Oxetane as a part of modern medicinal chemistry toolbox: the case of 3,3-disubstituted building blocks

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Dedicated to brave Ukrainian people whose everyday deed makes this publication possible

Abstract: Despite numerous potential advantages of oxetanes, their restricted synthetic accessibility and propensity to ring-opening hampers their wide application in drug design. In this work, we disclose our 10-year experience in oxetane chemistry and provide a comprehensive analysis of the oxetane core tolerance towards the reaction conditions of the typical toolbox of organic and medicinal chemists. The scope includes oxidation, reduction, alkylation, acylation, nucleophilic substitution, C–C/C=C/C≡C bond formation, hydrolysis and protecting groups cleavage, and also demonstrates the stability of the oxetane's moiety towards acidic and basic conditions. Over 30 transformations were applied to generate the oxetane chemical stability profile and prepare novel 3,3-disubstituted oxetanes as accessible small building blocks (over 100 examples). The work's additional aim included optimizing the synthetic protocols with the possibility of scaling on up to 1 kg in a single run, also addressing the potential instability of the oxetane ring. These results benefit the development of oxetanes as a part of the toolbox of modern medicinal chemistry, as well as their incorporation into drug development programs.

Introduction

Since the development of the first preparative method for the parent oxetane (originally called trimethylene oxide) in 1949,[1] this simple heterocyclic core has remained exotic for the chemical community for many years, mainly due to its uncertain reactivity. According to classical heterocyclic chemistry textbooks, oxetane's ability to undergo ring-opening reactions lies in between the reactivity of oxiranes and tetrahydrofurans. It is well-known that oxiranes have found application as useful reactive intermediates with a thoroughly characterized reactivity profile,while tetrahydrofuran backbone is regarded as a stable moiety, highlighted by THF as one of the most popular solvents in organic chemistry. In a chapter of "PATAI'S Chemistry of Functional Groups" published in 1967,[2] one can find practical guidance underlining that oxetane fragment generally tolerates alkali conditions excepting Grignard reagents and complex hydrides. At the same time, this ring is rather unstable in an acidic environment and is easily cleaved by external nucleophiles available in the reaction medium. Additionally, ring-opening reactions were indicated to be possible under thermal and transition metal-catalyzed conditions. However, all the available data were scarce and inconsistent for providing a comprehensive grasp of the oxetane's reactivity profile, thus leading to limited applications of this class of compounds as either reactive intermediates in organic synthesis or "stable" fragments in functional-oriented design for many years. Nevertheless, the continuous discovery of oxetane-bearing natural products[3]paved the way for the development of the chemotherapy medication paclitaxel, primarily isolated in 1971 from *Taxus brevifolia* and approved by the FDA for medical use in 1993. Commonly known by its brand name Taxol®, it shares the title of the only oxetane-containing FDA-approved drugs with its semi-synthetic analogs Docetaxel (Taxorete®) and Cabazitaxel (Jevtana®). This fact called for the further seminal insightful investigations by the Carreira's group in collaboration with Hoffmann-La Roche (Roger-Evans, Müller),[4–6] which uncovered distinct patterns of oxetane's core drug-like properties and isosteric relationships with carbonyl and *gem*-dimethyl groups. Particularly, structural variations revealed improved metabolic stability and lower lipophilicity of the oxetane fragment compared to groups commonly exploited in MedChem projects, thus promoting it to an "emerging motif" in drug discovery.[7] Nowadays, oxetanes have entered routine medicinal chemistry, as pointed out by the explosive increase in the number of oxetane-based substances used in drug discovery (Figure 1, box A). The collection and analysis of such an impressive data array allow for a precise formulation of the oxetane role in medicinal chemistry, which is discussed in several review articlesreviewed.[8–10] Meanwhile, the number of oxetane ring cleavage examples observed in synthetic practice is increasing as well (Figure 1, box B). Apparently, there were attempts to systemize all the information on the issue. However, as far as we know, only one review article discussed possible synthetic application of oxetane cleavage reactions.[11]

A

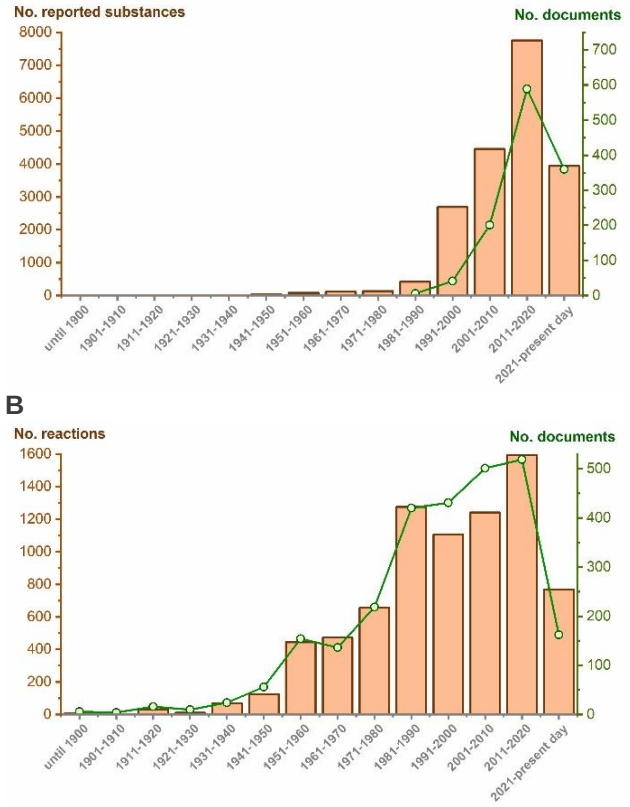


Figure 1. **A**: The number of biologically active oxetanes deposited in the Reaxys database along with the number of the corresponding references; **B:** The number of oxetane ring cleavage reactions deposited in the Reaxys database along with the number of the corresponding references.

Still, detailed data regarding the chemical stability of the oxetane ring remains unavailable,[10] impeding further advancements in this area and hindering the growth of diversity and nomenclature of commercially available oxetane-derived building blocks. Our recent analysis of commercially accessible building blocks revealed only 891 examples of those containing oxetane ring;[12] this value is extremely lower compared to other MedChem-relevant classes of compounds.

As mentioned above, it is well-known that oxetane ring is prone to the ring-opening reaction mostly in acidic conditions, even upon isolation of oxetanes from the reaction mixtures or their storage.[13] Our research is intended to share the experience gained while performing in-house programs directed to enriching the stock with 3,3-disubstituted oxetane-derived building blocks (Figure 2) using 3-oxetanone as a common starting compound available on a kilogram scale. The investigated transformations cover a series of functional group interconversions, including oxidation, reduction, alkylation, acylation, nucleophilic substitution, hydrolysis, and protecting group cleavage, as well as C–C/C=C/C≡C bond formation. Among others, the evaluated protocols include the application of acidic / basic reaction conditions. If the oxetane core was unstable under the model reaction conditions, we modified and/or optimized them in order to make the required transformations possible.

This paper provides a brief overview of our many years of efforts in the discussed research area and summarizes hundreds of test experiments (both successful and unfruitful). The proposed optimized and efficient transformations can give rise to a series of novel small sp^3-enriched building blocks, promising for modern practice-oriented organic and medicinal chemistry. Additionally, this work offers an outline of oxetane core tolerance toward different reaction conditions by analogy with the “robustness screen” approach applied earlier for the catalytic reactions,[14] which could be a helpful comprehensive manual for synthetic and medicinal chemists working in the field (Figure 2).

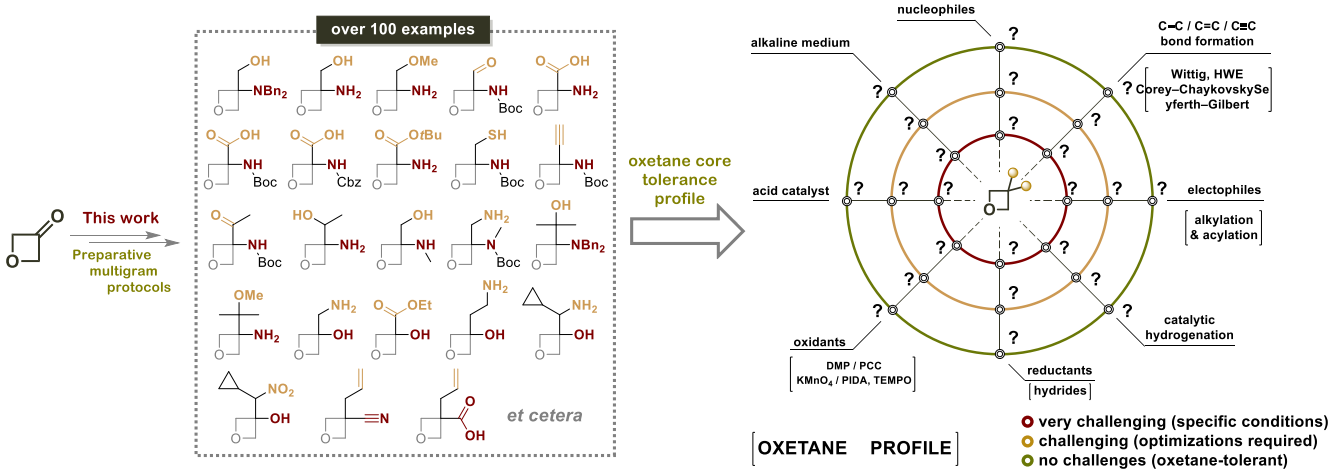


Figure 2. Synopsis of the research

Results and Discussion

First, we have aimed to obtain a series of common oxetane-containing precursors with a 3,3-disubstituted pattern. For this purpose, we utilized commercially available bulk oxetan-3-one (**1**) as the starting material. Initial transformations (T) involved a series of well-established ketone functionalization reactions (Figure 3). In particular, the Strecker synthesis with TMSCN as the cyanide source and dialkylamine yielded 3-cyano-3-dibenzylamino oxetane. It opened pathways to a diverse scope of oxetane amino acids and their derivatives. The oxetane-tolerant introduction of the aminomethyl group alongside a tertiary hydroxyl group was achieved via the Henry synthesis with nitromethane and other nitroalkanes. In turn, the Horner–Wadsworth–Emmons (HWE) reaction transformed oxetan-3-one into α,β-unsaturated ester derivatives, facilitating further functionalization through Michael addition and dihydroxylation (Scheme 1).[15–18]

Next, we have systematically explored a wide range of reactions and conditions from the common toolbox of organic chemists, aiming to maximize the synthetic utility of this fragment.
Following the aforementioned Strecker synthesis, the subsequent transformation was the hydrolysis of the nitrile fragment. This step was crucial as it enabled the formation of a series of amino acid derivatives, significantly expanding the range of accessible compounds. The hydrolysis was performed under the oxetane-tolerant basic conditions following the previously described strategies.[19] This approach proved to be highly efficient and provided the desired productsin high purity and yield of. The acidic catalysis facilitated the ring-opening of oxetane and the formation of unwanted byproducts, which is the particular reaction limiting the use of oxetanes. Notably, the treatment with acids is also common upon the isolation step of the product according to the common protocols. This has inspired us to conduct a detailed study and optimize the methods of further reactions in this work to develop efficient procedures that are tolerant to oxetane core.

CO_2R (Me, Et) to CH_2OH
- T1 $LiAlH_4$, –30 to –10 °C, 1 –2 h
- T1 $NaBH_4$, 0 °C, 16 h (for a-NHBoc)
- T1 $LiAlH_4$, < –40 °C (slow)
- T1 $LiAlH_4$, > 0 °C (decomposition)

$C(O)NR_2$ to CH_2NR_2
- T2 AlH_3, –78 to –50 °C
- T2 AlH_3, > –30 °C (decomposition)
- T2 BH_3·R, any °C (decomposition)
- T2 $LiAlH_4$, < 0 °C (no reaction)
- T2 $LiAlH_4$, > 0 °C (decomposition)

CO_2H to CH_2OH
- T3 mixed anhydrive, $NaBH_4$ (low yields)
- T3 $LiAlH_4$, < 0 °C (no reaction)
- T3 $LiAlH_4$, > 0 °C (decomposition)

CN to CH_2NH_2
- T4 $CoCl_2$, $NaBH_4$, MeOH, Boc_2O (rapid)
- T4 H_2 (80 atm), Ni-Ra, 60 °C
- T4 $LiAlH_4$, any °C (decomposition)

NO_2 to NH_2
- T5 H_2 (60 atm), $Pd(OH)_2/C$, 55 °C
- T5 H_2 (80 atm), Ni-Ra, 60 °C (prolonged, lower yields and purity)

CH_2OH to CO_2H
- T12 TEMPO, PIDA, rt 12 h (for α-NHBoc-substituted, partial decomposition in some cases)
- T12 $KMnO_4$, 0 °C to rt, 16 h (for α-alkyl-substituted)

***N*-Boc cleavage**
- T6 TFA, CH_2Cl_2, rt, 1 h
- T6 HCl, Et_2O, rt, 1 h (70% partial decomposition)
- T6 HCl, 1,4-dioxane, rt, 1 h (complete decomposition)

CN or CO_2R to CO_2H
- T7 alkaline hydrolysis (LiOH, NaOH, KOH)
- T7 acidic hydrolysis (decomposition)

CH_2OH to CHO
- T8 DMP, rt, 3 h (for α-NHBoc-substituted)
- T8 PCC, rt, 3 h (for α-alkyl-substituted)

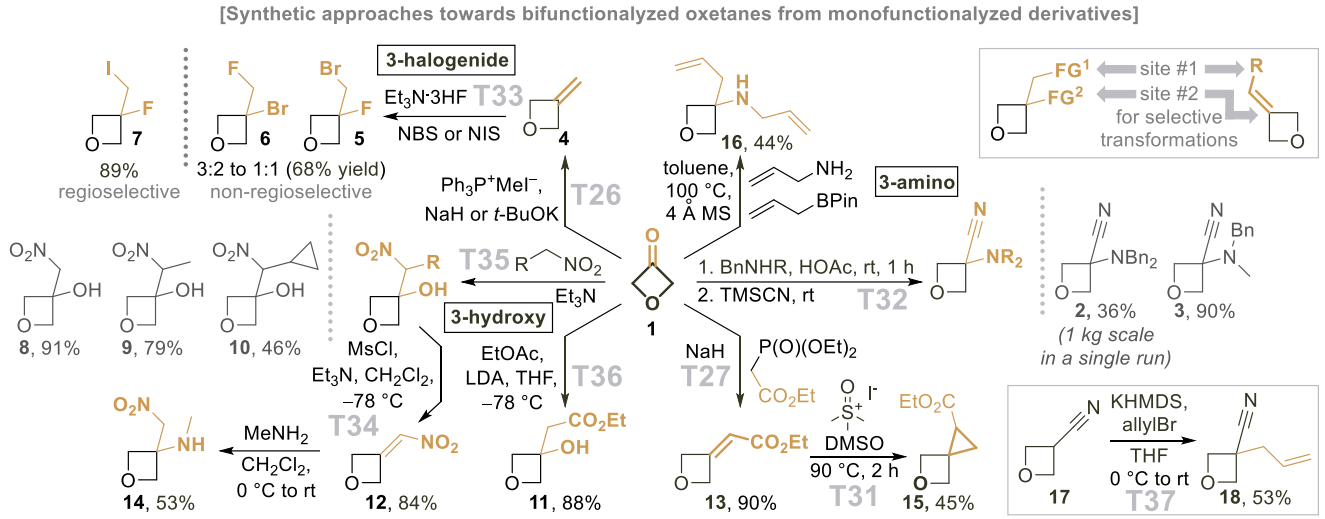
CO_2H to CO_2R
- T9 MeI, DIPEA, MeCN, 60 °C
- T9 acidic catalysis: HCl, MeOH (decomposition)

CH_2N_3 to CH_2NH_2
- T10 PPh_3, H_2O, THF, rt
- T10 H_2, Pd/C (low yields and purity)

CH_2OMs to CH_2SAc or CH_2SMe
- T11 KSAc or NaSMe, 20 °C (no reaction)
- T11 KSAc or NaSMe, 40 °C (for α-NHBoc)
- T11 KSAc or NaSMe, 60 °C (rearrangement)

- T13 **OH to F:** DAST / morph-DAST, –78 °C to rt
- T14 **OMs to F:** 60 °C
- T15 **iodocyclization:** 0 to 50 °C
- T16 **ketone reduction:** $LiAlH_4$, –30 °C or $NaBH_4$, 0 °C to rt
- T17 **C=C hydrogenation:** H_2, Pd/C
- T18 ***O*/*N*-Bn cleavage:** H_2 (80 atm), $Pd(OH)_2/C$, 60 °C
- T19 **Cbz cleavage:** H_2 (50 atm), $Pd(OH)_2/C$, Et_3N
- T20 **Grignard reaction:** MeMgBr, –20 °C to rt
- T21 **OH alkylation:** NaH or *t*-BuOK, THF or DMF, 0 to 80 °C
- T22 ***N*-protection with Boc**: Boc_2O, MeOH, 50 °C
- T23 **nucleophilic subtitution of hailde:** KCN or KOAc, DMF
- T24 **Seyferth–Gilbert reaction:** Ohira-Bestmann, 0 °C to rt
- T25 **RCM:** rt to 120 °C
- T26 **Wittig:** $Ph_3P^+Me\ I^-$, NaH or *t*-BuOK or $Ph_3P{=}CH_2$
- T27 **Horner-Wadsworth-Emmons:** NaH
- T28 **2° alcohol to ketone:** Dess-Martin (DMP) or PCC, rt, 3 h
- T29 **alkylation of carboxylic acids:** PhCOOH, DIPEA, 60 °C
- T30 **trifluoroacetyl cleavage:** KOH, MeOH, 60 °C
- T31 **Corey–Chaykovsky reaction:** DMSO, 90 °C, 2 h
- T32 **Strecker reaction:** BnNHR, HOAc, rt, 1 h, then TMSCN, rt
- T33 **fluorohalogenation of alkenes:** $Et_3N{\cdot}3HF$, NBS or NIS
- T34 **mesylation:** MsCl, Et_3N, CH_2Cl_2, 0 °C (–78 °C)
- T35 **Henry reaction:** RCH_2NO_2, Et_3N
- T36 **aldol reaction:** EtOAc, LDA, THF, –78 °C
- T37 ***C*-alkylation:** KHMDS, RBr, THF, 0 °C to rt
- T38 **CO_2H to amides:** $MeNH_2$ (·HCl), HATU, DIPEA, DMF, rt
- T39 **deoxofluorination to CHF_2:** Morph-DAST, CH_2Cl_2, –78 °C
- T40 **CF_3-addition to carbonyl:** $TMSCF_3$, TBAF, THF, 0 °C to rt
- T41 **Appel reaction:** PPh_3, CBr_4, CH_2Cl_2, –20 °C
- T42 **deoxofluorination to CF_3:** DAST or BAST, up to 100 °C (no reaction) or SF_4, HF (decomposition)
- T43 **nucleophilic subtitution of mesylate with NaN_3:** < 40 °C (no reaction); > 40 °C (recyclization)

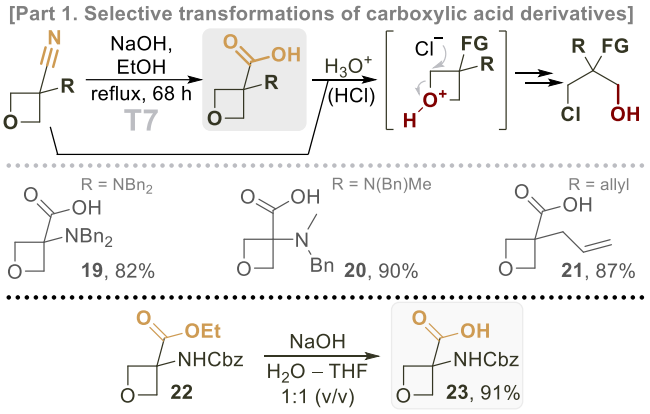
Figure 3. The toolbox of transformations (T) in the chemistry of oxetanes (green– suitable method; yellow – despite the method generally could be used, the conditions are not optimized, therefore providing low yields and/or purity of products; brown – the formation of products was not observed, the starting materials were regenerated; red – the set of conditions led to the decomposition of the starting materials). Detailed procedures and reaction schemes are given in the Supporting Information.



Scheme 1. The utility of oxetanone for the preparation of functionalized derivatives tolerating the oxetane moiety

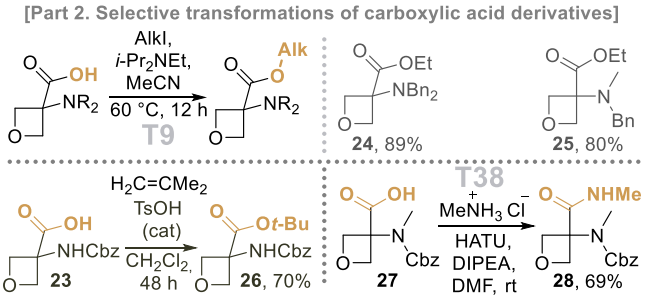
A set of other essential transformations included the Corey-Chaykovsky cyclopropanation with trimethyl sulfoxonium-derived ylide, which provided a pathway to spirocyclic 5-oxaspiro[2.3]hexane-1-carboxylate, shown for the case of the acrylate mentioned above (Scheme 1, T31).

Recognizing the success of the use of the basic conditions, we applied the same strategy for ester hydrolysis in subsequent stages, again preventing ring-opening reactions and producing high-purity products on the multigram scale (Scheme 2, T7).



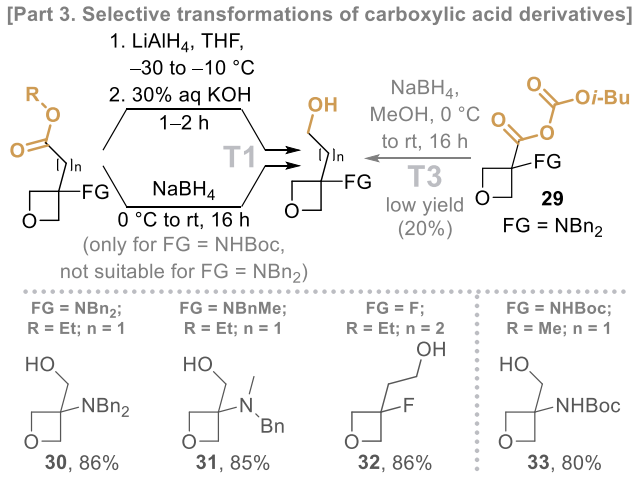
Scheme 2. Synthesis of oxetane-3-carboxylic acids

The presence of acidic carboxylic group itself is compatible with the oxetane core; the ring-opening reaction is observed only in the case of treatment with strong acids. This limited the esterification reaction to basic conditions, including the use of alkyl halides. The mild reaction conditions included the treatment with Hunig's base (Scheme 3, T9). In contrast, attempts to perform the esterification using the corresponding alcohol in the presence of HCl expectedly led to decomposition. The synthesis of *tert*-butyl esters involved a reaction with isobutylene in the presence of a catalytic amount of TsOH, with oxetane ring remaining intact.



Scheme 3. Synthesis of amino ester derivatives via esterification

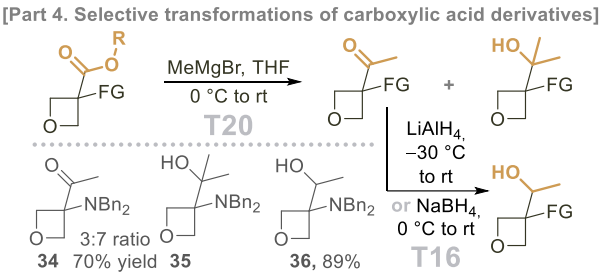
As expected, esters facilitated a straightforward pathway to the corresponding primary alcohols. However, initial attempts to use aluminum and boron hydride reagents proved suboptimal. Our first experiments with $LiAlH_4$ at temperatures above 0 °C resulted in the decomposition of oxetane carboxylates, contrary to results reported in the literature.[20,21] Performing the reaction at the temperatures between –30 and –10 °C was successful in most cases. The reaction was relatively slow in the case of derivatives with the *N*-Boc-protected group and provided moderate yields of the target hydroxymethyl derivatives. Alternatively, using $NaBH_4$ at 0 °C was more fruitful (Scheme 4, T1). Despite being uncommon and unsuitable for most of the existing ester, this approach minimized the side decomposition reaction while maintaining reasonable reaction rates, leading to higher yields of the desired alcohols.



Scheme 4. Reduction of oxetane-3-carboxylates to hydroxyalkyl-substituted derivatives

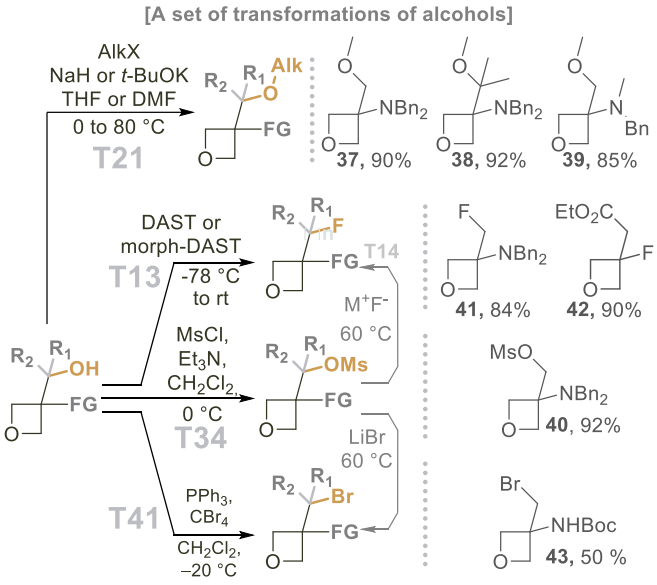
It should be noted that the direct reduction of carboxylic acids to primary alcohols was challenging and low-yielding. The treatment with $LiAlH_4$ did not show signs of any reaction below 0 °C, and rapid decomposition was observed at at elevated temperatures, which is in agreement with the literature data.[22]

An attempt to use mixed anhydride in the reaction with $NaBH_4$ resulted in limited success[23]. The treatment of oxetane-3-carboxylate with a Grignard reagent (MeMgBr), at –20 °C to rt, resulted in the formation of ca. 3:7 mixture of the mono- and double addition products, i.e., ketones andtertiary alcohols, that were separated by column chromatography (Scheme 5, T20) [24–28]. Further reduction of the ketone to secondary alcohol was performed successfully using the conditions described above for esters, i.e., $LiAlH_4$ at –30 °C or $NaBH_4$ at 0 °C (Scheme 10, T16).



Scheme 5. The reaction with Grignard reagents, and reduction of ketones

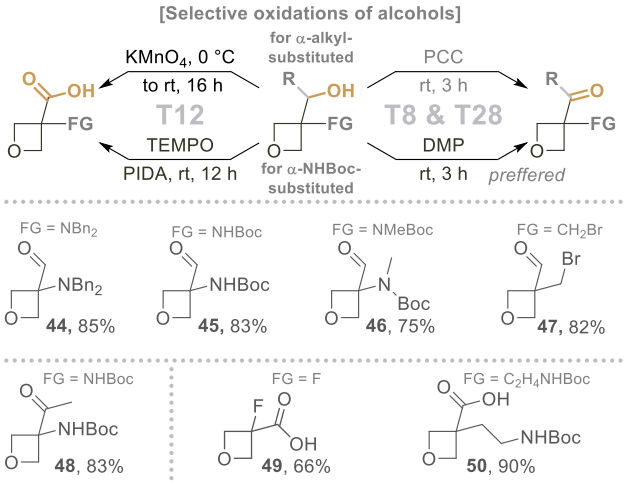
The obtained hydroxy groups (Scheme 5, derivatives **35**, **36**, etc) allowed for a wide range of diversification providing oxetane-containing building blocks. The corresponding ethers were synthesized via Williamson alkylation in the presence of NaH or *t*-BuOK at temperatures varying from 0 to 80 °C (depending on the reaction, Scheme 6, T21)[29–32]. The mesylation reaction proceeded smoothly with MsCl and Et_3N in CH_2Cl_2 at 0 °C (Scheme 6, T34).[33–36] Several successful strategies were developed for the synthesis of fluorine-containing oxetanes. For this purpose, we utilized oxygen-containing functional groups in the direct deoxyfluorination (Scheme 6, T13). Notably, DAST and morph-DAST were successfully used to transform alcohols to fluorides at –78 to 0 °C with the oxetane ring left intact. However, the deoxyfluorination attemptswere unsuccessful for the carboxylic acids due to insufficient reactivity even at elevated temperatures up to 100 °C. The use of more robust SF_4 and HF resulted in substrate decomposition rather than the desired trifluorination.



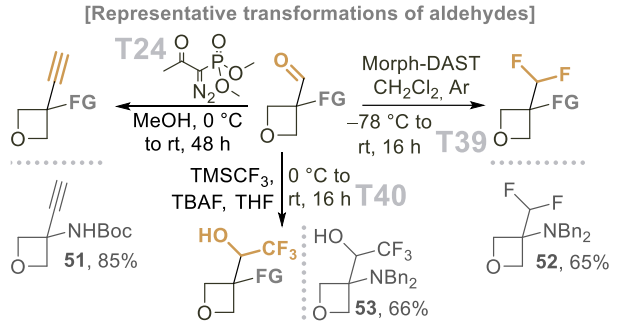
Scheme 6. Transformations of oxetan-3-ylmethanols

The oxidation of hydroxymethyl-substituted oxetanes with Dess-Martin reagent (DMP) or PCC was an efficient approach to the synthesis of the corresponding aldehydes when additional protected functional groups were present. It was found that DMP was most suitable in the case of the presence of α-NHBoc substituent, while chromium(VI) reagents worked well in the case of alkyl-substutited heterocycles (Scheme 7, T8, and T28). Similarly, oxidation to carboxylic acids was substrate-specific. The radical pathway using TEMPO with PIDA, despite being most suitable for α-NHBoc-substituted substances, sometimes led to partial decomposition. Less reactive α-alkyl-substituted compounds were successfully converted to the corresponding carboxylic acid via the robust treatment with $KMnO_4$; no decomposition was observed in this case (Scheme 7, T12).[39,40]

The carbonyl group of aldehydes and ketones could be used to prepare other classes of oxetanes. Model reactions included the defluorination of aldehydes (Scheme 8) as an important reaction for the incorporation of the CHF_2 substituent to the oxetane core. The Seyferth-Gilbert reaction using the Ohira-Bestmann reagent is suitable for introducing the highly valuable acetylene fragment into the oxetane core (Scheme 8, T24).



Scheme 7. Oxidation of alcohols to aldehydes and carboxylic acids

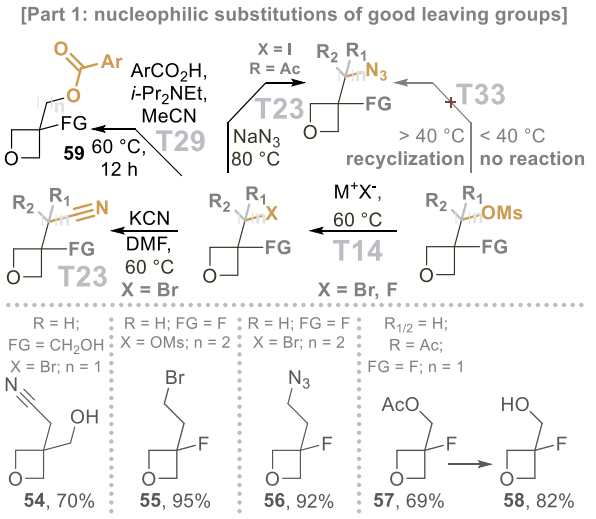


Scheme 6. Reactions of oxetane-derived aldehydes with nucleophilic reagents

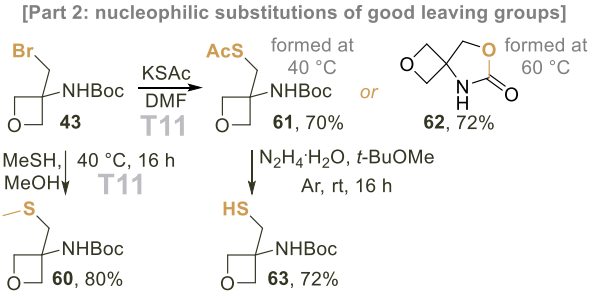
An alternative route for the incorporation of fluorine atoms involved mesylation followed by the nucleophilic substitution reaction with a fluoride source at 60 °C (Scheme 9, T14).

Nucleophilic substitution of mesylate with the azide anion failed, showing no reaction below 40 °C. Upon further heating, cyclization products were identified. The issue was resolved via the deoxybromination. The bromide moiety was rapidly substituted by azide to incorporate N_3-fragment in the oxetane core (Scheme 9),[37]. Several substrates, however, proved to be suitable for the nucleophilic substitution of MsO-group, providing azides after reaction with NaN_3 at 80 °C in DMF (Scheme 9, T33), or bromides when treated with LiBr at 60 °C for 5 h (Scheme 9, T14).

Sulfur-containing derivatives were obtained from the aforementioned mesylates. The reaction proceeded with reasonable yields within a narrow temperature range (ca. 40 °C) with KSAc or NaSMe as the sulfur sources (Scheme 10, T11).[38] Significantly, no conversion was observed at 20 °C, while raising to 60 °C led to partial or complete rearrangements of starting materials. The use of hydrazine monohydrate was successful in cleaving *S*-acetyl moiety to give thiol from the corresponding thioacetate.

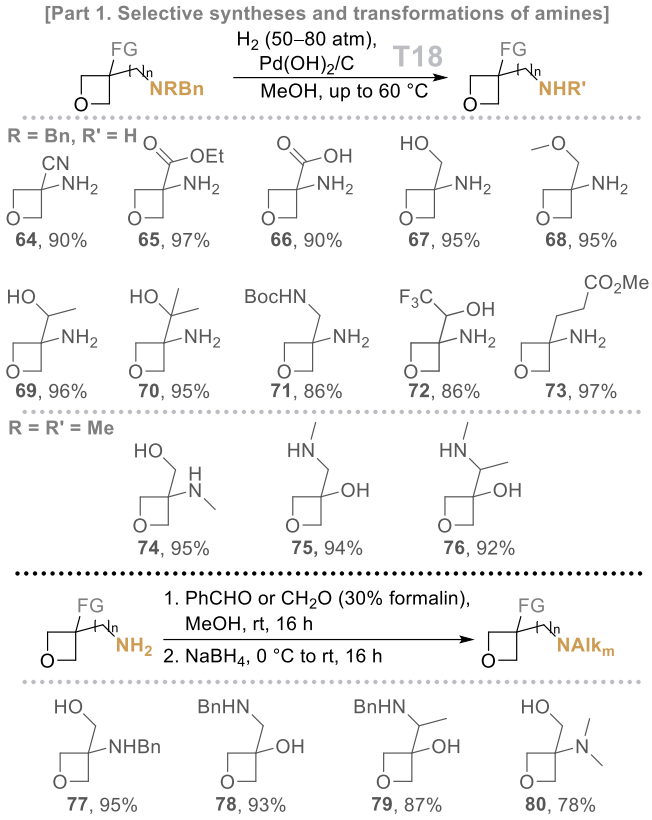


Scheme 9. A set of nucleophilic substitution reactions for the preparation of halides, azides, nitriles, and benzoates

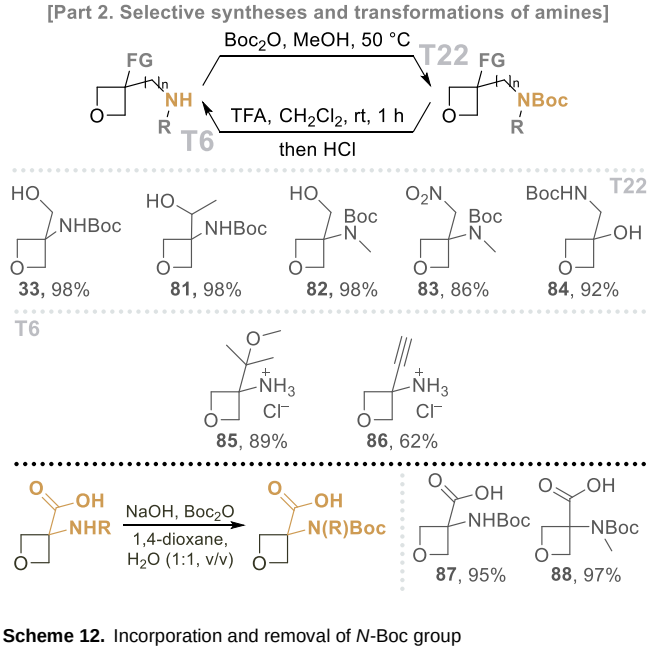


Scheme 10. Results of the use of *S*-nucleophiles for the substitution of bromide

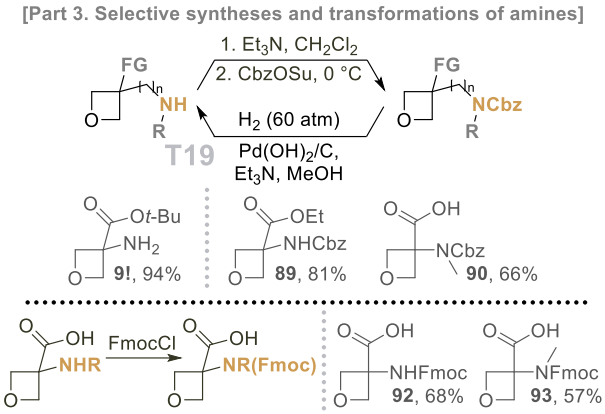
Since most of the aforementioned compounds were bifunctional, the important task was related to the selective installation and cleavage of the corresponding protecting groups. In particular, quantitative oxetane-tolerant cleavage of the *N*-Bn group of 3-aminooxetnes was achieved using an enriched 20% Pearlman's catalyst under 80 bar of H_2 at 60 °C (Scheme 11, T18).[41,42].Introducing *N*-Boc protection using Boc_2O at 50 °C was straightforward, mild, and relatively successful in all cases (Scheme 12, T22) . However, its removal proved more challenging due to the commonly required use of acids (mostly HCl or TFA). The standard treatment with HCl in Et_2O or 1,4-dioxane resulted in partial or complete decomposition of the substrate at rt after 1 h. In contrast, the reaction with TFA in CH_2Cl_2 proceeded smoothly, providing a reliable method for *N*-Boc removal and tolerating the oxetane fragments present in the molecule (Scheme 12, T6). For the Cbz removal, fruitful results were obtained in the presence of Et_3N under 60 bar of H_2 (Scheme 13, T19) [43]. These methods proved more effective and oxetane-tolerant than the procedures applied for related compounds previously and could be applied to multigram syntheses.[44]



Scheme 11. Catalytic debenzylation for the preparation of primary and secondary amines (higher pressure up to 80 atm only provided more rapid conversion; no changes in yields or purity were observed); reductive amination



Scheme 12. Incorporation and removal of *N*-Boc group

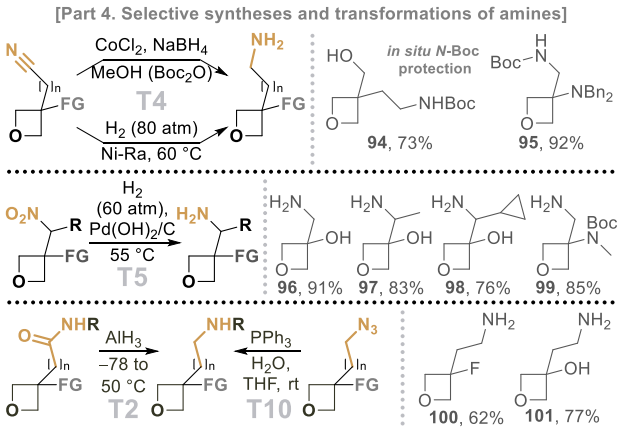


Scheme 13. Incorporation and removal of *N*-Cbz and *N*-Fmoc groups

The oxetane-tolerant reduction with cobalt boride (obtained *in situ* from $CoCl_2$ and $NaBH_4$) of nitriles in the presence of Boc_2O was rapid and well-suited for the efficient preparation of primary amines in multigram scale (Scheme 14, T4). We also studied two more common methods for this reaction. In particular, $LiAlH_4$ decomposed the oxetane core at any temperature in the range of …. However, Ra-Ni at 60°C under 80 atmospheres of H_2 was an oxetane-tolerant successful approach; no undesirable side reactions were observed.

However, these conditions were not appropriate for reducing the nitro group to amine, as they required prolonged reaction times and provided products with low purity. The milder conditions, specifically, hydrogenation under 50 atm in the presence of $Pd(OH)_2/C$, solved the latter issue (Scheme 14, T5). This method proved to be a preparative approach for obtaining 3-hydroxy-3-methylamino oxetanes via the Henry reaction.

The transformations of azides to the corresponding primary amine relied on the standard Staudinger procedure with PPh_3 and H_2O (Scheme 14). Attempts to perform this transformation with Pd/C catalysis yielded a low amount of product with unsatisfactory purity.[45]

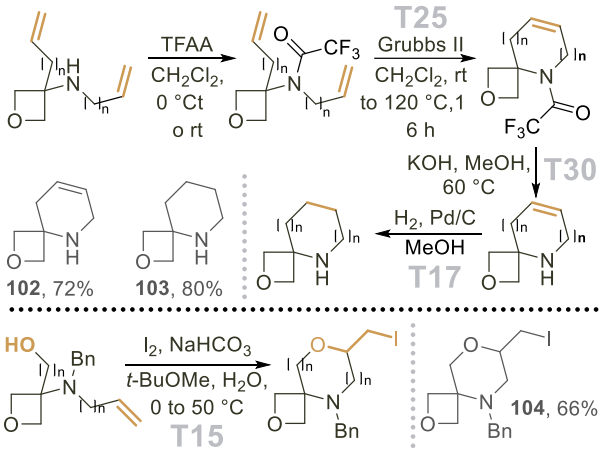


Scheme 14. Synthesis of aminomethyl- and aminoethyl-substituted oxetanes

Yet another way to access amines involved amide reduction using AlH_3 at –78 °C to –50 °C. Attempts to use $NaBH_4$ or $LiAlH_4$ procedure under various conditions resulted in the decomposition of the starting oxetane-containing amides.

A strategy developed for the construction of spirocyclic oxetane derivatives involved ring-closing metathesis of two allyl fragments attached to the oxetane core using the Grubbs catalyst at 120 °C (Scheme 15, T25)[46]. The corresponding diallyl fragment was accessed via the Petasis reaction performed with the corresponding allyl amine. [47] The trifluoroacetyl protecting group proved to be the most suitable for the reaction of interest. Its removal posed no significant issues and was achieved through the basic hydrolysis at 60 °C (Scheme 15, T30). The C=C double bond of the side chain can be easily reduced by catalytic hydrogenation (Scheme 15, T17).

The other type of the spirocyclic scaffold construction relied on the iodocyclization reaction that also tolerated the oxetane fragment (Scheme 15, T15).



Scheme 15. Synthesis of spirocyclic derivatives via the metathesis or iodocyclization reaction

Conclusions

This comprehensive study of 3,3-disubstituted oxetanes significantly expands the synthetic toolkit available for this heterocyclic core known for its instability via ring-opening reactions. This work demonstrated a significantly broader tolerance of oxetanes to various reaction conditions than it was previously assumed, summarizing the reactivity profile of this heterocycle (Figure 4). Starting from oxetan-3-one, a series of common ketone transformations(i.e., Strecker, Horner–Wadsworth–Emmons, Grignard reactions, etc,) enabled the introduction of various functional groups in the oxetane-tolerant manner on up to a hundred-gram scale. The basic hydrolysis of nitriles and esters was applied as an efficient and scalable method for obtaining the corresponding amino acids while avoiding the undesirable side reaction of ring opening observed in the case of acidic mediators.

The most challenging reduction methods that required precise optimization, proved effective for transforming various functional groups adjacent to the oxetane core. The scope of possible optimized carbonyl group reduction reactions included esters, amides, and ketones. Preferentially lower temperatures optimized reagents were obligatory to achieve selectivity and avoid byproduct formation.

Several strategies were advised for introducing amino and aminoalkyl groups into oxetanes. In contrast to heterogeneous reduction conditions, the azide transformations via the Staudinger reaction proceeded smoothly. Additional optimization was required for the reduction of nitro and nitrile groups.

Protection and deprotection strategies were applied extensively to a series of derivatives, including using Pearlman's catalyst to remove *N*-Bn and *N*-Cbz groups. The introduction of *N*-Boc protection was relatively straightforward, although its removal required significant optimization with satisfactory results only in the case of TFA as the reagent.

In contrast, standard oxidation methods for the selective preparation of oxetane-derived aldehydes using DMP or PCC were fruitful. At the same time, carboxylic acid formation was achieved via TEMPO/PIDA oxidation or less selective $KMnO_4$ for the alkyl-substituted substrates.

Fluorination was achieved through deoxy-/deoxofluorination, as well as via the nucleophilic substitution of mesylates with fluoride. Other functionalization included alkylation of hydroxy groups using NaH or *t*-BuOK, mesylation, and subsequent nucleophilic substitution, which provided a convenient method for accessing sulfur and halogen derivatives. Esterification and acylation could be easily conducted upon basic conditions.

The Seyferth-Gilbert reaction, which employed the Ohira-Bestmann reagent for acetylene introduction, Corey-Chaykovsky cyclopropanation, and ring-closing metathesis in the presence of a Grubbs catalyst demonstrated the formation of various carbon-carbon bonds.

Some additional limitations and challenges were identified in addition to those previously mentioned. When nucleophilic substitution was employed with a range of nucleophiles, unsatisfactory results were obtained due to the formation of either rearrangement or elimination products. Furthermore, the trifluorination of carboxylic acids was found to be ineffective when tested with a series of various reagents.

This work summarizes a diverse set of optimized methods for synthesizing and functionalizing 3,3-disubstituted oxetanes. The demonstrated stability under various conditions dispels the conventional wisdom about oxetane fragility. Many reactions were successfully scaled up to multigram quantities, enhancing their practical utility. These findings should facilitate the incorporation of this small heterocycle in medicinal and synthetic organic chemistry, which can open the for modern drug discovery efforts, enabling the exploration of novel chemical space and the development of compounds with improved physicochemical properties.

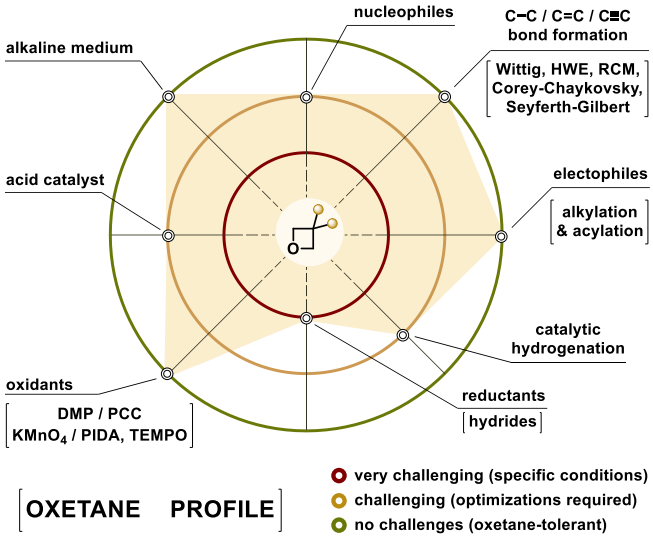


Figure 4. The resulting profile of the reactivity of oxetanes

Experimental Section

The solvents were purified according to the standard procedures.[48] All starting materials were available from Enamine Ltd. All other starting materials were purchased from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are shown in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: oxetanes, reactivity, stability, building blocks, core tolerance

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