pro-chiral oxetanes has taken great strides, through the desymmetrization of prochiral 3-substituted, and 3,3-disubstituted oxetanes. Very high ee's 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 openings could lead to applications in medicinal chemistry, for example as covalent irreversible inhibitors with an oxetane 'warhead'. Alternatively, as a labelling 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 towards 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 stereocontrolled 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 4-membered ring in these and other fields. Numerous challenges remain in synthesis, reactivity and understanding of oxetanes properties but we expect further exciting developments in coming years.

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11. Biographies

James A. Bull

James Bull is a University Research Fellow in the Department of Chemistry at Imperial College London. He obtained his MSci degree from University of Cambridge, then spent a year at GlaxoSmithKline. He returned to University of Cambridge to obtain his PhD 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 (URF) from The Royal Society.

Rosemary A. Croft,

Rosemary 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,

Owen Davis received his First Class Honours MSci degree in Chemistry from Imperial College London in 2012. He then continued his PhD studies at Imperial College where he was awarded an EPSRC DTG scholarship with Dr James Bull. His PhD studies which focussed on the synthesis and functionalisation 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

Robert Doran, from Co. Wicklow, Ireland graduated from University College Dublin (UCD) in 2010 with a 1st class Honours BSc degree in Chemistry. He was awarded an Embark Postgraduate Scholarship from the Irish Research Council (IRC) in 2010 to undertake PhD 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 PhD 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

Kate Morgan graduated from St. Andrews University in 2010 with a 1st class MChem degree in Chemistry with an Industrial Placement. Her final year project was based on the synthesis of glucosinolates under the supervision of Dr. Nigel Botting. In 2011 she moved to London to undertake PhD studies, sponsored by AstraZeneca, in organic chemistry under the supervision of Dr. James Bull. Kate was awarded a PhD 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.

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