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Oxetanes

# Oxetanes as Versatile Elements in Drug Discovery and Synthesis

*Johannes A. Burkhard, Georg Wuitschik, Mark Rogers-Evans,* Klaus Müller,* and Erick M. Carreira**

drug discovery · heterocyclic compounds · oxetanes · spiro compounds

*Sizable resources, both financial and human, are invested each year in the development of new pharmaceutical agents. However, despite improved techniques, the new compounds often encounter difficulties in satisfying and overcoming the numerous physicochemical and many pharmacological constraints and hurdles. Oxetanes have been shown to improve key properties when grafted onto molecular scaffolds. Of particular interest are oxetanes that are substituted only in the 3-position, since such units remain achiral and their introduction into a molecular scaffold does not create a new stereocenter. This Minireview gives an overview of the recent advances made in the preparation and use of 3-substituted oxetanes. It also includes a discussion of the site-dependent modifications of various physicochemical and biochemical properties that result from the incorporation of the oxetane unit in molecular architectures.*

## 1. Introduction

For more than 130 years since the first preparation of the parent structure by Reboul,[1] oxetanes have largely remained a neglected unit in medicinal chemistry. Although there are structures that incorporate the oxetane motif, little information has been available concerning their physicochemical properties. Recently, there has been a series of publications describing the remarkable ability of oxetane units to influence parameters, such as solubility, basicity, lipophilicity, and metabolic stability in both cyclic and acyclic frameworks.[2] The initial entry into this area was aimed at studying oxetanes as potential surrogates for *gem*-dimethyl groups, thus allowing the introduction of enhanced polarity with a similar molecular volume. The ability to graft bulky substituents onto a scaffold of interest without increasing the lipophilicity (that is, liponeutral bulk increase) would stand in contrast to the commonly employed strategies in medicinal chemistry that inevitably lead to an increase in the lipophilicity. Moreover, low aqueous solubility and fast metabolic degradation are often linked to drug candidates having a high lipophilicity. Thus, at the outset, the goals of the investigations in this area were simple: to identify a stable, tractable, compact, and liponeutral module that would break the entwinement of bulk and lipophilicity. The development of such a concept could result in innovative alternatives for many other common motifs, such as isopropyl, cyclopropyl, or *tert*-butyl groups.

Our own studies in this area have focused on oxetanes that are substituted only in the 3-position, since such units are achiral and their incorporation into molecular scaffolds does not create a new stereocenter. Our studies have demonstrated that oxetane is an intriguing module with notable attributes. This Minireview focuses on a number of aspects of 3,3-disubstituted oxetanes, such as their synthesis, utility as a building block, and, importantly, as useful modules that can improve the properties of small molecules as drug candidates.

The practice of modern medicinal chemistry has its own logic of chemical synthesis. Unlike natural product synthesis, where the objective is to prepare a single, distinct target of interest, one of the aims of medicinal chemistry is to prepare a finite collection of druglike molecules. These are subjected to various discriminating bioassays as well as in vitro/in vivo absorption, distribution, metabolism, excretion (ADME),

[*] J. A. Burkhard, Dr. G. Wuitschik, Prof. Dr. E. M. Carreira
Laboratorium für Organische Chemie
ETH Zürich, HCI H335
8093 Zürich (Switzerland)
Fax: (+41) 44-632-1328
E-mail: carreira@org.chem.ethz.ch
Dr. M. Rogers-Evans, Prof. Dr. K. Müller
F. Hoffmann–La Roche AG
Pharmaceuticals Division
4070 Basel (Switzerland)
Fax: (+41) 61-688-6965
E-mail: mark.rogers-evans@roche.com

and safety screens to examine, refine, as well as predict druglike attributes of the candidate structures. As predictive tools and assays become available the process is conducted increasingly earlier in the drug discovery process so as to minimize attrition at the later (and more expensive) preclinical and clinical phases as a result of toxicity or lack of efficacy. In medicinal chemistry it is common to identify robust surrogates for typical functional groups. These surrogates are modules that may share a limited set of key properties with the parent functional group, such as acidity/basicity, size, and conformational biases. For example, common replacements for carboxylic acids ($RCO_2H$) and *gem*-dimethyl groups are tetrazoles ($RCN_4H$) and cyclopropanes, respectively. Although on one level these surrogates are perceived as interchangeable in the discovery process, it is well appreciated that the equivalence is merely superficial, because each functional group has its own intrinsic structural or electronic characteristics. Nonetheless, the replacement groups permit the medicinal chemist to navigate among various structural classes and bridge to diverse regions of chemical space beyond the structures that initiated the research endeavor. The collection of molecules generated result in a multidimensional network of structure–activity relationships that provide the basis for identifying and defining the pharmacophore.

Our own studies were initiated by the idea that oxetanes could be viewed as a *gem*-dimethyl equivalent, wherein the two methyl groups are bridged by an oxygen atom. It was reasoned that the polar oxygen bridge would be able to compensate for the intrinsic lipophilicity of the methylene groups, such that the net change in lipophilicity would be small or even vanish (Figure 1). Further research on oxetanes has undergone additional twists and turns that have revealed a number of other intriguing structural relationships. Thus, for

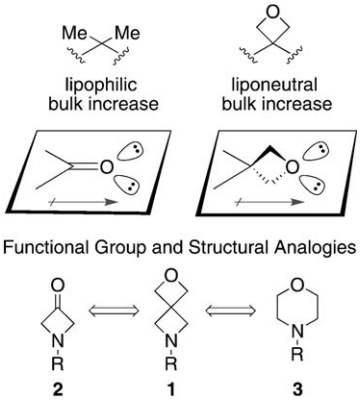



***Figure 1.*** Oxetane analogies in medicinal research.

*Johannes Burkhard was born in Zurich, Switzerland in 1983. In 2006, he received his Masters in chemistry from the ETH Zurich under the supervision of François Diederich. For his PhD studies he stayed at the ETH, where he joined the research group of Erick M. Carreira in 2007. His research is focused on the development of small heterocyclic building blocks and their evaluation in the context of drug discovery.*

*Georg Wuitschik, born in Bad Tölz, Germany in 1980, received his Diploma in chemistry in 2004 from the TU Munich for work carried out in the group of Barry M. Trost under the supervision of Wolfgang A. Herrmann. He then joined the group of Erick M. Carreira, and received his PhD in 2008. He is currently working as an Alexander-von-Humboldt postdoctoral fellow in the group of Steve V. Ley, where he works on natural product synthesis.*

*Mark Rogers-Evans was born in London in 1963. After his PhD and postdoctoral studies in England (Brian Marples and Raymond Bonnett) and Canada (Victor Snieckus), he joined Hoffmann—La Roche in Switzerland (1996) as a Process Research Chemist, transferring to Discovery Chemistry in 2001. In 2009 he joined the newly formed Roche Chemistry Technologies & Innovation group and has co-authored over 60 patents and publications.*

*Klaus Müller, born in 1944 near Lucerne, Switzerland, studied chemistry at ETH Zurich (PhD with Albert Eschenmoser). After several years in the US (Chicago, Harvard), he returned to ETH Zurich, where he completed his habilitation in Physical and Theoretical Organic Chemistry in 1977. In 1982 he joined F. Hoffmann–La Roche, Basel, to set up programs in molecular modeling, structural biology, and bioinformatics. In 1990 he became extraordinary professor at the University of Basel. Since his retirement in Spring 2009, he has continued as a chemistry consultant for Roche and holds a teaching position at ETH Zurich.*

*Erick M. Carreira was born in Havana, Cuba, in 1963. He received his BSc from the University of Urbana-Champaign working with Scott Denmark, and his PhD from Harvard University working under the direction of David A. Evans. After postdoctoral research at the California Institute of Technology with Peter Dervan, he joined the faculty there. Since 1998, he has been full professor at ETH Zürich.*

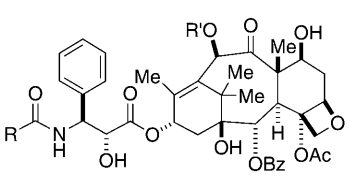
example, it is possible to envision an oxetane as being analogous to a carbonyl group. This concept leads in turn to the generation of fascinating building blocks that provide new opportunities for the generation of molecular diversity. As an example, oxetane **1** first arose from the consideration of an oxetane as a C=O equivalent; interestingly the parent ketone analogue **2** is not represented in drug candidates. The spirocycle **1** can be considered from an entirely different perspective, namely, as a surrogate for the ubiquitous morpholine (**3**).

Despite the attractiveness of the ideas outlined above, the use of oxetane as a useful subunit in drug discovery initially seemed questionable. As a small-ring, strained ether, oxetane would be expected to be highly vulnerable to oxidative metabolism or perhaps even plasma instability under physiological conditions. Furthermore, it is common to associate the (bio)chemical reactivity of oxetanes with that of epoxides. Unlike epoxides, however, there is a paucity of synthesis routes that provide access to oxetanes, and thus oxetanes are less frequently employed as building blocks or intermediates. Indeed, the methods that are available tend to lack the ease and flexibility required for modern medicinal chemistry. These combined perceptions have likely contributed to the fact that, until recently, little information was available concerning the pharmacological properties of oxetanes.

The area of oxetanes has evolved considerably from their initial consideration as surrogates of *gem*-dimethyl groups into bonafide modules which allow the medicinal chemist access to uncharted regions of chemical space. This has found resonance in the community at large.[3] Consequently, there have been accompanying developments involving novel methods for the preparation of a wide range of oxetanes and their use as synthetic intermediates.

## 2. Oxetanes in Nature and on the Market

All marketed drugs containing the oxetane ring are derived from one family of natural products.[4] Taxol (**4**) was first developed commercially by Bristol–Myers–Squibb. It was isolated[5] from the bark of the western yew (*Taxus brevifolia*) and is, together with the structurally related Docetaxel (**5**; first marketed by Chugai Pharmaceuticals as Taxotere), currently used in cancer chemotherapy (Figure 2). Both compounds act by interfering with normal breakdown of microtubules during cell division.[6] The structural consequences of the oxetane in Taxol were the subject of a computational study, from which it was concluded that the oxetane unit leads to rigidification of the overall structure[7] and acts as a hydrogen-bond acceptor for a threonine-OH group in the putative binding pocket.[8] Consistent with this appraisal, replacement of the oxetane in taxol with azetidine, thietane, and selenetane invariably resulted in lower activity.[9] However, the role of the oxetane moiety remains unclear, as it is difficult to factor out its specific effects in the context of such a large scaffold.



**4**: R = Ph, R' = Ac, Paclitaxel (Taxol)
**5**: R = O*t*Bu, R' = H, Taxotere (Docetaxel)

***Figure 2.*** Marketed drugs containing oxetanes. Bz = benzoyl.

Oxetanes are found only in a few other natural products, many of them terpenoids (Figure 3). Oxetanocin A (**6**) was first isolated[10] from the soil bacterium *Bacillus megaterium* NK84-0218. It inhibits the reverse transcriptase of HIV by mimicking adenosine, a feature which triggered considerable commercial and synthetic interest.[11] Thromboxane $A_2$ (**7**) is a compound predominantly synthesized by platelets that promotes vasoconstriction, platelet aggregation, and bronchoconstriction. It has a half-life of only 30 seconds in plasma, before the oxetane ring, which is part of an acetal, hydrolyzes to give inactive thromboxane $B_2$.[12] Merrilactone A (**8**) was first isolated from *Illicium merrillianum*[13] and shown to stimulate the growth of rat neurons. The biological activity coupled with the sheer complexity of the condensed polycyclic structure has inspired several total syntheses in recent years.[14]

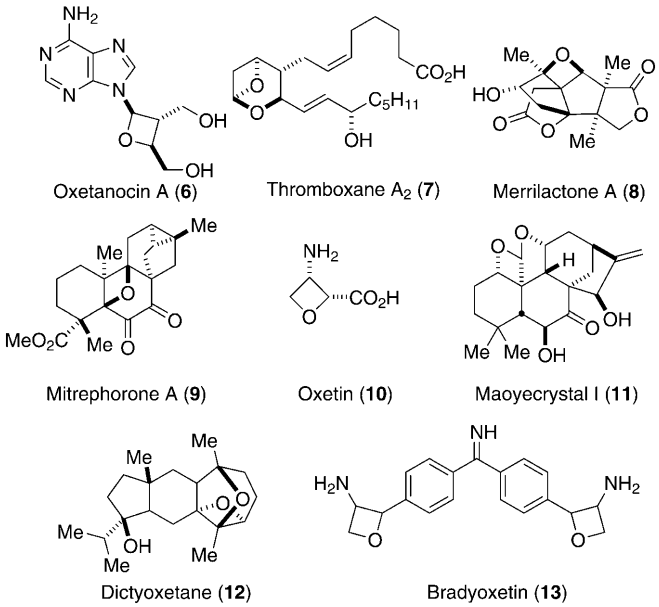



***Figure 3.*** Natural products containing oxetanes.

Mitrephorone A (**9**) was isolated from *Mitrephora glabra* and found to be cytotoxic to a variety of cancer cell lines.[15] Oxetin (**10**) was isolated from the fermentation broth of *Streptomyces* sp. OM-2317 and found to elicit herbicidal as well as antibacterial effects; further investigation of its biological activity is ongoing.[16] Maoyecrystal I (**11**) was isolated from *Isidon japonicus* and displays cytotoxicity.[17] Dictyoxetane (**12**) is a diterpenoid first isolated from the brown algae *Dictyoata dichotoma*.[18] Its polycyclic ether core has triggered considerable synthetic interest.[19] Bradyoxetin

(**13**) was found to be an important semiochemical for *Bradyrhizobium japonicum*, involved in symbiotic gene regulation in soybean.[20]

There are anthropogenic small molecules (Figure 4) that also incorporate oxetane rings, both as scaffold (EDO) and side chain (oxasulfuron). The insecticide EDO (**14**) is 25 times

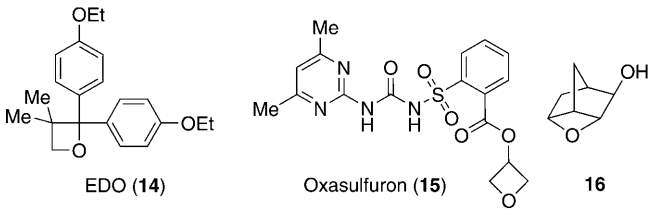



***Figure 4.*** Oxetane-containing pesticides.

more potent than dichlorodiphenyltrichloroethane (DDT), and is also active against DDT-resistant strains of *Musca domesti*ca. In contrast to the notorious environmentally persistent DDT, EDO is biodegradable.[21] Oxasulfuron (**15**)[22] acts by inhibiting the biosynthesis of valine and isoleucine in cells. It is used, for example, in the cultivation of soybeans to keep weeds under control. This agrochemical is effective because it undergoes rapid metabolism in the crop as opposed to weeds.[23] Despite its promising properties and activity, its production was stopped in 2007 as a consequence of an incidence of resistance in the targeted weeds.[24] Norbornane **16** was found to be a potent herbicide and plant-growth regulator.[25]

### 2.1. Physicochemical Properties of Oxetanes

In addition to its isosteric relationship with *gem*-dimethyl groups, what makes the oxetane a potentially attractive structural motif for drug discovery is its high polarity and outstanding ability to function as an acceptor of hydrogen bonds. This is borne out when it is compared to the other common alicyclic ethers, which all show a lower Lewis basicity than oxetane. Thus, the equilibrium constant for the formation of a hydrogen-bonded complex between ethers and 4-fluorophenol is a maximum for oxetane among the cyclic ethers, being 20% and 35% higher than those for tetrahydrofuran and tetrahydropyran, respectively.[26] The high affinity of oxetane for hydrogen bonds results from two competing effects: For cyclic ethers, a decrease in the ring size is accompanied by a diminution in the corresponding endocyclic C-O-C angle; this has the effect of exposing the oxygen atom more effectively to hydrogen-bond donors.[27] A factor that counteracts this greater accessibility is related to the hybridization of the ether oxygen atom. An increase in the s character of the nonbonding orbitals of the electron lone pairs renders these less available to engage in hydrogen bonding. Several studies suggest that only oxiranes experience a significant change in the hybridization associated with the electron lone pairs on the oxygen atom. The balance of the two effects makes oxetanes optimal among the cyclic ethers as acceptors of hydrogen bonds.[28] The two effects account for the marked difference between epoxides and oxetanes as well as the attenuated acceptor ability as the ring size increases.

Oxetanes are known to form complexes with iodine[29] and dinitrogen pentoxide.[30] Analysis of the binding constants in the series oxirane/oxetane/tetrahydrofuran reveals that the difference in binding to iodine is more pronounced than that observed for hydrogen-bond formation: oxetane has a 62% higher binding constant than THF. This might result from the higher steric demand in the association complex with iodine, thus highlighting the accessibility of the nonbonding electron pairs in oxetane.

As shown in Figure 5, the propensity for the formation of hydrogen bonds by oxetane exceeds that of aliphatic ketones, aldehydes, and esters;[29,31] only amides outperform the four-

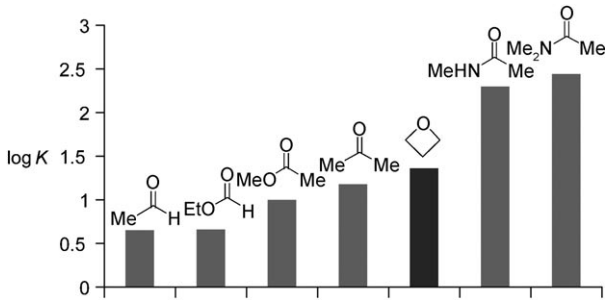



***Figure 5.*** Affinity of oxetane and different carbonyl compounds to act as acceptors for hydrogen bonds.

membered ring cyclic ether. A related investigation of isomeric cyclic ethers revealed that among tetrahydropyran and 1- or 2-methyltetrahydrofuran, 3,3-dimethyloxetane had the highest aqueous solubility.[32] A survey of X-ray structures of 3-substituted oxetanes registered in the Cambridge Structural Database reveals some additional intriguing features (Figure 6): In contrast to cyclobutane, the oxetane ring is only weakly puckered or essentially planar, as determined by microwave spectroscopy.[33] Pitzer strain between adjacent C–H bonds in cyclobutane is reduced by the replacement of a methylene group by an ether oxygen atom.

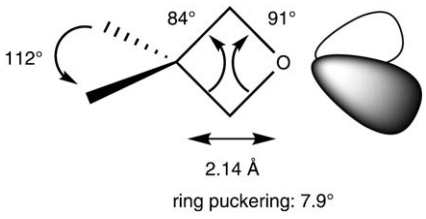
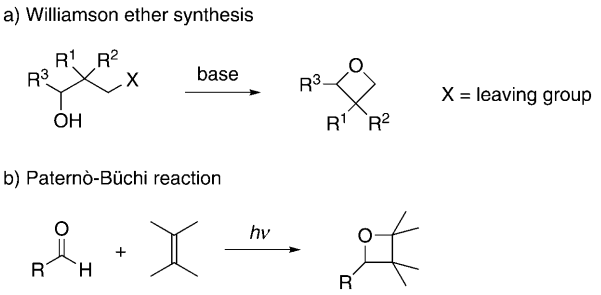



***Figure 6.*** Averaged structural parameters of 3-substituted oxetanes.

## 3. Preparation of Oxetanes

There are a number of strategies for the synthesis of oxetanes. Of these, two general approaches enjoy the widest application (Scheme 1). The first involves an intramolecular Williamson ether synthesis, that is, a ring-closing etherification reaction. The second entails a [2+2] cycloaddition, such

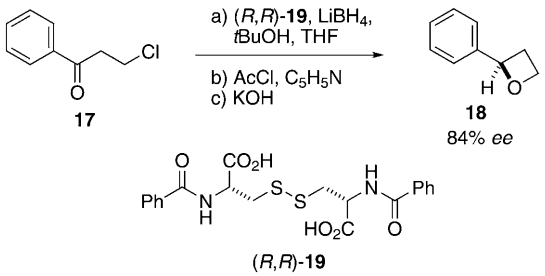



***Scheme 1.*** Fundamental synthetic pathways towards oxetanes.

as the Paternò–Büchi reaction.[34] Both transformations have been extensively discussed;[35] consequently this Minireview will only highlight variants that are general and versatile.

### 3.1. Stereoselective Syntheses

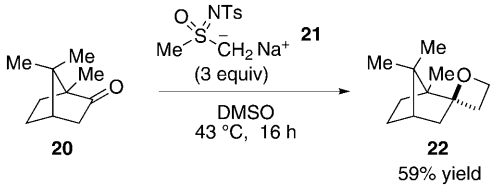
The enantioselective synthesis of substituted oxetanes is a particular challenge. Soai et al. documented an efficient approach for the preparation of optically active 2-substituted oxetanes (Scheme 2). The enantioselective reduction of a β-




***Scheme 2.*** Enantioselective synthesis of 2-aryloxetanes by Soai et al.[36]

haloketone followed by ring closure furnishes the targeted heterocycle.[36] For example, treatment of 3-chloropropiophenone (**17**) with a catalyst prepared in situ from $LiBH_4$ and cystine-derived chiral ligand (*R*,*R*)-**19** afforded the corresponding optically active secondary alcohol, which is subsequently subjected to cyclization to give 2-phenyloxetane (**18**) with 84% *ee*.

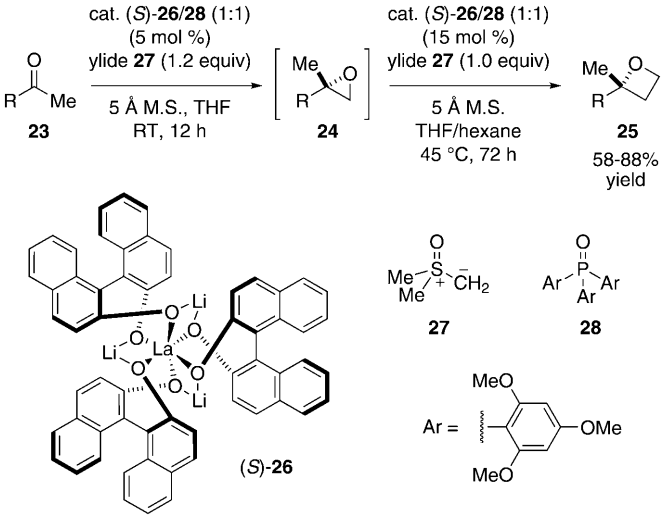
Oxetanes have been prepared directly from ketones via intermediate epoxides through the implementation of an intriguing variant of the Corey–Chaykovsky reaction (Scheme 3). Following oxirane formation, excess ylide attacks the epoxide to give an oxydialkylsulfoximine intermediate,[37] which in turn undergoes displacement with ring closure. The




***Scheme 3.*** Construction of 2,2-disubstituted oxetanes through sequential additions of sulfur ylides. Ts = toluene-4-sulfonyl.

2,2-disubstituted oxetane products are formed in good yield and selectivity.[38] For example, the treatment of camphor (**20**) with three equivalents of **21** in DMSO afforded oxetane **22** in 59% yield. The reaction of **21** with a collection of other aliphatic ketones afforded the corresponding oxetanes in similar yields.

Okuma et al. showed that dimethyloxosulfonium methylide (**27**) can be used in the conversion of ketones into oxetanes.[39] Following these findings and their previous studies on the asymmetric Corey–Chaykovsky reaction, Shibasaki and co-workers developed an asymmetric synthesis of 2,2-disubstituted oxetanes (Scheme 4).[40] The starting

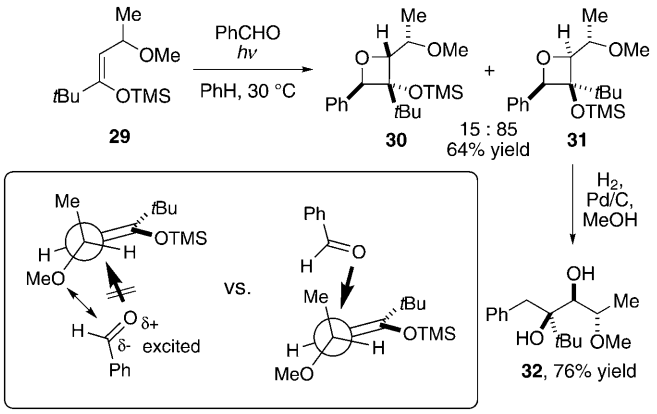



***Scheme 4.*** One-pot sequential addition of sulfur ylides to ketones to form 2,2-disubstitued oxetanes according to Shibasaki and co-workers.[40] M.S. = molecular sieves.

methyl ketones **23** were treated with dimethyloxosulfonium methylide (**27**, 1.2 equiv) and catalytic amounts of **26** (5 mol%) in the presence of an equal amount of a $Ar_3P{=}O$ additive (**28**) and molecular sieves to give the corresponding epoxides **24**. The low reaction rate in the subsequent epoxide opening reaction was compensated by the addition of another equivalent of ylide and 15 mol% of catalyst in addition to heating. The one-pot sequential addition of a sulfur ylide to methyl ketones furnished 2,2-disubstituted oxetanes **25** in good yield and up to >99.5% *ee*. A resolution process was observed in the second step of the sequence, as the intermediate epoxides were observed to be formed with lower enantioselectivity than the isolated oxetane products. The direct conversion of ketones into oxetanes was also possible at 45 °C by using 2.2 equivalents of ylide and 20 mol% each of the catalyst and additive.

The Paternò–Büchi reaction offers rapid access to substituted oxetanes. However, the control of facial selectivity in the [2+2] cycloaddition reaction is not easily realized. Recent studies by Bach et al. revealed that the photochemical reaction of benzaldehyde and silyl enol ethers can lead to the diastereoselective ring formation.[41] Thus, the cycloaddition reaction of alkoxy silyl enol ether **29** affords adducts as an 85:15 mixture of stereoisomers (Scheme 5). The diastereose-

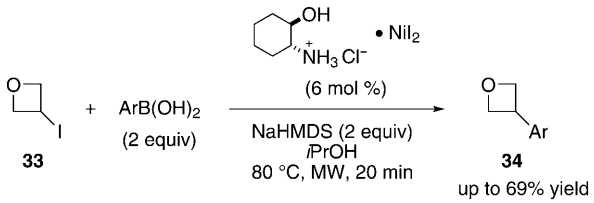



***Scheme 5.*** Paternò–Büchi reaction between benzaldehyde and a silyl enol ether. TMS = trimethylsilyl.

lectivity arises from the inherent conformational preferences that arise from 1,3-allylic interactions with the trisubstituted olefin partner.

### 3.2. Elaboration of Oxetanes

The preparation of 3-aryl-substituted oxetanes by means of nickel-mediated Suzuki coupling reactions was recently reported (Scheme 6).[42] Treatment of 3-iodooxetane (**33**) with




***Scheme 6.*** Nickel-mediated Suzuki coupling of 3-iodooxetane with arylboronic acids. NaHMDS = sodium hexamethyldisilazide, MW = microwaves.

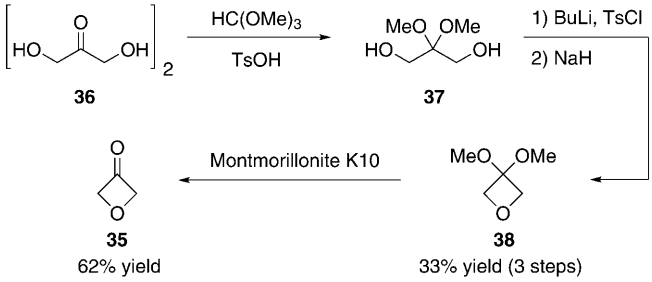
arylboronic acids in the presence of 6 mol% of $NiI_2$/*trans*-2-aminocyclohexanol hydrochloride[43] and NaHMDS (2 equiv) at 80 °C under microwave irradiation provides access to a wide range of substituted oxetanes **34**. 3-Arylazetidines were shown to be accessible in the same fashion from *N*-Boc-protected (Boc = *tert*-butoxycarbonyl) 3-iodoazetidine. Alternatively, similar heteroaryl oxetanes and azetidines can be readily accessed by a Minisci reaction.[44]

The methods described above provide access to a range of substituted oxetanes. These will certainly be beneficial for a variety of applications.

### 3.3. Chemistry Based on Oxetan-3-one

The initial investigations on oxetanes as useful modules in drug discovery largely focused on 3,3-disubstituted oxetanes. This stems from the aim of not augmenting the complexity by generating a stereogenic center upon grafting an oxetane unit onto a given scaffold. In developing a general approach for the facile, versatile incorporation of 3-substituted oxetanes, we have concentrated on oxetane-3-one as a starting point.

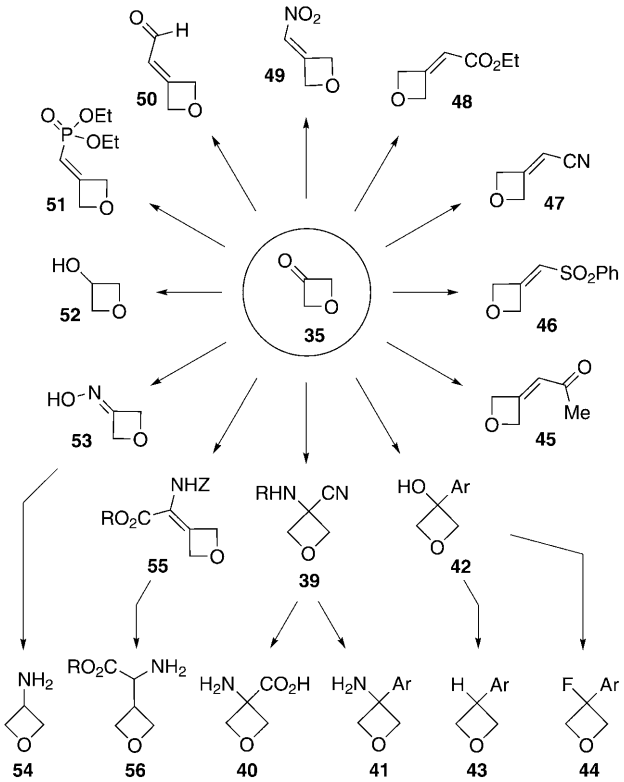
Several syntheses of oxetan-3-one (**35**) had been reported; however, in our assessment each has practical shortcomings, such as the use of preparative gas-chromatographic techniques.[45–47] Consequently, a straightforward route was developed starting from dihydroxyacetone dimer (**36**; Scheme 7).




***Scheme 7.*** Synthesis of oxetan-3-one.

In this procedure, dihydroxyactone is converted into the corresponding dimethyl ketal **37**, which is subsequently treated with TsCl and subjected to ring closure.[2a] Acidic cleavage of the ketal **38** and distillation furnishes oxetan-3-one (**35**).

Oxetan-3-one is amenable to extensive functionalization and elaboration (Scheme 8).[47b,48] It undergoes addition reactions with organometallic reagents to yield oxetan-3-ols

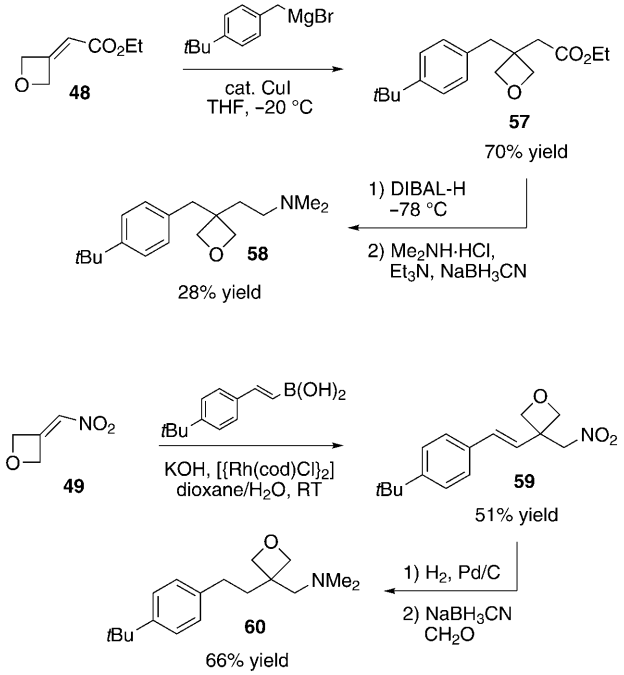



***Scheme 8.*** Reactions of oxetan-3-one in the literature.[47b,48] Z = benzyloxycarbonyl.

**42**, which can then be derivatized further into the respective 3-fluoro- (**44**) or 3-hydrooxetane (**43**). Strecker adduct **39** can also undergo a Bruylants reaction to provide, upon hydrogenative debenzylation, access to 3-amino-3-aryloxetanes **41**, in analogy to the respective azetidines.[49] A collection of acceptors was prepared to further elaborate the 3-position. These can be accessed in high yields from oxetan-3-one simply by olefination reactions such as Wittig or Horner–Wadsworth–Emmons reactions.

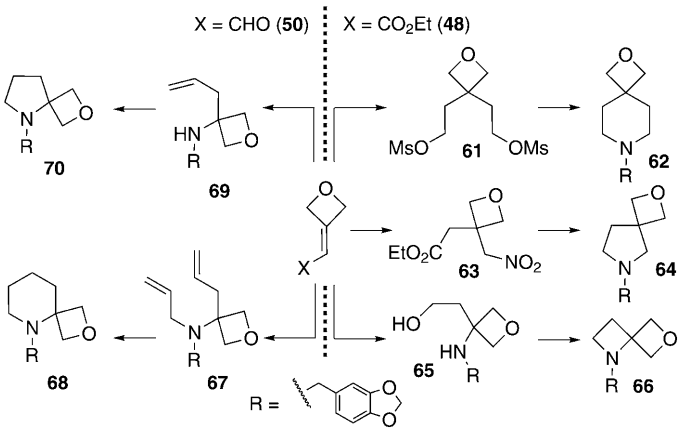
The conjugate acceptors are highly reactive in nucleophilic addition reactions with a wide range of heteroatom and carbon nucleophiles as well as hydrides. Heteroatom nucleophiles include amines and alcohols, and a broad range of carbon nucleophiles can be employed, such as ester enolates, cuprates, cyanide, and aryl or vinylboronic acids. Thus, the selection of the acceptor and nucleophile partners offers access to a variety of substituted oxetanes from the same point of departure, namely, oxetan-3-one. Selected examples of these transformations are shown in Schemes 9 and 10.




***Scheme 9.*** Synthesis of open-chain compounds containing an oxetane unit. cod = cycloocta-1,5-diene, DIBAL-H = diisobutylaluminum hydride.

Short synthetic sequences allow the introduction of oxetanes at distinct positions of a carbon skeleton. Thus, conjugate addition of nucleophiles to Michael acceptors **48** and **49** followed by functional-group manipulations afforded target structures **58** and **60** in only a few steps. Likewise, similar transformations afforded compounds with the oxetane positioned at the other carbon centers of the scaffold.

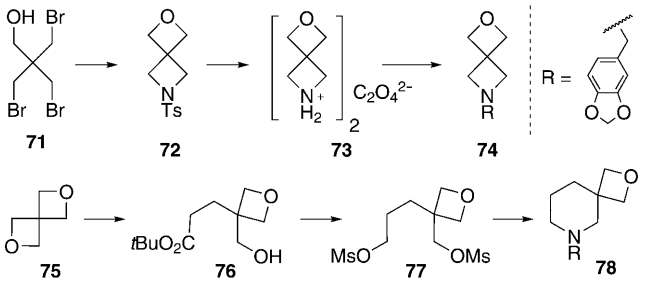
The primary addition products of oxetanone and its derivatives are amenable to further manipulation, thus enabling the synthesis of novel building blocks. These oxetane derivatives are largely inert to nucleophilic ring opening




***Scheme 10.*** Synthesis of spirocyclic oxetanes starting from Michael acceptors **48** and **50**. Ms = methanesulfonyl.

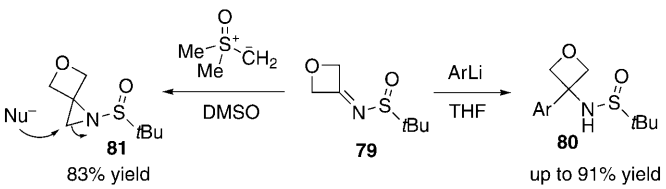
under alkaline conditions, as well as to reducing agents such as lithium aluminum hydride at low temperature.

As shown in Scheme 11, additional spirocyclic oxetanes can be prepared from commercially available tribromopentaerythritol (**71**) and spirocyclic oxetane **75**, which is accessible in one step from dibromopentaerythritol.[50] Spirocyclic oxetane **75** can be selectively opened by an ester enolate to give 3-hydroxymethyloxetane **76**.




***Scheme 11.*** Synthetic routes to spirooxetanes from pentaerythrite starting materials.

Oxetan-3-*tert*-butylsulfinimine (**79**) was very recently described as a readily accessible intermediate that provides an alternative convenient route to the important class of 3-aryl or alkyl-substituted 3-aminooxetanes (Scheme 12).[51] Thus, lithiated nucleophiles were reported to add to **79**, thereby affording products **80** in high yields. Strained spirocycle **81** was obtained from **79** and used for subsequent aziridine-opening reactions with a variety of nucleophiles ($Nu^-$) to generate homologated 3-aminooxetanes.



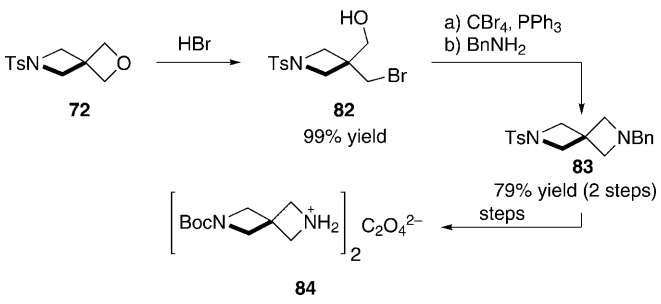

***Scheme 12.*** Formation of substituted 3-aminooxetanes.

## 4. Ring-Opening Reactions of Oxetanes

As small saturated heterocycles, oxetanes display chemical as well as physical characteristics whose origins can be traced back to their inherent ring strain. In oxetane itself, the strain energy has been determined to be 106 kJ mol$^{-1}$, only 6 kJ mol$^{-1}$ less than in oxirane and 81 kJ mol$^{-1}$ more than in tetrahydrofuran.[52] Oxetane undergoes hydrolysis catalyzed by sulfuric or perchloric acid in aqueous dioxane almost as rapidly as does ethylene oxide. In the presence of base, however, ring opening of oxetane is very slow: oxirane undergoes hydrolysis three orders of magnitude faster than oxetane under alkaline conditions.[53] Theoretical studies carried out on the origin of this difference in reactivity led to different possible explanations. Hoz and co-workers conclude that in the case of three-membered oxirane more strain is released in the transition state, which leads to a lower activation energy than in four-membered rings.[54] For the related case of cyclopropane versus cyclobutane, Sawicka and Houk point out that the transition state for three-membered rings has aromatic character which stabilizes it compared to four-membered rings, which have a transition state with antiaromatic character.[55] This reactivity difference towards nucleophiles means that ring-opening reactions of oxetanes often require the use of strong Brønsted or Lewis acids or high temperatures. Additionally, oxetanes with substitution at the 3-position display reduced susceptibility to ring opening, because any ring cleavage by a nucleophilic displacement reaction would suffer from unfavorable nonbonding interactions, analogous to those observed at neopentylic centers.[56]

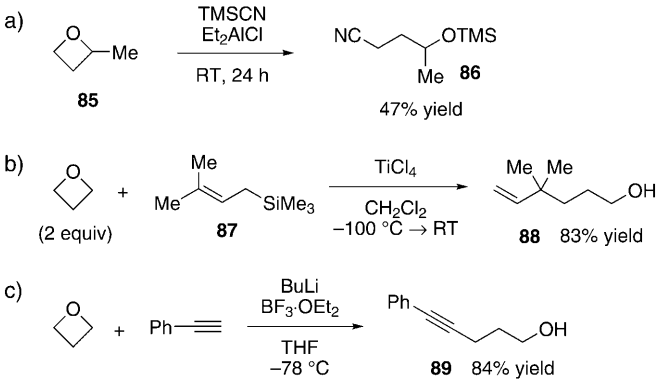
Inspired by the analogy to morpholine, we became interested in 2,6-diazaspiro[3.3]heptanes as structural surrogates for piperazines, a common unit in pharmaceutically active compounds. In contrast, its spirocyclic counterpart is an underrepresented structural motif in drug discovery, mainly because of the lack of an efficient synthesis. In the course of our investigations it was discovered that spirocyclic oxetane **72** was an ideal precursor for the preparation of "homospiropiperazines" (Scheme 13).[57] Selective opening of the oxetane ring with anhydrous HBr gave the bromoalcohol **82**, which after conversion into the dibromide was easily cyclized with benzylamine to give the azetidine. This three-step procedure afforded 2,6-diazaspiro[3.3]heptane **83** with differently protected amines in an overall yield of 76% on a multigram scale. The most convenient synthetic building block, mono-Boc-protected oxalate salt **84**, is accessible in four additional high-yielding steps.




***Scheme 13.*** Synthesis of 2,6-diazaspiro[3.3]heptanes from spirocyclic oxetane **72**. Bn = benzyl.

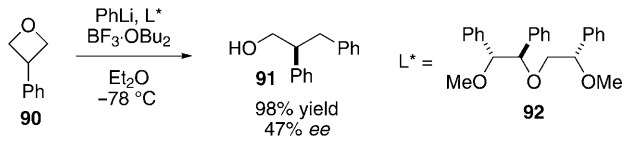
### 4.1. Lewis Acid Mediated Intermolecular Reactions

In the 1980s further investigations on oxetane-opening reactions were reported by the research groups of Weber and Yamaguchi (Scheme 14). Mullis and Weber discovered the regioselective opening of 2-methyloxetane (**85**) with a combination of TMSCN and $Et_2AlCl$.[58] The resulting nitrile product was isolated in 47% yield as the only regioisomer (Scheme 14a). Carr and Weber reported the opening of oxetane and 2-methyloxetane with allyl trimethylsilanes (**87**) under the influence of $TiCl_4$ (Scheme 14b).[59] Yamaguchi et al. developed the alkynylation of oxetane and substituted variants to give γ-hydroxyacetylenes (**89**, Scheme 14c).[60] The products were usually isolated in good yields, with $BF_3{\cdot}OEt_2$ being the optimal Lewis acid.




***Scheme 14.*** Lewis acid mediated opening of oxetanes.

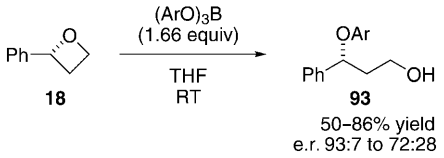
Recently, the enantioselective ring opening of oxetanes has gained attention. Among the first reports is the enantioselective opening of 3-phenyloxetane (**90**) with PhLi coordinated to the chiral tridentate ligand **92** (Scheme 15).[61] By using the optimal Lewis acid $BF_3{\cdot}OBu_2$, the product **91** was obtained in excellent yield (98%) and a satisfying 47% *ee*. Butyllithium and lithiated phenylacetylene can also be added, albeit in lower yields and selectivity.




***Scheme 15.*** Enantioselective opening of 3-phenyloxetane.

Enantiomerically enriched 2-phenyloxetane (**18**) can be opened regio- and stereoselectively with various aryl borates to give β-aryloxy alcohols **93** (Scheme 16).[62] It was found that the ring-opening reaction proceeded largely with retention of configuration.

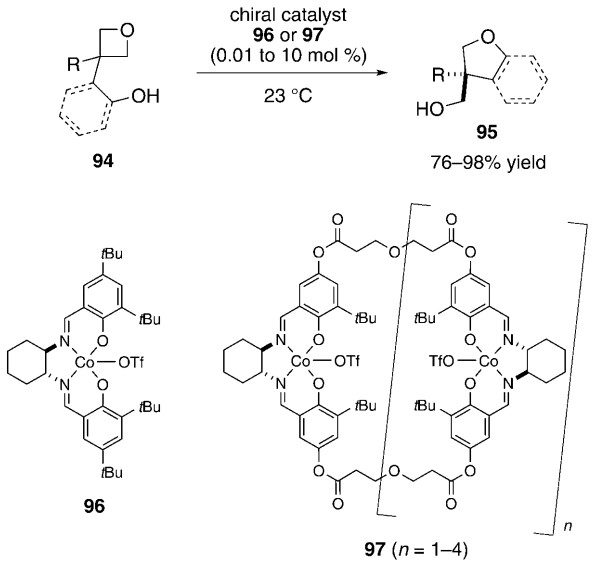
  




***Scheme 16.*** Selective opening of 2-phenyloxetane with aryl borates.

### *4.2. Intramolecular Ring-Opening Reactions*

Bach et al. examined the intramolecular opening of 2,3,3-trisubstituted oxetanes to give ring-expanded ethers, thioethers, and carbonates.[63] Loy and Jacobsen documented the enantioselective Lewis acid mediated intramolecular ring opening of oxetanes.[64] Achiral 3,3-disubstituted oxetanes bearing a remote hydroxy group were treated at ambient temperature either neat or at high concentrations (for example, 6 M in $CH_3CN$) with catalytic amounts of cobalt(III) salen complexes. The ring-opening reactions afforded a variety of tetrahydrofurans **95** in high yield and enantioselectivity (Scheme 17). In accordance with epoxide-opening reactions,[65] dimeric complexes **97** ($n=1$) were found to be

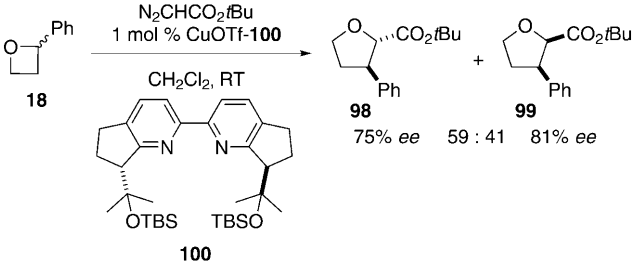



***Scheme 17.*** Cobalt(III)-catalyzed enantioselective intramolecular opening of oxetanes according to Loy and Jacobsen.[64] OTf = trifluoromethane sulfonate.

superior to the monomeric cobalt(III) salen counterpart (**96**). Thus, the use of catalysts of type **97** allowed catalyst loadings as little as 0.01 mol% to be used, with the rearranged products formed in up to 98% yield and 99% *ee*. The enhanced reactivity of catalyst **97** ($n=1$) can be explained by cooperative bimetallic mechanisms involving simultaneous activation of the nucleophile as well as Lewis acid activation of the oxetane.

### *4.3. Ring-Expansion Reactions of Oxetanes*

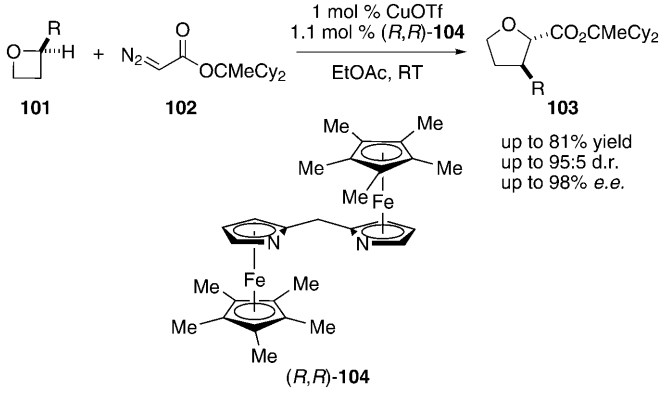
As part of their studies of transition-metal-catalyzed enantioselective reactions, Noyori and co-workers documented the copper-catalyzed asymmetric ring expansion of oxetanes to afford tetrahydrofurans.[66] They found that the insertion of a salicylaldimine-chelated copper carbenoid into the C–O bond can effect the formation of enantiomerically enriched substituted tetrahydrofurans. Inspired by this work, Katsuki and co-workers were interested in further improving the reaction. The use of $C_2$-symmetric bipyridine ligands for copper(I) was advantageous for the generation of enantioenriched products (Scheme 18).[67] Treatment of racemic 2-phenyloxetane (**18**) with *tert*-butyl diazoacetate and a mixture of 1 mol% of CuOTf and bipyridine ligand **100** afforded the




***Scheme 18.*** Asymmetric ring expansion of oxetanes according to Katsuki and co-workers.[67] TBS = *tert*-butyldimethylsilyl.

products **98** and **99** in a diastereomeric ratio of 59:41 in favor of the *trans* isomer.[67a,b] The conversion of 2-alkynyloxetane into the corresponding tetrahydrofuran proved to be superior, as the product was formed in 88% yield (as a *cis*/*trans* mixture). This transformation was applied in the total synthesis of the *trans*-Whisky lactone and the formal total syntheses of (−)-avenaciolide and (−)-isoavenaciolide.[67c–e]

In 2001, Lo and Fu described the use of a copper(I) bis(azaferrocene) complex in an oxetane ring-expansion reaction.[68] By using enantiomerically highly enriched 2-substituted oxetanes and a diazoacetate with 1 mol% of a copper(I) catalyst, the ring-expanded products could be obtained in good yield as well as high diastereomeric and enantiomeric ratios (Scheme 19). Sterically demanding car-




***Scheme 19.*** Ring expansion of oxetanes according to Lo and Fu.[68] Cy = cyclohexyl.

bene precursors were necessary to obtain high *trans*/*cis* ratios. The best results were observed for the 1,1-dicyclohexyl-substituted ethyl diazoacetate (**102**). The diastereomeric ratio of the products was largely determined by the character of the copper complex. Application of the (*R*,*R*)-bis(azaferrocene) ligand **104** led to the formation of tetrahydrofurans with *trans*-configured substituents, whereas the same reaction with the other enantiomer of the ligand afforded predominantly *cis*-configured products.

## 5. Property Changes through Oxetanes

As outlined in the introduction, oxetanes can play a significant role in the optimization of key pharmacokinetic properties of drug candidates. This section focuses on the incorporation of oxetanes onto frameworks commonly seen in medicinal chemistry and their effect on the underlying scaffold.

### 5.1. Analogy of Oxetanes to gem-Dimethyl Groups

The introduction of steric hindrance often deflects chemical[69] or metabolic[70] liabilities from nearby functional groups. Especially in the case of metabolically unstable methylene groups as in a benzylic position, it is common practice to block metabolic attack by the introduction of a *gem*-dimethyl unit.[71] It is interesting that more than 10% of all launched drugs contain at least one *gem*-dimethyl group, thus highlighting its relevance in drug discovery.[4] However, for a typical small molecule in medicinal chemistry the replacement of hydrogen atoms by methyl groups leads to a significant increase in lipophilicity, which in turn may adversely affect its physicochemical and pharmacological properties.[72] Moreover, the *gem*-dimethyl group can itself become a target of metabolic degradation.[73] The case described for the *gem*-dimethyl group exemplifies the situation with various other substituents, which, similar to the *gem*-dimethyl group, intrinsically possess high lipophilicity, which is generally undesirable in drug discovery.[72] Therefore, a stable, compact module with reduced lipophilicity and susceptibility to metabolic attack is desirable. By bridging the two methyl groups of the *gem*-dimethyl unit with an oxygen atom, the so-formed oxetane fulfills precisely these requirements. The four-membered ring occupies a similar, or even smaller, volume than a *gem*-dimethyl group, as evident by comparison of the partial molar volumes of oxetane ($61.4\ cm^3\,mol^{-1}$) and propane ($70.7\ cm^3\,mol^{-1}$) in water. The slightly smaller volume observed for oxetane is probably attributable to its hydrogen-bonding capacity.[74]

### 5.2. Oxetanes—Bulky and Polar

While oxetanes were initially explored because they could provide steric bulk without increasing the lipophilicity, other opportunities arose when oxetanes were envisioned as carbonyl surrogates. The electron lone pairs on the ether oxygen atom in oxetanes and on the carbonyl oxygen atom display comparable spatial arrangements, and both functionalities are polarized similarly. Consequently, an analogy can be readily drawn (Figure 7, left). According to this logic, replacement of a carbonyl group with an oxetane ring could

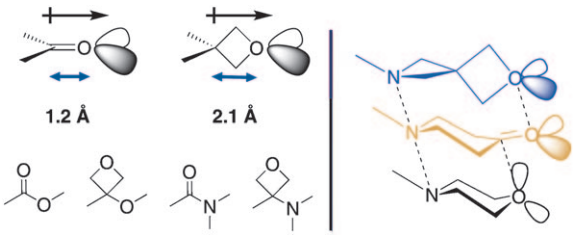



***Figure 7.*** Comparison of oxetanes and other polar functionalities.[2b]

be beneficial, since carbonyl groups, such as in aldehydes, ketones, or Michael acceptors,[4] are generally absent in drug discovery because of their inherent chemical and metabolic liability. Moreover, the relative ease of α-deprotonation in ketones and aldehydes renders stereogenic centers at this position sensitive towards epimerization. Carboxylic acid derivatives, such as esters and amides, are chemically rather stable but are prone to enzymatic cleavage in an organism. Therapeutic agents with oxetanes in place of the carbonyl group might, therefore, provide intriguing alternatives.

As shown in Figure 7 (right), a spirocyclic oxetane could serve as a viable substitute for morpholine, another widespread moiety in pharmaceutical chemistry. Morpholine is often used as a hydrophilic solvation anchor for lipophilic compounds, but often appears to be the target of oxidative metabolic attack.

### 5.3. Influence on the Basicity of Proximal Amines

While the oxygen atom of an oxetane can donate electron density as a Lewis base, the oxetane motif itself acts as an electron-withdrawing group on neighboring functional groups. This distance-dependent inductive effect of the oxetane can be used to temper the basicity of a proximal amine. Data that has been accumulated from oxetanes **58**, **60**, **106**, and **107** as well as the control compound **105** show distinct patterns in amine basicities (Figure 8).[2a] The basicity reduction may be close to 3 $pK_a$ units if the oxetane is grafted in the α position to the amine. It is continuously attenuated with increasing topological distance to the oxetane. Even at large distances, for example, in the δ position to the oxetane, as in structure **107**, a decrease of 0.3 $pK_a$ units is observed.

### 5.4. Lipophilicity and Aqueous Solubility

Having seen that the presence of an oxetane can markedly influence the basicity of a proximal amine, it was important to assess its influence on the lipophilicity of the underlying scaffold. To aid comparisons with neutral compounds (for example, lactam derivatives) and to avoid potential compli-

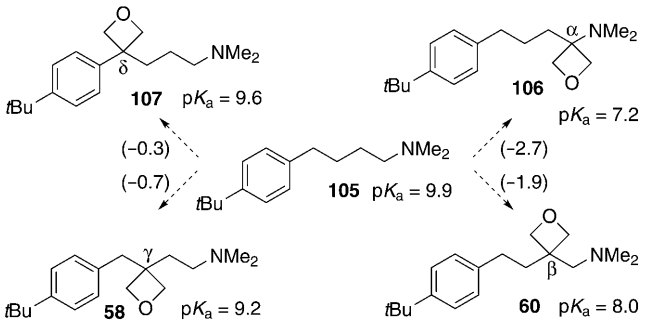



***Figure 8.*** Change in the $pK_a$ value of an amine upon replacement of a methylene group with an oxetane ring (difference in brackets). $pK_a$ values are amine basicities measured spectrophotometrically at 24 °C in $H_2O$.

cations arising from basic lipophilic compounds forming micelles at a neutral pH value, intrinsic solubilities at high pH values and lipophilicities (log*P*) for the neutral amines were determined.[2a,b] As demonstrated in Figure 9, there is a significant decrease in lipophilicity on going from *gem*-dimethyl compound **112** to its oxetane derivative **62** ($\Delta\log P = -2.4$), but the corresponding amino ketone **108** is even less lipophilic by 0.4 logarithmic units. Whereas compounds **64** and **109** differ by more than 1 log*P* unit, there is only a small difference in the intrinsic lipophilicity between oxetane **66** and β-lactam **110**.

All the available evidence taken together shows that an oxetane-containing molecule is typically much less lipophilic than the respective *gem*-dimethyl analogue, and that the corresponding carbonyl compounds are even more hydrophilic. Thus, the oxetane positions itself between a carbonyl and a *gem*-dimethyl group, but is somewhat closer to the former.

The observed trend in lipophilicity manifests itself in intrinsic aqueous solubilities.[2a,b] A carbonyl compound, under the same experimental conditions, is usually more soluble than its oxetane or *gem*-dimethyl analogues. The changes seen in the series **58**, **60**, **105**,–**107**, and **116** emphasize the effects the introduction of the polar ethereal oxygen atom can have, especially when employed away from other polar functional groups. When situated close to a basic amino group, the observed gain in solubility may be moderate because of the reduction of basicity and concomitant increase in the intrinsic lipophilicity (Figure 10; **60** and **106**). However,

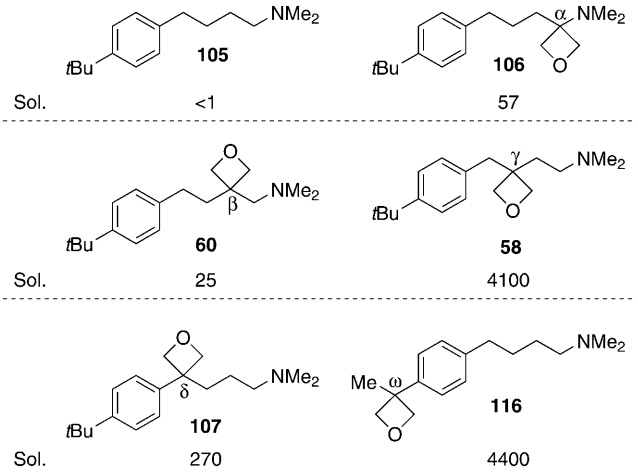



***Figure 10.*** Change in the aqueous solubility at pH 9.9 upon substitution with an oxetane unit. Sol. = intrinsic thermodynamic solubility (mg mL$^{-1}$) in 50 mM phosphate buffer measured at pH 9.9 and (22.5 ± 1) °C.

if introduced more remotely, the oxetane may increase the (intrinsic) solubility by several orders of magnitude (see **116**). It is interesting to note that there is not a linear relationship between the solubility and the distance of the basic amine group from the oxetane, as substitution in the γ position (**58**) led to a higher solubility than oxetanes attached at the β or δ positions.

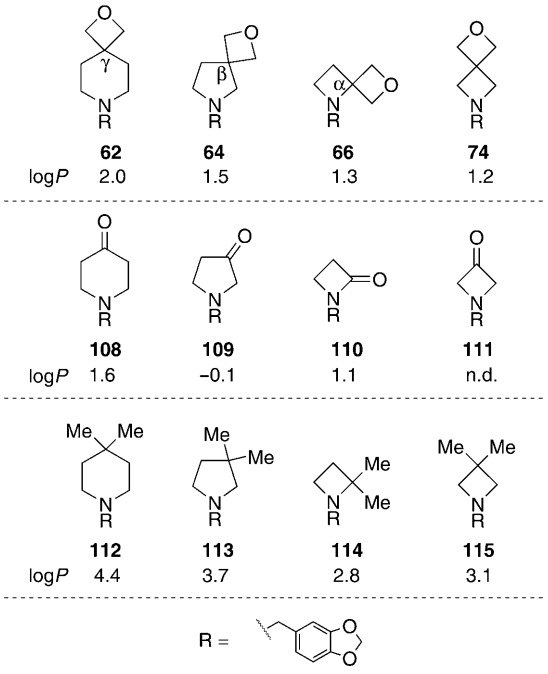



***Figure 9.*** Change in lipophilicity upon exchange of a carbonyl or a *gem*-dimethyl group with an oxetane ring. log*P* = intrinsic lipophilicity of the neutral base. n.d. = not determined because of chemical instability.

### *5.5. Metabolic and Chemical Stability*

Many promising lead structures do not reach the clinical phase because of their metabolic instability. Several biological pathways are subsumed under the term metabolic degradation.[75] The influence an oxetane has on oxidative phase I metabolism has been studied and compared with compounds having carbonyl or *gem*-dimethyl groups at the corresponding position.[2a,b] It was found that compounds bearing oxetanes tend to have a low to modest proclivity towards metabolic degradation, and that in many cases the corresponding *gem*-dimethyl or carbonyl compounds have higher intrinsic

clearance rates in human liver microsomes. When the oxetane is positioned in a piperidine ring at the β or γ position to the amine, the metabolic degradation is significantly reduced when compared to the respective amino ketones or *gem*-dimethyl compounds (Figure 11). In contrast, when the oxetane is located in the α position of the amine, the oxetane compound shows a more pronounced metabolic liability—not surprising in view of the marked basicity-reducing effect of the α-oxetane unit and concomitant increase in the lipophilicity. The intriguing morpholine substitute **74** displayed excellent metabolic and chemical stability, whereas the metabolic profile of its carbonyl counterpart **111** could not be measured because of its chemical instability. Although metabolic clearance is dependent on all the structural elements of a molecule, and trends should, therefore, not be generalized in terms of selected subunits, it is worth noting that similar results were obtained with other basic amine compounds bearing oxetanes at the respective positions.

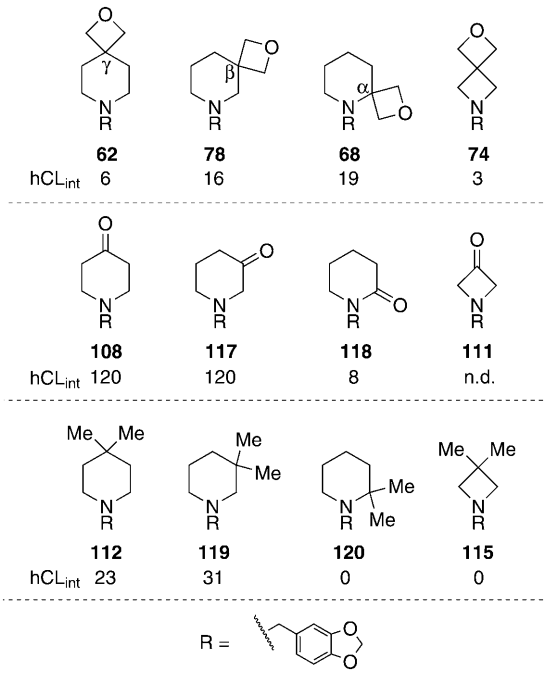



***Figure 11.*** Intrinsic clearance rates in human liver microsomes for selected oxetane, carbonyl, and *gem*-dimethyl compounds. hCL$_{int}$ = intrinsic clearance rates [min$^{-1}$/(mg$_{protein}$ μL$^{-1}$)]; n.d. = not determined because of chemical instability.

3,3-Disubstituted oxetanes typically exhibit good chemical stability and are assayed routinely in aqueous solutions buffered at pH values ranging from 1 to 10 for 2 h at 37 °C. This is also reflected by the stability of the oxetane unit under reaction conditions that avoid strong acids or combinations of strong Lewis acids and reactive nucleophiles at elevated temperatures. Thus, the oxetane unit can often be introduced early in a reaction sequence, and oxetane-containing building blocks can be subjected to a variety of sequential transformations without affecting the oxetane unit. By contrast, monosubstituted oxetanes are in general chemically somewhat less stable. Thus, in aqueous solution at pH 1 (but not at higher pH values) some decomposition of monosubstituted oxetane derivatives has been observed, and chemical transformations involving such oxetane intermediates have to be performed with care.

### *5.6. Applications of Oxetanes in Medicinal Chemistry*

Gier and Searles disclosed in 1958 the anesthetic, sedative, and anticonvulsant properties of simple oxetanes, such as 3,3-diethyloxetane, in rats.[76] A more-recent study described the anaesthetic properties of some fluorinated oxetanes, but found no advantage compared to commonly used anaesthetics.[77] A search through the modern structural databases reveals that the most common use of oxetanes as modules is found in oligonucleotide analogues. Conformationally restrained oxetane derivatives of cytidine (**121**) and thymidine (**122**) have been examined for their use in antisense oligonucleotides (AONs; Figure 12). The resulting AON-RNA heterodimers displayed increased stability towards degradation by nucleases.[78] However, it is altogether unclear whether the stability is directly related to the introduction of the oxetane unit itself or merely follows from the unique conformational constraints imposed by the *cis*-ring fusion.

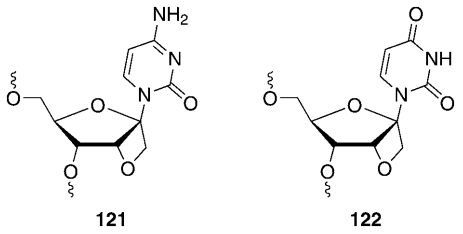



***Figure 12.*** Oxetane analogues of cytidine and thymidine used in novel antisense oligonucleotides.[78]

Oxetanes can also be found in transition-state analogue inhibitors of renin, an aspartate protease that is important in blood-pressure regulation (Figure 13).[79] In the case of the dihydroxy isoster **123** it is believed that the diol interacts with both aspartate residues in the active site.[80] A rationale for the increased binding affinity of oxetane **125** compared to

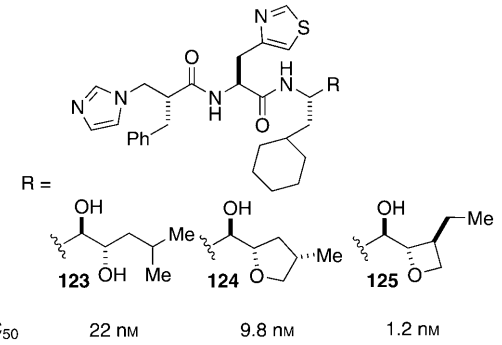



***Figure 13.*** Oxetanes as transition-state analogues for renin with measured IC$_{50}$ values.

tetrahydrofuran **124**, however, was not provided and is far from clear.

Recent work by Diederich and co-workers has showcased the use of oxetanes to enhance the water solubility of a drug candidate (Figure 14).[81] In their study, a cytosine core decorated with two exocyclic appendages was optimized for

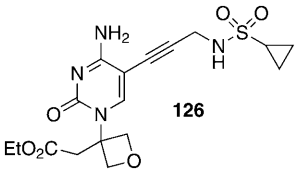



***Figure 14.*** An oxetane-containing cytosine inhibitor of IspE.

inhibition of the protein IspE (4-diphosphocytidyl-2*C*-methyl-D-erythritol kinase), an enzyme of the non-mevalonate pathway for isoprenoid biosynthesis. As this enzyme is absent in humans, it is an interesting target for the treatment of pathogens such as malaria and tuberculosis. Nucleoside **126** displayed inhibitory activity for IspE from *E. coli* ($K_i$ = 28.7 μM). Although several other compounds of this series showed improved activity, cytosine **126** turned out to be the only fully water-soluble lead compound that did not require cosolvents (DMSO or EtOH) in an in vitro binding assay. In addition, an X-ray crystallographic structure of IspE from *A. aeolicus* in a complex with **126** was successfully determined to 2.2 Å resolution.

The later part of this decade has marked a resurgence of interest within the pharmaceutical community in "compact modules", that is, low-molecular-weight mono-, bi-, or fused heterocyclic scaffolds that can be easily derivatized to provide surrogates for established medicinal-chemistry-like elements or building blocks. Oxetanes have provided one avenue in this renaissance, stimulated by publications and patents that have recognized their potential value for the modification of physicochemical, safety, and metabolic properties of the compounds containing this module embedded in their structures. It has become apparent that companies identify an immediate and clear intellectual property advantage and are, therefore, routinely including, for example, oxetanes in their claims. Notwithstanding this, the recent Novartis patent "Phenyl-oxetanyl-derivatives"[3f] also highlighted the therapeutic potential of aryloxetanes in their own right. This growth in interest was also fueled by expanded access from Asian, European, and most recently also American providers of novel, commercially available (amino-)oxetane modules. Restriction to a survey of oxetane usage within Roche during only 2009 reveals six patent applications in the fields of amyloid beta modulators, antiviral agents, purinergic receptor antagonists, phosphoinositide 3-kinase inhibitors, NK3 receptor antagonists, orexin receptor antagonists, and GABA-A inverse agonists. About 800 oxetane-containing pharmaceutical patents were filed by all companies in the pharmaceutical sector in 2009. It is worth noting that the large-scale production of the Syngenta agrochemical Oxasulfuron (**15**) has demonstrated the possibility of the bulk production of an oxetane compound. With an increasing number of reliable synthetic procedures for the incorporation of oxetanes into structures of interest, we envision the four-membered heterocycle will be applied more extensively in the future.

## 6. Summary

In recent years, oxetanes have received considerable interest in the synthetic community as well as in various fields of chemical industry. Thus, new methods for the construction of oxetane-containing compounds were developed. Approaches include the elaboration of suitable building blocks that can easily be further derivatized, as well as stereoselective reactions such as diastereoselective cycloaddition reactions and enantioselective methylene insertion reactions. Moreover, oxetanes have been used in ring-opening reactions to afford valuable materials that are otherwise cumbersome to prepare.

The ease of synthetic access has triggered the use of the oxetane building block in medicinal chemistry. It has been demonstrated that this four-membered heterocycle can be introduced as a more polar surrogate for highly lipophilic moieties, such as the *gem*-dimethyl group, or as a replacement for metabolically and chemically labile carbonyl groups. The remarkable stability of 3,3-disubstituted oxetanes and their characteristic property-modulating effects will stimulate their use not only in the pharmaceutical industry, but also in other industrial fields such as material and agrochemical sciences.

The revival of oxetane in organic synthesis and the evaluation of its properties in pharmaceutical chemistry have only just begun. It is expected that further methods will be devised for its easy incorporation into target scaffolds, and continued studies will deepen our understanding of its impact on the properties of compounds. The door is open for a rich spectrum of applications in drug discovery and beyond.

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