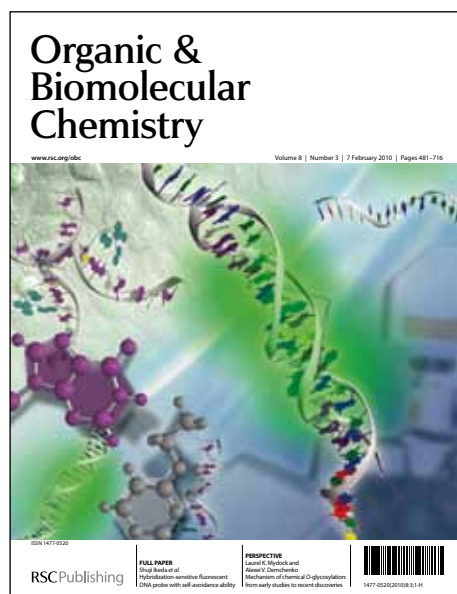


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REVIEW

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Oxenoids in Organic Synthesis

Yury Minko,^a and Ilan Marek^{a*}

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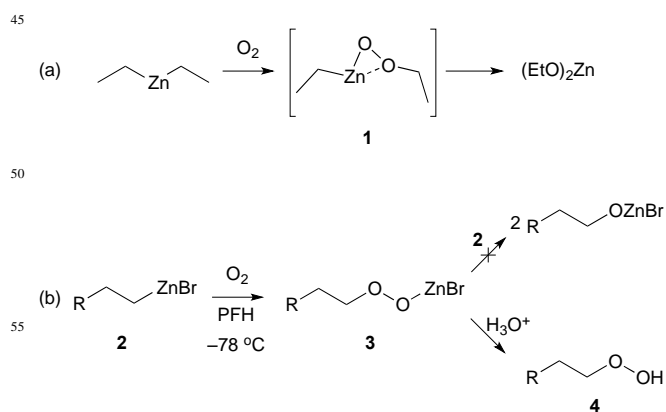
Recent studies focused on the reactivity of metalated peroxides as oxenoids (electrophilic oxidants) revealed their unique properties allowing for highly selective and efficient oxidation processes involving nucleophilic organometallics. In this short review we present the most successful examples of the application of this class of reagents towards organic synthesis.

10 Introduction

Oxidation reactions occupy a significant niche in a variety of organic transformations. In this context, selective oxygen transfer processes that lead to valuable synthetic intermediates and final products are of high importance. For example, major advances have been achieved in asymmetric epoxidation,¹ sulfoxidation reactions² as well as in the formation of oxygenated substrates such as alcohol and carbonyl compounds. While atmospheric oxygen remains the cheapest oxidant available to chemists, its biradical nature often restricts the use of aerobic oxidation since stereochemical control is often complicated by radical reaction pathways.³ The transfer of an electrophilic oxygen atom to a nucleophilic substrate (or *vice versa*) represents an important alternative to oxidation reactions involving dioxygen. Such transformations are feasible by means of oxenoid compounds of general structure M–O–LG, oxo-analogues of carbenoids M–CH₂–LG (where M is a metal atom and LG is a leaving functional group or atom).⁴ Since the latest comprehensive review⁵ on the chemistry of carbenoids, oxenoids and nitrenoids by Boche and Lohrenz in 2001, oxenoid species were reported to participate in several elegant synthetic transformations leading to greater complexity of organic substrates. In this short review we would like to present the most successful examples of the use of lithium-, magnesium-, zinc-, titanium- and copper oxenoids in organic chemistry and bring attention of the readers to the great potential of this class of compounds.

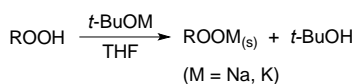
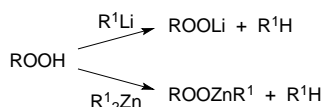
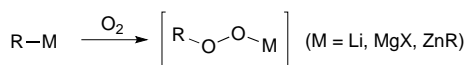
Generation, structure and electrophilic nature of oxenoids

As has been mentioned in the introductory part, herein we will use the term “oxenoid” only for compounds bearing a metal and a leaving group (or atom) bound to an oxygen atom. Following this definition, metal oxo-complexes,⁶ hydrogen and organic



Scheme 1 Reactions of diethylzinc and alkylzinc bromide with molecular oxygen. PFH = perfluorohexanes.

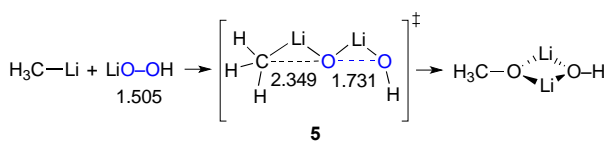
peroxides,⁷ peracids,⁸ dioxiranes⁹ and oxaziridines¹⁰ will not be considered as they do not correspond to this class of compounds and are therefore beyond the scope of this short review. Berthollet produced the first and simplest oxenoid compound, sodium hypochlorite NaOCl, in 1789 by reacting chlorine gas with an aqueous sodium carbonate solution. It is widely known and used as bleaching and disinfectant agent, but except in the work of Jacobsen and Katsuki¹¹ reporting the asymmetric catalytic epoxidation reaction, this compound, or its alkali and alkaline earth metal analogues, to the best of our knowledge, has not been studied, neither structurally, experimentally, nor by computational methods.⁵ Frankland has reported one of the first examples for the formation of oxenoids by oxidation of diorganozinc reagents with molecular oxygen¹² (Scheme 1(a)) and following this pioneering work oxenoid-type compounds were often proposed as intermediates in several oxygen-mediated oxidation reactions of organometallic species.



Scheme 2 General Methods for the generation of metallated peroxides.

For instance, oxenoids **1** have been proposed in the works of Abraham,¹³ Normant and Chemla¹⁴ while preparing alcohols from alkylzinc species. Knochel who used aerobic oxidation of organozinc reagents in perfluorinated solvents could isolate the corresponding organoperoxides (Scheme 1(b)).¹⁵ Alternatively, most of these compounds can be easily prepared by simple deprotonation of organic hydroperoxides by an alkali metal hydroxides or alkoxides¹⁶ or by the corresponding organometallics such as Grignard reagents, organolithium or organozinc compounds (Scheme 2). Of particular interest is the formation of lithiated hydroperoxides by Müller and Töpel,¹⁷ that generated a large number of experimental and theoretical studies which have been reported in the literature emphasizing the difference of reactivity of oxenoids and O₂ with nucleophilic reagents.

The first X-ray crystallographic studies of a lithium organoperoxide have been performed and reported by Boche and coworkers.¹⁸ The *t*-BuOOLi (readily generated by a reaction between equimolar quantities of commercially available *tert*-butylhydroperoxide (TBHP) and LDA at low temperature in THF)¹⁸ is a dodecamer of cyclic structure [*t*-BuOOLi]₁₂ in the solid state. Interestingly, the length of O–O bonds in this compound is 1.475 Å and only slightly longer as compared to hydrogen peroxide or common organic peroxide motifs. According to computational studies, the cluster formation resulting in the additional stabilization of the negative charge on the anionic oxygen atom of the lithiated peroxide was confirmed to be the main reason for such an effect on the O–O bond length in this type of oxenoids.¹⁸ However, the situation changes dramatically in the presence of a strong nucleophilic reactant. Thus, a model reaction profile of an oxidation of CH₃Li with LiOOH has been studied by quantum chemical calculations.¹⁸ These studies clearly confirmed a significant elongation of the peroxy-bond (from 1.505 Å to 1.731 Å) and linear orientation of the nucleophilic carbon in CH₃Li with the electrophilic oxygen atom of lithiated peroxide in the transition state (Scheme 3).

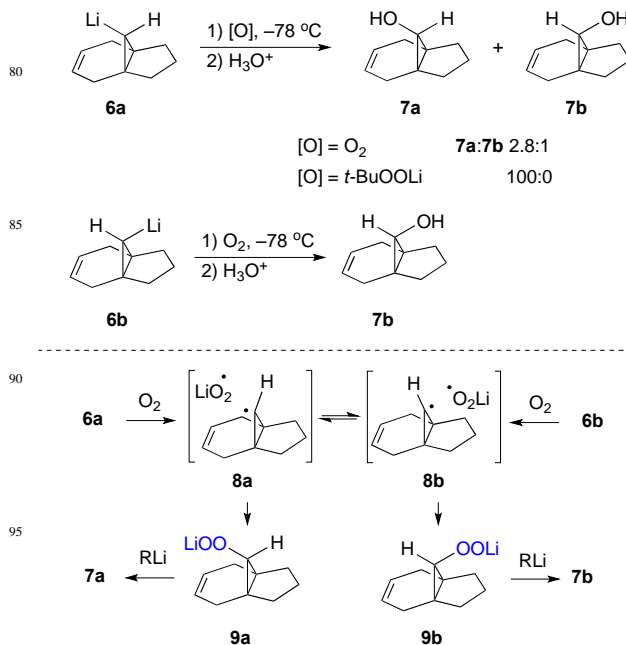


Scheme 3 Theoretical calculations (MP2(fc)/6-31G(d) level) of the oxidation of CH₃Li with HOOLi (bond lengths [Å]).

A similar pattern was confirmed by computational methods also in reaction profiles for the oxenoid interaction with different nucleophilic reagents (NH₃, R₂S, ethylene).^{18,19} In all cases increased O–O bond length in oxenoids and transition state geometry resembling of an S_N2 process were calculated suggesting the highly electrophilic nature of metallated peroxide species.

Reactions of nucleophilic organometallic compounds with oxenoids

Experimental studies emphasizing the difference between aerobic oxidation of nucleophilic organometallic compounds and related reactions with oxenoids were initiated after the discovery of lithiated organic hydroperoxides.¹⁷ Warner and Lu reported one of the first detailed studies on the electrophilic character of these compounds in the oxidation of stereochemically defined cyclopropyllithium compounds **6** (Scheme 4).²⁰

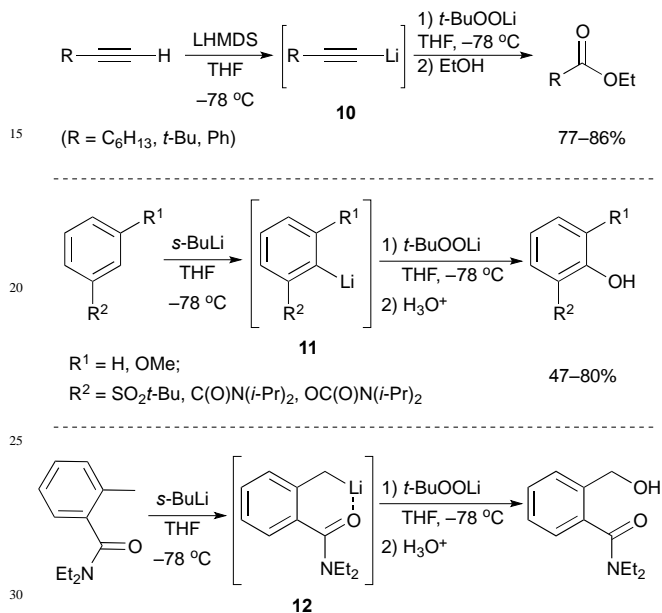


Scheme 4 Mechanistic studies comparing aerobic and oxenoid-mediated oxidation of cyclopropyllithium.

While isomer **6a** treated with O₂ resulted in a mixture of cyclopropanols **7a** and **7b**, the isomer **6b** leads exclusively to **7b** with the same source of oxidation, which gave support for a single electron transfer (SET) mechanism for this transformation. The authors suggested that the initial formation of interconverting radical pairs **8** in the oxidation by dioxygen results in epimerization of the final product. They noted that it is not clear whether the exclusive formation of **7b** from **6b** arises from faster recombination of the radical pair **8b** or if this species is energetically more stable than **8a**. However, the aerobic pathway results in the intermediate formation of lithium oxenoids **9** that upon reaction with residual organolithium produces cyclopropanols **7**. Comparing these results to the reaction with

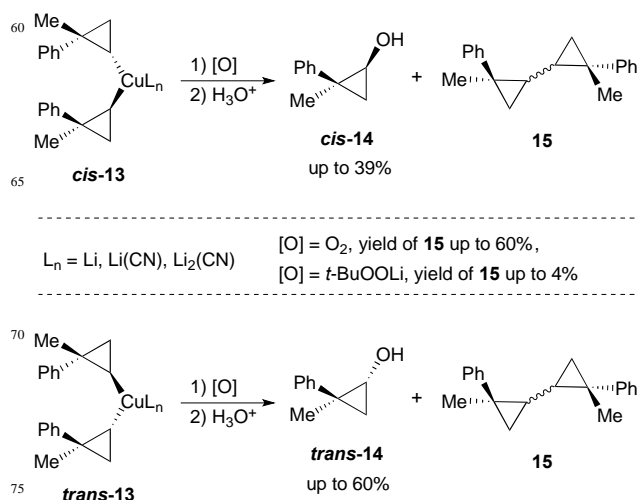
oxenoid *t*-BuOOLi, the reaction of **6a** resulted in the exclusive formation of **7a** (the corresponding oxidation was not reported for isomer **6b**). The electrophilic oxygen transfer by an S_N2-type mechanism (excluded for the aerobic conditions) has been suggested for the transformation mediated by *t*-BuOOLi; however, the authors did not exclude the possibility of single electron transfer within a solvent cage.²⁰

Julia and coworkers could use the ambiphilic nature of oxenoids for the mild oxidation of sensitive functionalized organolithium reagents **10–12**. (Scheme 5).²¹



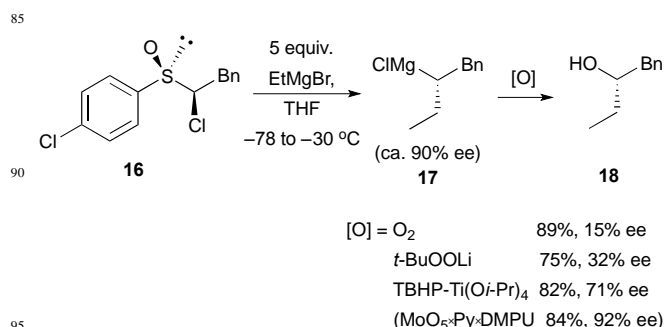
Scheme 5 Oxidation of functionalized organolithium species with *t*-BuOOLi.

Boche and coworkers studied the mechanism of oxidation^{3a} of aliphatic and aromatic organolithium, organomagnesium and organozinc reagents using either oxygen, *t*-BuOOLi and PhMe₂COOLi. In contrast to the oxidation with O₂, the corresponding oxenoid reagents led to the metal alkoxides in good to high yields without the formation of free radical intermediates. This conclusion is based on the results of experiments involving oxidation of diastereomeric configurationally stable cyclopropyl metal species, similar to that performed by Warner (Scheme 6).^{3a,20} The same study revealed the extraordinary selectivity in the oxidation of Gilman-type cuprates.^{3a,22} This reaction is of particular interest since cuprates are known to undergo extremely rapid degradation (i.e. oxidative R–R dimerization) upon reaction with molecular oxygen.^{22,23} Thus, comparing to the aerobic conditions, oxenoid reagents reacted with stereochemically defined cyclopropylcuprates **13** to lead to copper alcoholates and after hydrolysis to cyclopropanols **14** with a complete retention of configuration with only traces of the dimerization product **15**. On the other hand, oxygen resulted in the formation of the dimer as a major product with a significant loss of stereochemistry (Scheme 6).^{3a}



Scheme 6 Oxidation of cyclopropylcuprates with oxygen and oxenoid reagents.

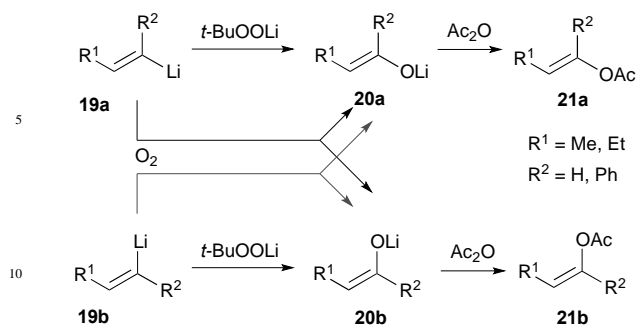
In contrast to these results, Hoffmann and coworkers reported that use of *t*-BuOOLi for the oxidation of configurationally stable and enantiomerically enriched Grignard reagent **17** was not significantly better in terms of retention of configuration as compared to aerobic oxidation (Scheme 7).²⁴



Scheme 7 Oxidation of the enantiomerically enriched Grignard reagent.

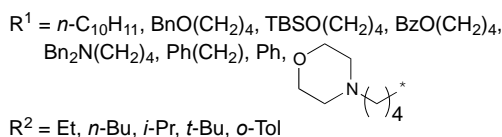
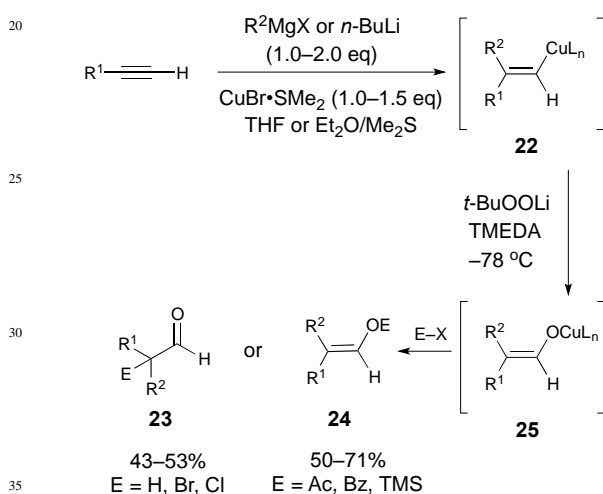
This reaction gave the alcohol **18** in only moderate enantiomeric excess (32% ee). It should be noted that while TBHP – Ti(O-*i*-Pr)₄ mixture and MoO₅-Pyridine-*N,N'*-dimethylpropylene urea resulted in much better results (71% and 92% ee respectively),²⁴ the large excess of Grignard used in this transformation may be one of the reasons for the low enantioselectivity in the case of oxenoid reagent (exchange reactions).

Whitesides reported similar results for the oxidation of stereodefined vinylolithium species **19** with either molecular oxygen or oxenoid (Scheme 8).²⁵ He could establish, that oxidation of C(sp²)-Li bond with molecular oxygen results in the loss of stereochemistry presumably due to the rapid formation of a linear vinyl radical intermediate.²⁶ On the contrary, oxidation of **19** either with *t*-BuOONa or *t*-BuOOLi led to the formation of the lithium enolates **20** with complete retention of configuration as was confirmed by trapping the intermediate with acetic anhydride to form substituted vinylacetates **21**.



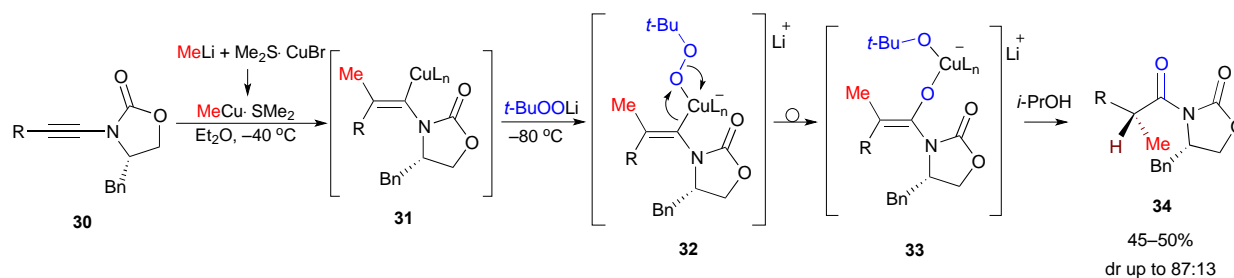
Scheme 8 Stereochemical course of oxidation of geometrically defined vinyl lithium reagents with O_2 and oxenoid reagent.

Following these discoveries, Ready and Zhang reported the tandem carbometallation-oxygenation reaction of terminal alkynes with the help of oxenoids (Scheme 9).²⁷



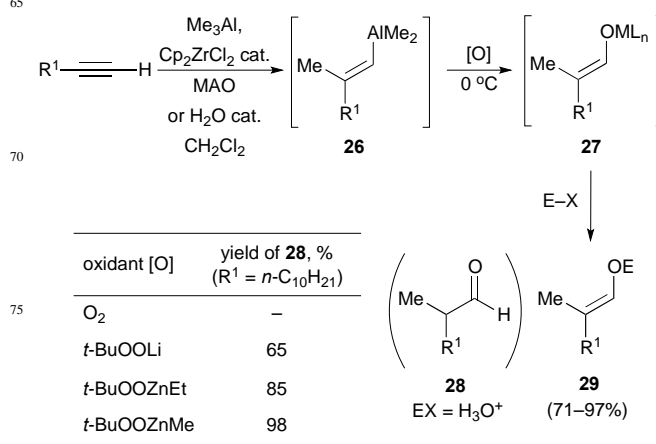
Scheme 9 Sequential carbometallation/oxidation of terminal alkynes.

In this study, terminal alkynes underwent a regioselective carbocupration reaction²⁸ generating stereodefined vinylmetal species **22**. The authors proposed that subsequent treatment of



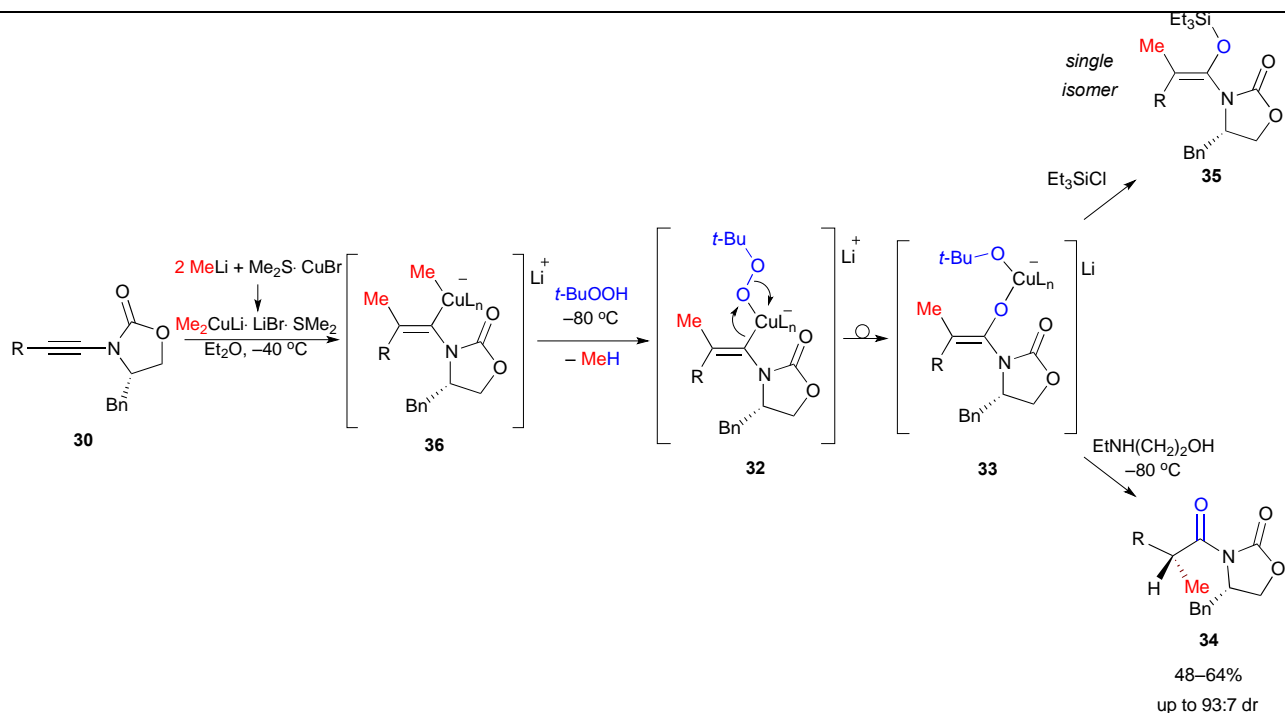
Scheme 11 Formation of trisubstituted copper enolate species by combined carbocupration/electrophilic oxidation sequence.

these reagents with $t\text{-BuOOLi}$ leads to the formation of the intermediate enolate species **25** that upon trapping with electrophiles provided a broad scope of α -branched aldehydes **23** and enol ethers **24** in good yields with a complete retention of configuration of the double bond (Scheme 9).²⁷ The authors mentioned, that in contrast to previous results where the use of oxenoid reagent prevented the oxidative dimerization from organocopper species, an equimolar amount of TMEDA was necessary in this particular case to suppress this side-reaction.²⁷ However, the developed method tolerates functional groups in the substrates and is not sensitive to steric effects (primary, secondary, and tertiary alkyl groups *syn* to the metal). As the methylcupration reaction does not proceed efficiently on terminal alkynes, the same authors developed the zirconocene-catalyzed methylalumination reaction producing alkenylaluminum species **27** that was subsequently oxidized in a similar way (Scheme 10).²⁹



Scheme 10 Tandem zirconium-catalyzed carbometallation/electrophilic oxidation of terminal alkynes.

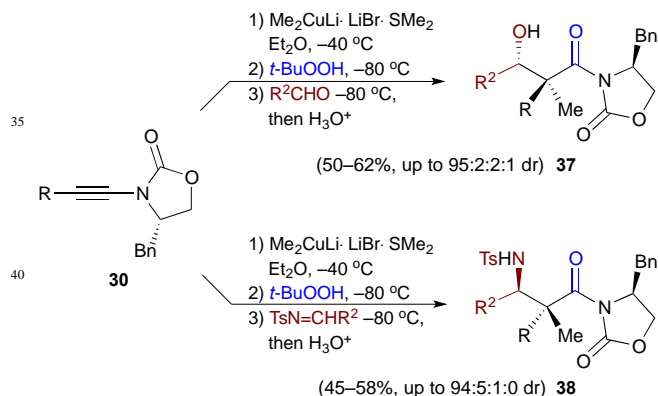
The straightforward generation of stereodefined enolates from simple precursors such as sp^2 organometallic species shows the utility of oxenoids in organic synthesis. Indeed, preparation of fully substituted stereochemically defined chiral enolates deserves attention as their reactions with various electrophiles should allow for an easy and straightforward access to compounds possessing quaternary stereogenic centres.³⁰ Stereoselective generation of trisubstituted vinylcopper species **31** obtained by carbometallation reaction of heterosubstituted alkynes **30** has been extensively studied and evolved into a well developed preparative synthetic procedure.^{31,32} As sp^2



Scheme 12 Direct electrophilic oxidation of dissymmetric alkenyl-alkyl cuprates **36**.

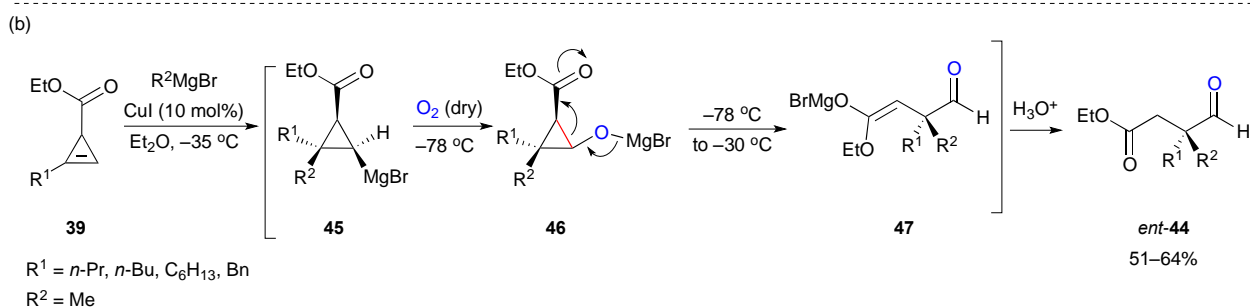
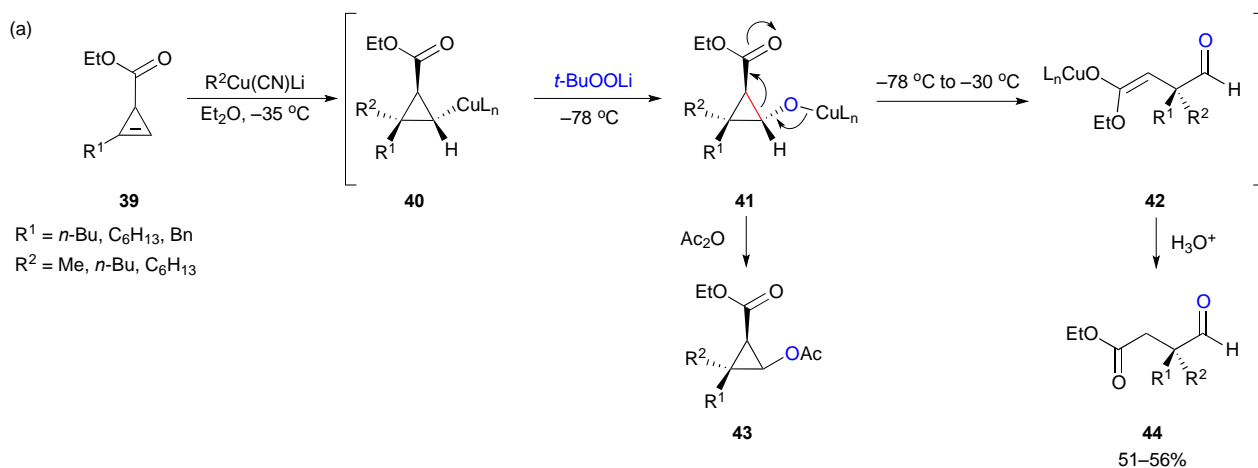
organometallics react smoothly with oxenoids, it should be an interesting and unexplored approach to the formation of trisubstituted enolates for aldol and related reactions.³³ The possibility to use oxenoid-mediated transformation of **31** into the desired stereodefined enolates **33** was initially examined by reaction of the vinylcopper species **31** with pre-formed *t*-BuOOLi. It was found that this reaction proceeds efficiently towards the imido-compounds **34** after acidic protonation (Scheme 11).³¹

Although this method provides reliable results, generation of lithiated peroxide in a separate reaction vessel followed by transfer of this reagent to the vinylcopper species at low temperature may pose experimental difficulties. Therefore, an improved protocol has been developed involving direct oxidation of vinylalkyl cuprate **36** with TBHP. The authors proposed an *in situ* generation of the oxenoid intermediate **32** by initial protonation of the most basic C(sp³)–Cu bond by hydroperoxide followed by metal oxo-rearrangement leading to the desired species **33** (Scheme 12).³¹ The formation of **32** from **31** should proceed in a similar mechanistic pathway starting from a ligand exchange at the copper centre, and the formation of **33** should proceed by the same 1,2-metalate rearrangement. This oxidation reaction was confirmed to proceed with complete retention of configuration as the trapping of the enolate leads to a single geometrical isomer of silyl enol ether **35**. This newly developed method for an easy formation of stereodefined enolates allowed for a rapid access to the diastereo- and enantiomerically enriched aldol **37** and Mannich-type **38** products possessing quaternary stereocentres in acyclic systems (Scheme 13).^{31,32}



Scheme 13 Single-flask protocol for the diastereo- and enantioselective formation of aldol and Mannich-type products bearing quaternary stereogenic centres.

Recently, diastereodivergent formation of all-carbon quaternary stereocentres in α -branched non-cyclic aldehydes has been achieved by sequential carbometalation-oxidation-selective ring opening of cyclopropenylcarboxylic acid esters **39** (Scheme 14(a)).^{34a} When the carbocupration is performed with lithium cyanocuprates R²Cu(CN)Li, the diastereomerically pure cyclopropylcopper species **40** are generated in remarkable yields. Then, **40** was reacted with an equimolar amount of oxenoid reagent *t*-BuOOLi at low temperature (–78 °C), warmed to –30 °C, to promote a selective C–C bond cleavage of the cyclopropane ring to lead directly to the formation of **44** in good yields. Copper cyclopropanolate **41** could be trapped with acetic anhydride at low temperature to provide **43**.



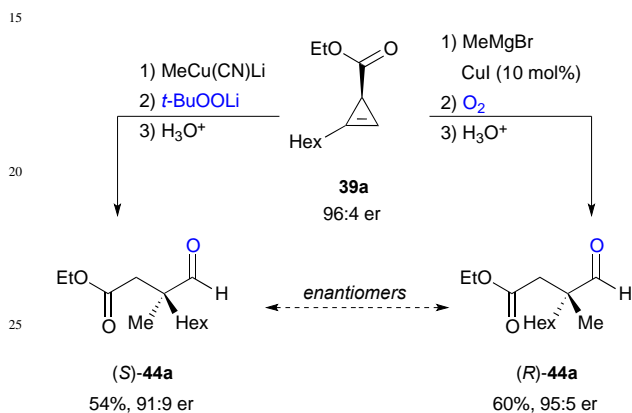
Scheme 14 One-pot carbometallation/oxidation/C–C bond activation of cyclopropenyl esters.

The formation of the opposite enantiomer is possible if a copper-catalyzed carbomagnesiation/aerobic oxidation/ring opening sequence is used (Scheme 14(b)).^{34a} It should be mentioned, that the formation of *syn*-isomer **45** in this case could be rationalized by chelation between the ester group of the cyclopropene substrate and Lewis acidic organometallic species (or associated salts) in the transition state for the carbometallation step.^{34a} The cyclopropylmagnesium intermediate species is oxidized rapidly by dioxygen following the same mechanistic pathway, as discussed earlier.^{3,23} However, no dimerization occurs in this case, and subsequent C–C bond activation in **46** leads to the enantiomer of **44**. Since the transition-metal-catalyzed enantioselective cyclopropanation is a well established method,³⁵ **39** is readily obtained in enantiomerically pure form.

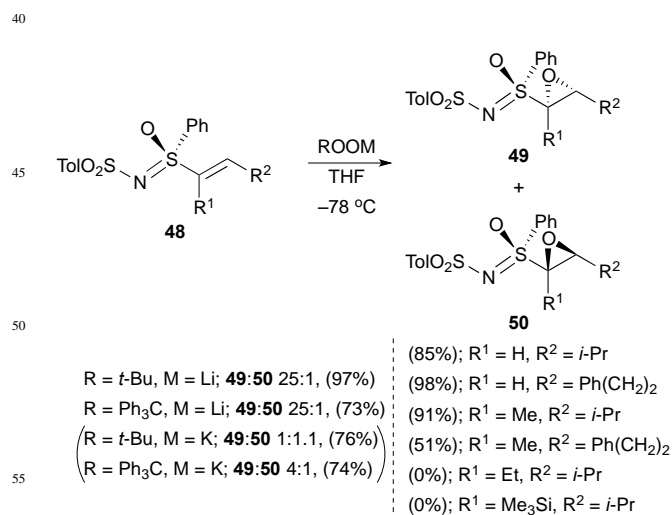
The developed oxidation methods allowed the authors to achieve complete enantiodivergence in the formation of aldehydes **44a** in good yields and outstanding enantioselectivity (Scheme 15).^{34a}

35 Asymmetric epoxidation, sulfoxidation and hydroxylation reactions mediated by oxenoids

The oxygen atom transfer to activated carbon-carbon double bonds has been extensively studied for several decades and represents an important transformation in organic synthesis.



Scheme 15 Synthesis of enantiomerically enriched aldehydes **44a**.

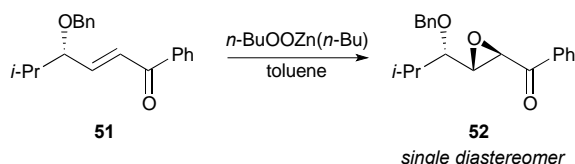


Scheme 16 Diastereoselective epoxidation of substituted vinylsulfoximines with metalated organoperoxides.

Thus, lithium *tert*-butyl peroxide was reported to be an efficient reagent for the highly diastereoselective low-temperature epoxidation of vinylsulfoximines (Scheme 16).³⁶

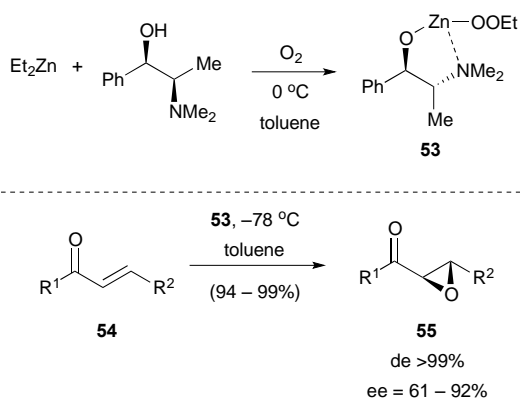
While α,β -unsaturated sulfoximines **48** bearing a C=C double bond substituted only in the β -position ($R^1 = H$) demonstrated a remarkable reactivity in the epoxidation reaction to give *trans*-oxiranes with exceptional diastereoselectivity, substrates **48** with substituents larger than methyl in the α -position (e.g. $R^1 = Et, TMS$) failed to react.^{36a}

The epoxidation of α,β -unsaturated ketones by alkylperoxy zinc compounds was initially reported by Yamamoto.³⁷ In this work, a highly diastereoselective epoxidation of protected γ -hydroxy- α,β -unsaturated ketone **51** was achieved by reaction with *n*-butylzinc *n*-butyl peroxide as stoichiometric oxidant (Scheme 17).³⁷



Scheme 17 The first example of diastereoselective epoxidation of α,β -unsaturated ketones.

In following studies, González and coworkers demonstrated that epoxidation of unprotected γ -hydroxy- α,β -unsaturated ketones with lithium *tert*-butyl peroxide is highly solvent dependent and proceeds with good diastereoselectivity only when THF was used.³⁸ Enders and coworkers reported the asymmetric epoxidation of conjugated enones through aerobic oxidation reaction in the presence of Et_2Zn and *N*-methylpseudoephedrine as a ligand.³⁹ The authors proposed that the corresponding chiral alkoxy-peroxy-zinc complex **53** is obtained *in situ* by partial alcoholysis of diethyl zinc with aminoalcohol followed by dioxygen insertion into the remaining C–Zn bond (Scheme 18).³⁹

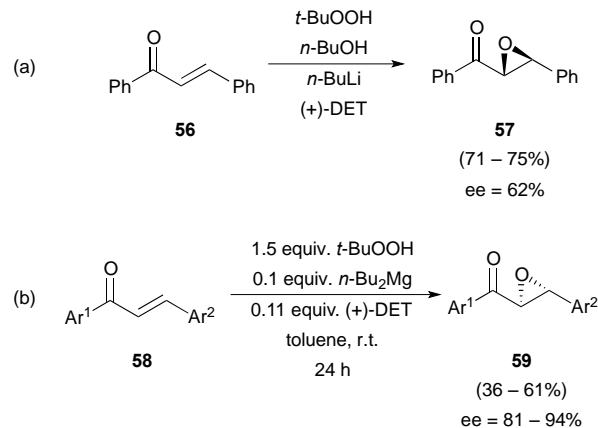


Scheme 18 Asymmetric epoxidation of conjugated enones with chiral zinc peroxo complex **53**.

The epoxidation occurs through an initial coordination of the carbonyl group of the enone substrate with the zinc atom followed by simultaneous attack of the ethylperoxy anion in the β -position of the substrate. This method leads to α,β -epoxyketones **55** in excellent yields and good enantioselectivity.

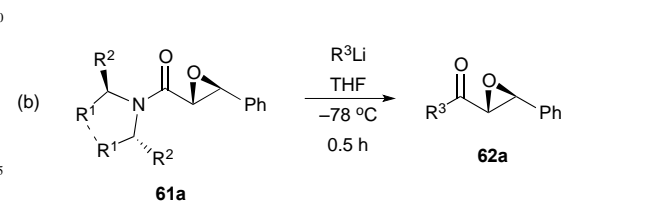
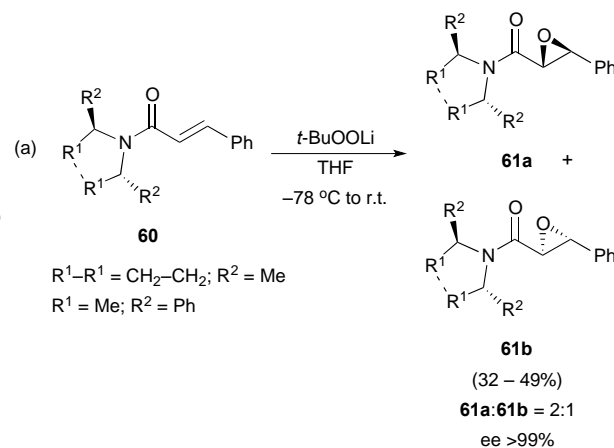
Following this discovery, Jackson developed the asymmetric

epoxidation of chalcones mediated by lithium and magnesium *tert*-butyl peroxides in the presence of (+)-diethyl tartrate ((+)-DET) as chiral ligand.⁴⁰ The optimized protocol for the stoichiometric epoxidation of chalcone **56** with *t*-BuOOLi/(+)-DET system required an additional equivalent of lithium alkoxide in a non-coordinating solvent (toluene). In these conditions, epoxide **57** was isolated in good yield, and moderate enantiomeric excess (Scheme 19(a)).⁴⁰



Scheme 19 Stoichiometric and catalytic asymmetric epoxidations of chalcone derivatives.

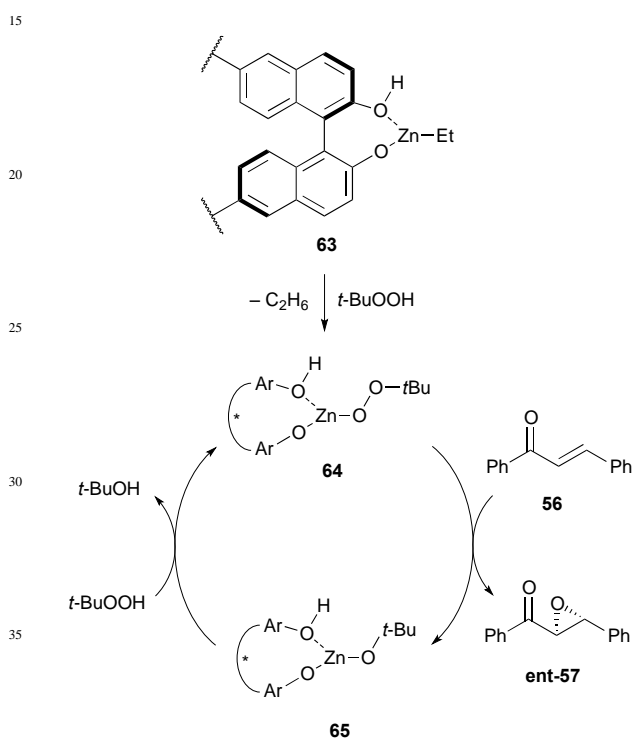
The authors reported that all attempts to modify this system to reach a better control of the stereochemistry or to use a substoichiometric amount of the oxenoid were not successful.⁴⁰ However, the use of substoichiometric quantities of the chiral ligand coupled with di-*n*-butylmagnesium resulted in much better enantioselectivities albeit in somewhat reduced chemical yields (Scheme 19(b)).⁴⁰



Scheme 20 Enantioselective epoxidation of α,β -unsaturated homochiral tertiary amides as an alternative way to epoxyketones.

In related studies, Meth-Cohn and Chen observed a complete enantiocontrol on the epoxidation of α,β -unsaturated homochiral tertiary amides **60** with the *in situ* generated *t*-BuOOLi (Scheme 20(a)).⁴¹ Despite the low diastereomeric ratio (2:1), the two epoxyamides **61a** and **61b** are readily separable by simple flash column chromatography and were isolated as enantiomerically pure products. Since the auxiliary chiral amide moiety can be easily cleaved by treatment of the resulting epoxides **61** with alkyl lithium reagents, the developed method allowed for a simple route to highly enantiomerically enriched α,β -unsaturated epoxyketones **62** (Scheme 20(b)).⁴¹

Polybinaphthyl zinc complexes were reported as efficient catalysts for the asymmetric epoxidation of α,β -unsaturated ketones using *t*-BuOOH (Scheme 21).⁴²



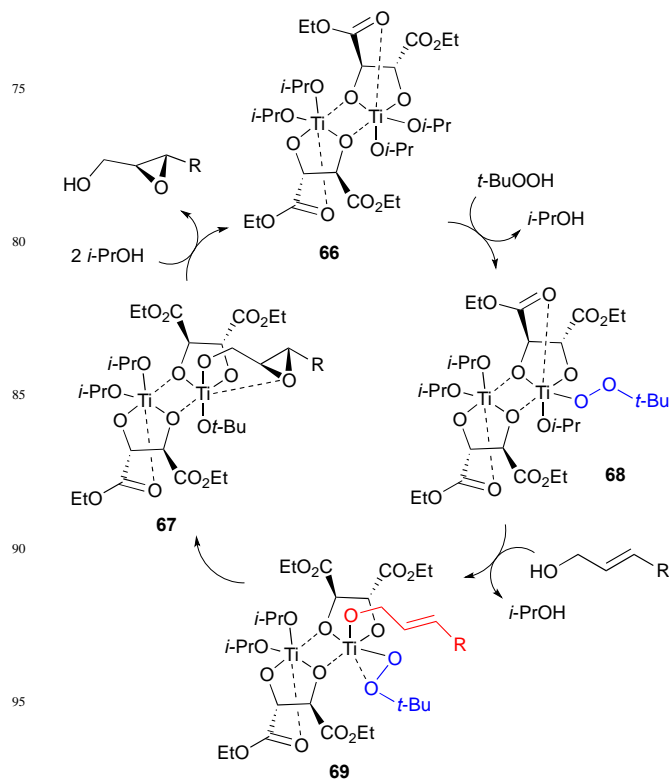
Scheme 21 A plausible catalytic cycle for the asymmetric epoxidation of chalcone by polybinaphthyl zinc complexes.

The authors proposed that complexes **63** form the corresponding zinc oxenoid species **64** upon reaction with hydroperoxide. This compound reacts with the unsaturated substrate to produce epoxyketone **57** in moderate (up to 71% ee) enantioselectivity. The catalytic cycle then proceeds by a simple ligand exchange in **65** to regenerate the active oxidant.^{42,43}

The asymmetric epoxidation of allylic alcohols mediated by Ti(IV) peroxo-complexes developed by Sharpless has become one of the most widely used stereoselective catalytic reactions in synthetic organic chemistry (Scheme 22).⁴⁴ Based on detailed spectroscopic and solid-state studies of the relevant complexes,⁴⁵ the formation of a dimeric Ti(IV) complex **69** where the peroxo-ligand has a bidentate coordination to the metal centre has been proposed.^{45,46} A mechanistic proposal following from these studies suggests the attack of the alkene moiety along the O–O bond with the concomitant formation of the epoxide C–O bonds.

Thus, this transformation occurs through transfer of an electrophilic oxygen atom to the alkene π -system and can be considered as an oxo-analogue to the cyclopropanation reactions mediated by carbenoid reagents.^{4c,5,35}

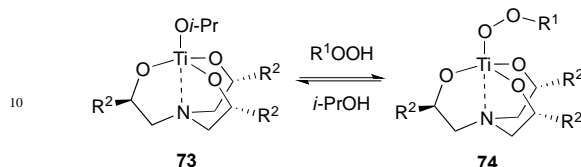
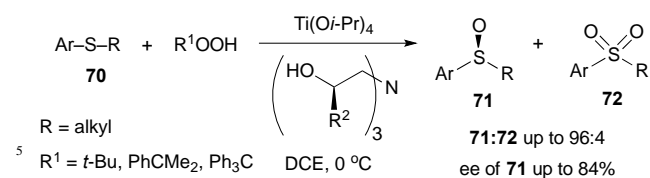
The asymmetric steric environment at the titanium (IV) centre in the catalytically active complex formed by equilibrium between alkoxy ligands allows for the favourable formation of one of the enantiomers of epoxide over the second one.⁴⁵ As was logically expected, pre-existing chirality in the allylic alcohol substrate has a tremendous effect on the kinetics of the epoxidation reaction.⁴⁷ This observation has led to the development of Sharpless kinetic resolution of racemic mixtures of allylic alcohols leading to the nearly enantiomerically pure (>99% ee) products.



Scheme 22 Mechanism of the Sharpless asymmetric epoxidation.

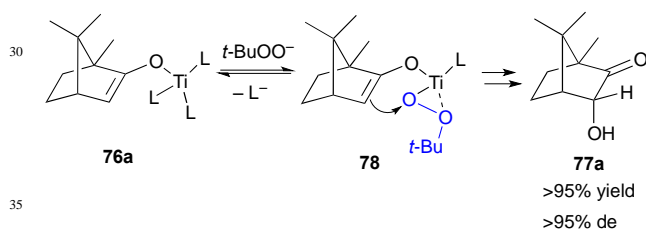
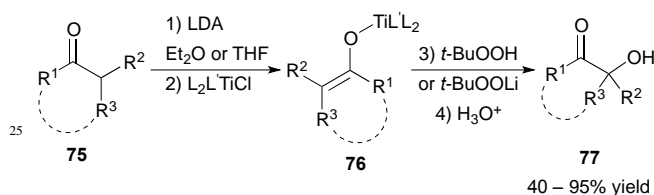
Analogous d^0 transition metal oxenoids were proven to be highly selective in the oxidation reactions of dialkyl or diaryl sulphides.^{48–50} Thus, the peroxotitanium complex **74** formed by simple exchange of *i*-PrO-ligand in titanium(IV) complex **73** with alkylhydroperoxides was proposed to be active oxidant in the asymmetric sulfoxidation reaction (Scheme 23).^{48,49}

Although this reaction provides sulfoxides in only moderate enantiomeric excess, the mechanistic studies and theoretical calculations reported later revealed that compound **74** has a biphlic nature in terms of the oxygen atom transfer.⁴⁹ The authors proposed that **74** acts as an electrophilic oxidant (oxenoid) towards sulphides, while coordination of a sulfoxide to the titanium centre promotes an unprecedented alteration of the electronic character of the oxygen transfer step leading to the nucleophilic oxidation pathway in oxidation of sulfoxides to sulfones.



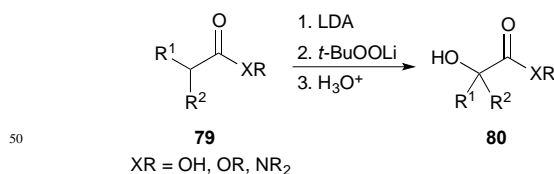
Scheme 23 Asymmetric sulfoxidation by titanium peroxo complexes.

The formation of a titanium(IV) peroxide of general structure $\text{L}_3\text{TiOO}t\text{-Bu}$ was proposed by Schulz and coworkers as the key step allowing for the diastereoselective α -hydroxylation of titanium enolates either with TBHP or its lithium salt (Scheme 24).⁵¹



Scheme 24 Diastereoselective hydroxylation of titanium enolates.

This reaction led to the formation of α -hydroxyketones **77** in moderate to good yields, and in the case of camphor enolate with excellent diastereoselectivity furnishing *endo*-**77a** exclusively. Julia showed that enolizable carboxylic acids and their derivatives could also be α -hydroxylated by means of *t*-BuOOLi (Scheme 25).²¹



Scheme 25 α -hydroxylation of carboxylic acids and derivatives by *t*-BuOOLi.

Conclusions

Selective oxidation reactions are one of the most important transformations in synthetic organic chemistry. Therefore, metalated organic hydroperoxides RO-O-M , possessing amphiphilic properties (i.e. nucleophilic or electrophilic depending on the nature of the substrate) in the oxygen transfer processes, are highly versatile and at the same time readily available reagents involved in a broad scope of valuable synthetic transformations. Recent studies focused on the reactivity of metalated peroxides as oxenoids (electrophilic oxidants) revealed remarkable selectivity and efficiency in the oxidation processes. Taking into consideration the unique properties of oxenoid compounds, further experimental and theoretical studies of these species and their applications in organic synthesis are expected to appear in future works.

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Notes and references

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- For reviews, see (a) O. A. Wong and Y. Shi, *Chem. Rev.*, 2008, **108**, 3958–3987; (b) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, and K.-X. Su, *Chem. Rev.*, 2005, **105**, 1603–1662.
- H. Srouf, P. Le Maux, S. Chevance and G. Simonneaux, *Coord. Chem. Rev.*, 2013, **257**, 3030–3050.
- (a) M. Möller, M. Husemann, G. Boche, *J. Organomet. Chem.*, 2001, **624**, 47–52; (b) J. Maury, L. Feray, S. Bazin, J.-L. Clement, S. R. A. Marque, D. Siri and M. P. Bertrand, *Chem. Eur. J.*, 2011, **17**, 1586–1595.
- (a) M. Julia, V. P. Saint James and J.-N. Verpeaux, *Synlett*, 1993, 233–234; (b) G. Boche, F. Bosold and J. C. W. Lohrenz, *Angew. Chem., Int. Ed.*, 1994, **33**, 1161–1163; (c) M. Pasco, N. Gilboa, T. Mejuch and I. Marek, *Organometallics*, 2013, **32**, 942–950.
- G. Boche and J. C. W. Lohrenz, *Chem. Rev.*, 2001, **101**, 697–756.
- (a) R. H. Holm, *Chem. Rev.*, 1987, **87**, 1401–1449; J. R. Winkler and H. B. Gray, *Electronic Structure of Oxo-Metal Ions In: Molecular Electronic Structures of Transition Metal Complexes I, Structure and Bonding* (Eds.: D. M. P. Mingos, P. Day and J. P. Dahl), Springer-Verlag, Berlin Heidelberg, 2012, **142**, pp. 17–28.
- (a) Z. Rappoport (Ed.) *The Chemistry of Peroxides, Patai's Chemistry of Functional Groups*, Wiley-VCH, Weinheim, 2006; (b) H. Klenk, P. H. Götz, R. Siegmeyer and W. Mayr *Peroxy Compounds, Organic In: Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag, 2012, **26**, pp. 325–360.
- D. Swern, *Chem. Rev.*, 1947, **45**, 1–68.
- (a) R. W. Murray, *Chem. Rev.*, 1989, **89**, 1187–1201; For the catalytic asymmetric epoxidation reactions using dioxiranes,

- see: (b) S. E. Denmark and Z. Wu, *Synlett*, 1999, 847–859; (c) M. Frohn and Y. Shi, *Synthesis*, 2000, 1979–2000.
- 10 F. A. Davis and A. C. Sheppard, *Tetrahedron*, 1989, **45**, 5703–5742.
- 5 11 (a) W. Zhang, J. L. Loebach, S. R. Wilson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1990, **112**, 2801–2803; (b) E. N. Jacobsen In: *Catalytic Asymmetric Synthesis*, Ed.: I. Ojima, VCH, Weinheim, 1993, pp. 159–202; (c) R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki, *Tetrahedron Lett.*, 1990, **31**, 7345–7348; For an overview of mechanistic aspects of the Jacobsen–Katsuki asymmetric epoxidation, see: T. Linker, *Angew. Chem., Int. Ed.*, 1997, **36**, 2060–2062.
- 12 E. Frankland, *Liebigs Ann. Chem.*, 1853, **85**, 329–373.
- 13 M. H. Abraham, *J. Chem. Soc.*, 1960, 4130–4135.
- 15 14 F. Chemla and J. Normant, *Tetrahedron Lett.*, 1995, **36**, 3157–3160.
- 15 I. Klement and P. Knochel, *Synlett*, 1995, 1113–1114.
- 16 A. Scarso and G. Strukul, *Product Class IV: Salts of Alkyl Hydroperoxides* In: *Science of Synthesis*, Georg Thieme, Verlag, 2008, **38**, 143–178.
- 20 17 E. Müller and T. Töpel, *Chem. Ber.*, 1939, **72**, 273–290.
- 18 G. Boche, K. Möbus, K. Harms, J. C. W. Lohrenz and M. Marsch, *Chem. Eur. J.*, 1996, **2**, 604–607.
- 25 19 (a) R. D. Bach, G. J. Wolber and B. A. Coddens, *J. Am. Chem. Soc.*, 1984, **106**, 6098–6099; (b) R. D. Bach, M.-D. Su, J. L. Andres and H. B. Schlegel, *J. Am. Chem. Soc.*, 1993, **115**, 8763–8769; (c) K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 2*, 1994, 117–124; (d) G. Santoni, M. Mba, M. Bonchio, W. A. Nugent, C. Zonta and G. Licini, *Chem. Eur. J.*, 2010, **16**, 645–654.
- 30 20 P. Warner and S.-L. Lu, *J. Org. Chem.*, 1976, **41**, 1459–1461.
- 21 M. Julia, V. P. Saint Jalmes, K. Ple, J.-N. Verpeaux and G. Hollingworth, *Bull. Soc. Chim. Fr.*, 1996, **133**, 15–24.
- 35 22 For a review on oxidation reactions of organocuprates, see: (a) D. S. Surry and D. R. Spring, *Chem. Soc. Rev.*, 2006, **35**, 218–225; (b) S. J. Aves and D. R. Spring *Oxidation of Organocopper Compounds* In: *Patai's Chemistry of Functional Groups; Organocopper Compounds* (Eds.: Z. Rappoport and I. Marek), Wiley, Chichester, 2009, pp. 585–602.
- 40 23 G. M. Whitesides, J. SanFilippo Jr., C. P. Casey and E. J. Panek, *J. Am. Chem. Soc.*, 1967, **89**, 5302–5303.
- 24 R. W. Hoffmann, B. Hölzer, O. Knopff and K. Harms, *Angew. Chem. Int. Ed.*, 2000, **39**, 3072–3074.
- 45 25 E. J. Panek, L. R. Kaiser and G. M. Whitesides, *J. Am. Chem. Soc.*, 1977, **99**, 3708–3713.
- 26 J. E. Bennett and J. A. Howard, *Chem. Phys. Lett.*, 1971, **9**, 460–462.
- 27 D. Zhang and J. M. Ready, *Org. Lett.*, 2005, **7**, 5681–5683.
- 50 28 F. Chemla and F. Ferreira, *Carbocupration of Alkynes* In: *Patai's Chemistry of Functional Groups; Organocopper Compounds* (Eds.: Z. Rappoport and I. Marek), Wiley, Chichester, 2009, pp. 527–584.
- 29 J. R. DeBergh, K. M. Spivey and J. M. Ready, *J. Am. Chem. Soc.*, 2008, **130**, 7828–7829.
- 55 30 J. Christoffers and A. Baro (Eds.), *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, 2005; For a comprehensive review on the recent advances in asymmetric quaternary stereocentres formation in acyclic systems, see: J. P. Das and I. Marek, *Chem. Commun.*, 2011, **47**, 4593–4623.
- 31 Y. Minko, M. Pasco, L. Lercher, M. Botoshansky and I. Marek, *Nature*, 2012, **490**, 522–526.
- 32 Y. Minko, M. Pasco, L. Lercher and I. Marek, *Nature Protocols*, 2013, **8**, 749–754.
- 65 33 E. M. Carreira, *Aldol Reaction: Methodology and Stereochemistry* In: *Modern Carbonyl Chemistry* (Ed. J. Otera), Wiley-VCH, Weinheim, 2001, pp. 227–248.
- 34 (a) P.-O. Delaye, D. Didier and I. Marek, *Angew. Chem., Int. Ed.*, 2013, **52**, 5333–5337; For a review on applications of donor-acceptor cyclopropane derivatives in organic synthesis, see: (b) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151–1196.
- 35 For a review on stereoselective cyclopropanation reactions, see: I. Marek, S. Simaan and A. Masarwa, *Angew. Chem., Int. Ed.*, 2007, **46**, 7364–7376.
- 36 (a) P. L. Bailey, W. Clegg, R. F. W. Jackson and O. Meth-Cohn, *J. Chem. Soc., Perkin Trans. 1*, 1993, 343–350; (b) A. D. Briggs, R. F. W. Jackson, W. Clegg, M. R. J. Elsegood, J. Kelly and P. A. Brown, *Tetrahedron Lett.*, 1994, **37**, 6945–6948.
- 37 K. Yamamoto and N. Yamamoto, *Chem. Lett.*, 1989, 1149–1152.
- 38 (a) S. Rodríguez, A. Vidal, J. J. Monroig and F. V. González, *Tetrahedron Lett.*, 2004, **45**, 5359–5361; (b) I. López, S. Rodríguez, J. Izquierdo and F. V. González, *J. Org. Chem.*, 2007, **72**, 6614–6617.
- 39 D. Enders, J. Zhu and G. Raabe, *Angew. Chem. Int. Ed.*, 1996, **35**, 1725–1728.
- 40 C. L. Elston, R. F. W. Jackson, S. J. F. MacDonald and P. J. Murray, *Angew. Chem. Int. Ed.*, 1997, **36**, 410–412.
- 41 O. Meth-Cohn and Y. Chen, *Tetrahedron Lett.*, 1990, **40**, 6069–6072.
- 42 H.-B. Yu, X.-F. Zheng, Z.-M. Lin, Q.-S. Hu, W.-S. Huang and L. Pu, *J. Org. Chem.*, 1999, **64**, 8149–8155.
- 43 For related recent examples of epoxidation of *trans*-chalcones mediated by zinc and lanthanoid oxenoids, see: (a) M. Kubisiak, K. Zelga, I. Justyniak, E. Tratkiewicz, T. Pietrzak, A. R. Keeri, Z. Ochl, L. Hartenstein, P. W. Roesky and J. Lewinski, *Organometallics*, 2013, **32**, 5263–5265; (b) M. Bougauchi, S. Watanabe, T. Arai, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1997, **119**, 2329–2330.
- 44 T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974–5976; For a review, see: T. Katsuki and V. Martin, *Asymmetric Epoxidation of Allylic Alcohols: the Katsuki–Sharpless Epoxidation Reaction*. *Organic Reactions.*, Wiley, 2004, 1–299.
- 45 M. G. Finn and K. B. Sharpless, *J. Am. Chem. Soc.*, 1991, **113**, 113–126.
- 46 E. J. Corey, *J. Org. Chem.*, 1990, **55**, 1693–1694.
- 47 V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237–6240.
- 48 F. Di Furia, G. Licini, G. Modena, R. Motterle and W. A. Nugent, *J. Org. Chem.*, 1996, **61**, 5175–5177.
- 49 M. Bonchio, S. Calloni, F. Di Furia, G. Licini, G. Modena, S. Moro and W. A. Nugent, *J. Am. Chem. Soc.*, 1997, **119**, 6935–6936.
- 50 M. Seenivasaperumal, H.-J. Federsel and K. J. Szabó, *Adv. Synth. Catal.*, 2008, **351**, 903–919.
- 51 M. Schulz, R. Kluge, M. Schüßler and G. Hoffmann, *Tetrahedron*, 1995, **51**, 3175–3180.