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Comparative perspective and synthetic applications of transition metal mediated oxidative cyclisation of 1,5-dienes towards cis-2,5-disubstituted tetrahydrofurans

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Abstract
Cis-2,5-disubstituted tetrahydrofurans constitute the core of several natural products and synthetic analogues which exhibit a broad and interesting range of biological activities. This review highlights a personal perspective and provides a comparative note on the synthesis of cis-2,5-disubstituted tetrahydrofuran rings from 1,5-diene precursors using metal–oxo species. Also, mechanistic insights for these synthetically significant protocols are given and striking examples from the literature are reported, which draw an attention towards the scope and synthetic utility of metal oxidants in the domain of cis-2,5-tetrahydrofuran containing bioactive natural product synthesis.

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1. Introduction
Substituted tetrahydrofurans (THFs) are considered as one of the most valuable five-membered ring systems in modern synthetic chemistry because of their widespread prevalence in a large number of natural products and biogenetically intriguing polyoxygenated cytotoxic molecules such as salinomycin.
Among various established methodologies towards the synthesis of tetrahydrofuran (THF) rings, oxidative cyclisations involving metal–oxo-promoted process are one of the most attractive. A number of metal based oxidants have been explored and reported for the synthesis of 2,5-disubstituted THFs involving oxidative cyclisation of 1,5-dienes (Fig. 2a), 5,6-dihydroxyalkenes (Fig. 2b), 5-hydroxyalkenes (Fig. 2c), and sequential epoxidation–5-exo-tet cyclisation applied to 5-hydroxyalkenes (Fig. 2d), while biomimetic epoxide–ring-opening cascade has been articulately incorporated to provide a succinct route to achieve the synthesis of THF entities of a cytotoxic natural product, teurilene. In addition to this, Os(VI) chemistry has been elegantly extended to 5-hydroxy-6-protected aminoalkenes, 5,7- and 5,8-dihydroxyalkenes to synthesise cis-2,5-disubstituted THF motifs.
The prime focus of this review is to summarise the main synthetic routes to cis-2,5-disubstituted THFs directly from 1,5-diene precursors using metal–oxo reagents (Fig. 2a) along with mechanistic insight and synthetic applications. Oxidative cyclisation of 1,5-dienes is a powerful and economical methodology to construct THF rings in one step, which establishes four new carbon–oxygen (C–O) bonds and potentially up to four new chiral centres. Despite of all progressive developments in this area, there are significant concealed aspects to be explored by the scientific community. Potential leading future trends and directions in this field include development of chiral phase-transfer catalysts and reagents for efficient enantioselective variants of oxidative cyclisation, possibility of absolute stereoinduction with Os(VIII) and Ru(VIII) oxidants, polycyclisation using oxomanganese [Mn(VII)] and Os(VIII) species as observed for Ru(VIII) chemistry, mechanistic investigations to get further insight about the reactive conformations, and incorporation of oxidative cyclisation in multi-component reactions.

2 Permanganate-mediated oxidative cyclisation

Kötz and Steche attempted to oxidise geranyl acetate 9 with potassium permanganate under mildly basic conditions in 1924. At that time, the reaction product could not be identified and was described as “oxidodioxygeraniolmonoacetate”. In 1965, Klein and Rojahn re-investigated this protocol and elucidated the product as a cis-2,5-disubstituted THF diol 10, obtained in moderate yield (Scheme 1). Neryl acetate 11 underwent cyclisation as well to afford the cis-THF diol 12, using the same reaction conditions. Both reactions proceeded in a stereospecific fashion with respect to each alkene and only the
cis-isomers were observed, which is highly significant in the context of stereocontrolled synthesis of cis-2,5-disubstituted THF rings contained within many cytotoxic natural products.

![Scheme 1](image)

**Scheme 1** Klein and Rojahn’s investigations towards permanganate-catalysed oxidative cyclisation.

*Reagents and conditions:* (a) KMnO₄, acetone:H₂O (5:1), CO₂ bubbling, pH = 7.5, 0 °C, 30 min.

The structural elucidation of the products of oxidative cyclisation triggered a new direction and two mechanistic proposals were put forward separately by the research groups of Walba and Baldwin. In their pioneering study, Walba and colleagues investigated the effect of double bond geometry present in the 1,5-diene on the relative stereochemistry of the resultant alcohol moieties adjacent to the cis-THF ring. Oxidative cyclisation of several 1,5-dienes in a mixture of acetone:H₂O (5:1) followed by CO₂ bubbling led to the formation of the corresponding diols in approximately 97% cis-stereoselectivity (Fig. 3).

![Fig. 3](image)

**Fig. 3** An effect of alkene geometry on the relative stereochemistry of incipient THF rings and diols.

The Sharpless mechanistic proposal for the oxidation of olefins by oxo–transition metal species was advanced by Walba and co-workers to account for the permanganate-mediated oxidative cyclisations (Fig. 4). It was proposed that after an initial attack of Mn(VII) on the diene and the formation of bis-π-complex, an octahedral Mn(VII) intermediate is produced via two Sharpless–type [2+2] cycloadditions. Alkyl migration from Mn(VII) to one of the oxygen atoms with the retention of configuration provides Mn(V) intermediate, which after a reductive elimination affords Mn(III) diester. Oxidation of Mn(III) ester
followed by the hydrolysis gives MnO$_2$ and the desired cis-THF ring with the observed relative stereochemistry.

![Diagram](image)

**Fig. 4** Sharpless–type [2+2] cycloadditions based mechanistic proposal by Walba and colleagues.

Further investigations to explore the stereoselectivity of the reaction were carried out in the laboratory of Baldwin. For this purpose, deuterated dienes were subjected to permanganate oxidative cyclisation and the cis-stereoselectivity of the resultant THF diols was confirmed by NMR analysis.$^{15d}$ A different mechanistic route for the cyclisation is presented by Baldwin, which is based on sequential [3+2] cycloadditions (Fig. 5).$^{15d}$ According to his proposal, an initial [3+2] cycloaddition of permanganate ion to one of the two double bonds of 1,5-diene takes place, which leads to an intermediate Mn$^{(V)}$ ester. After rapid oxidation of the Mn$^{(V)}$ intermediate to Mn$^{(VI)}$, a second [3+2] intramolecular cycloaddition occurs on the remaining double bond, followed by hydrolysis of the Mn$^{(V)}$ diester to afford the cis-THF. Kinetic isotopic investigations$^{28a}$ and spectroscopic determination of the intermediate species$^{28b}$ reveal that operational mechanism in permanganate-promoted oxidative cyclisation of 1,5-dienes follow a [3+2] pathway. It was later supported by Density Functional Theory (DFT) calculations and labelling studies which confirm that concerted [3+2] cycloaddition is favoured by about 40 kcal/mol relative to the stepwise [2+2] counterpart.$^{28c}$ The role of water in the permanganate oxidative cyclisation has been investigated using computational methods and it suggests that water plays a significant role by lowering the activation energies.$^{28d}$
An asymmetric version of this reaction was sought based on controlling the initial facial attack of the oxidant. This was achieved by Walba and co-workers by incorporating Evans’ oxazolidinone as a chiral auxiliary into the diene substrate 13 (Scheme 2). The expected reaction product, cis-THF diol 14 and its minor diastereoisomer were obtained in good yield with moderate diastereoselectivity (dr 3:1). It was postulated that the origin of diastereoselectivity was due to an initial Re-face attack on the conjugated double bond, leading to cis-THF diol 14 as a major product. The stereoselectivity was enhanced by exchanging Evans’ auxiliary with Oppolzer’s camphorsultam. Dienoate 15 was subjected to permanganate oxidation and the resultant cis-THF diols 16 and its minor diastereoisomer were obtained in moderate yield with an improved diastereoselectivity (dr >9:1). The major diastereoisomer 16 also arose due to an initial attack from the Re-face of the enoyl olefin bond and same facial preference was previously reported by Oppolzer and Barras in dihydroxylation reactions.

Scheme 2 Asymmetric oxidative cyclisation of 1,5-dienes bearing chiral auxiliary.

Reagents and conditions: (a) KMnO₄, acetone:H₂O (10:1), CO₂ bubbling, pH = 7.5, –30 °C, 30 min.

Oxidative cyclisation of 1,5-dienes using permanganate has been particularly championed by Brown and co-workers. A considerable modification in this area of research is the use of phase-transfer catalyst...
(PTC) for the permanganate-induced oxidative cyclisation of 1,5-dienes. Geranyl benzoate 17 was oxidised using potassium permanganate in the presence of adogen 464 (PTC) to afford the cis-THF 18 in good yield (Scheme 3).\textsuperscript{15e} Asymmetric oxidation of dienes 19-21 was also attempted using chiral phase-transfer catalyst 22 and corresponding cis-THF diols 23-25 were produced in moderate yields with promising enantiomeric ratios.

![Scheme 3 Application of phase-transfer catalysts in KMnO\textsubscript{4} oxidative cyclisation by Brown and co-workers.](image)

Reagents and conditions: (a) KMnO\textsubscript{4} (2.0 eq.), AcOH, adogen 464 (40 mol %), Et\textsubscript{2}O; (b) KMnO\textsubscript{4} (1.6 eq.), AcOH, chiral phase-transfer catalyst 22 (10 mol %), CH\textsubscript{2}Cl\textsubscript{2}.

Permanganate oxidative cyclisation has also been elegantly applied to 1,5,9-triene systems in a regiocontrolled manner to gain an expedient access to synthetically significant adjacent bis-THF architectures. Farnesoate esters 26-29 were synthesised using reported procedures and subjected to cyclisation which provided adjacent bis-THF lactols 30-33 (Scheme 4).\textsuperscript{31} Subsequent oxidative cleavage of vicinal diol units in lactols afforded the desired lactones 34-37 and the relative stereochemistry of resultant lactones 35 and 36 correlates with polyether antibiotics such as semduramycin and CP-54883 respectively.\textsuperscript{32} Later on, (2R)-10,2-camphorsultam was used to carry out the cyclisation in a stereoselective fashion. Oxidation of 1,5,9-triene 38 followed by oxidative cleavage of the resulting lactol afforded the lactone 39 in good yield and diastereoselectivity.
**Scheme 4** Regiocontrolled and stereoselective oxidative cyclisation of 1,5,9-trienes.

*Reagents and conditions:* (a) KMnO$_4$ (3.0 eq.), AcOH, pH = 6.2 buffer, acetone-H$_2$O; (b) Pb(OAc)$_4$, CH$_2$Cl$_2$, Na$_2$CO$_3$; (c) NaIO$_4$-SiO$_2$, CH$_2$Cl$_2$.

The mechanism of cyclisation for 1,5,9-triene 29 is in accordance with the one originally proposed by Baldwin and co-workers for 1,5-dienes.$^{15d}$ After the formation of *cis*-THF diol 40, oxidation of the remaining double bond affords the hydroxy ketone 41, which subsequently undergoes an intramolecular cyclisation to furnish the lactol 33 (Fig. 6). In addition to this, Both racemic and asymmetric approaches to prepare 2,6-disubstituted tetrahydropyrans with an exclusive 2,6-*cis*-selectivity from the permanganate oxidative cyclisation of 1,6-dienes have also been reported, albeit in moderate yields and diastereocontrol.$^{33}$
From cytotoxic natural products to useful synthetic building blocks, permanganate oxidative cyclisation has been successfully employed to construct THF rings in racemic and enantioselective fashions. The asymmetric variant of cyclisation extended the utility of this methodology in total synthesis, and its first application was described by Kocienski and colleagues within a total synthesis of salinomycin (1). Extensive work in this domain has been published from the laboratory of Brown and a wider prospect of permanganate-catalysed oxidative cyclisation has been illustrated by completing enantioselective syntheses of a number of members belonging to *Annonaceous* acetogenin and oxasqualenoid families of natural products. These include mono-THF, adjacent bis-THF and non-adjacent bis-THF containing bioactive molecules such as cis-solamin (2), cis-sylvaticin (3), cis-uvariamicin I (4) and cis-reticulatacin (5) obtained from 1,5-diene precursors, membranacin (6) using bifuranyl synthetic approach applied to 1,5,9-triene substrate, membrarollin (7) from a dienyne motif, and a formal synthesis of eurylene (8) by chemoselective and regiocontrolled monocyclisations of 1,5,9-trienes. Recently, this chemistry has been applied to an efficient stereoselective synthesis of trans-(+)-linalool oxide, which is a monoterpenoid present in essential oils and one of the most commonly used compounds in beverages, foods, and perfumery.

3 Osmium-catalysed oxidative cyclisation

Piccialli and colleagues were the first to report the osmium tetroxide-mediated oxidative cyclisation under catalytic conditions using sodium periodate (NaIO₄) as a co-oxidant. Gernayl acetate 9 and neryl acetate 11 were oxidised to the corresponding cis-THF diols 10 and 12 respectively in good yields (Scheme 5). Interestingly, changing the co-oxidant from sodium periodate to N-methylmorpholine-N-oxide (NMO) failed to yield the desired cyclised products even though NMO is a well-known co-oxidant in the catalytic asymmetric dihydroxylation of olefins.
Scheme 5 First examples of OsO₄ mediated oxidative cyclisation.

Reagents and conditions: (a) OsO₄ (5 mol %), NaIO₄ (4.0 eq.), DMF, 16 h.

Intensive work in the field of OsO₄ promoted oxidative cyclisation has been carried out by the research group of Donohoe and synthetic application of an OsO₄/TMEDA combination for the stereoselective oxidative cyclisation of 1,5-functionalised dienes has been explored. 16b 1,5-Dienes 42 and 44 were oxidised in a regioselective way and it was expected to obtain the corresponding dihydroxylated products, however cis-THF diols 43 and 45 were obtained in good yields (Scheme 6). The OsO₄/TMEDA combination provides a hydrogen bond acceptor reagent, which is an efficient way to direct the regioselectivity during the dihydroxylation of allylic alcohols such as 44. 37

Scheme 6 Oxidative cyclisation of 1,5-dienes using OsO₄/TMEDA complex by Donohoe and co-workers.

Reagents and conditions: (a) OsO₄ (1.0 eq.), TMEDA (1.0 eq.), CH₂Cl₂, –78 °C then MeOH, HCl, rt; (b) (MeO)₂CMe₂, TFA.

The proposed mechanism for OsO₄/TMEDA cyclisation is believed to follow the principle of sequential [3+2] cycloadditions reported for the permanganate-mediated oxidative cyclisation of 1,5-dienes. 15d Initially, one of the double bonds of 1,5-diene substrate undergoes a regioselective osmylation, controlled by hydrogen bonding to form an osmate⁶(VI) ester, which has been characterised in some cases (Fig. 7). 16b An intramolecular cyclisation takes place involving the reduction of active osmate⁶(VI) to an osmate⁴(VI) ester, which on subsequent acidic hydrolysis affords the cis-THF adduct and OsO₂ that is oxidised back to OsO₄. It is proposed that acid either serves to promote the rapid ligand exchange to permit the cyclisation or protonates the oxo–ligand species. In latter situation, the metal would be more electron deficient hence more reactive in the cyclisation. The cis-selectivity of the five membered ring is believed to be due to the proposed transition state, in which the intact glycol osmium bonds impose the cis-stereochemistry across the incipient THF ring. 16b
To avoid an unattractive use of stoichiometric OsO$_4$, Donohoe and co-workers investigated the use of catalytic osmium along with trimethylamine $N$-oxide (TMO) as a co-oxidant under acidic conditions.$^{16c}$ Several structurally diverse 1,5-dienes 46-49 were subjected to catalytic OsO$_4$ promoted oxidative cyclisation to yield cis-THF diols 50-53, in good to excellent yields and as single diastereoisomers (Scheme 7). Notably, the choice of solvent and organic acid plays an influential role.

**Scheme 7** Catalytic use of OsO$_4$ under acidic conditions.

*Reagents and conditions:* (a) OsO$_4$ (5 mol %), TMO (4.0 eq.), CSA (6.0 eq.), CH$_2$Cl$_2$; (b) OsO$_4$ (5 mol %), TMO (4.0 eq.), TFA (excess), acetone:H$_2$O (9:1).

To control the facial selectivity of this reaction, an internal stereodirecting substituent on 1,5-diene precursor has been investigated. Facile and effective stereo-controlled syntheses of (+)-anhydro-D-glucitol ((+)-56) and (+)-D-chitaric acid ((+)-58) illustrate the synthetic utility of catalytic OsO$_4$ promoted
oxidative cyclisation of 1,5-dienes. Enantiomerically enriched 1,5-diene (+)-54 was synthesised from D-mannitol in 4 steps, which was subjected to catalytic OsO₄ oxidative cyclisation to offer a single stereoisomeric cis-THF diol (+)-55 in an excellent yield (Scheme 8).⁴⁶c Deprotection of benzyl ethers completed a synthesis of (+)-anhydro-D-glucitol ((+)-56) in 6 steps and 42.5% overall yield. Furthermore, selective monoprotection of primary alcohol motif of cis-THF diol (+)-55, alcohol oxidation and finally deprotection provided (+)-D-chitaric acid ((+)-58) in total 8 steps and 12.7% overall yield. Oxidative cyclisation of 1,4-dienes to generate 2,5-disubstituted THFs has also been reported using catalytic OsO₄ with Oxone® as co-oxidant in moderate yields.⁴⁸ For this particular transformation, exchanging OsO₄ with KMnO₄ and RuO₄ results in comparatively poor yields.

Scheme 8 Role of internal stereodirecting groups and stereoselective synthesis of (+)-anhydro-D-glucitol ((+)-56) and (+)-D-chitaric acid ((+)-58).

Reagents and conditions: (a) OsO₄ (5 mol %), TMO (4.0 eq.), CSA (6.0 eq.), CH₂Cl₂; (b) H₂, Pd/C, EtOH; (c) BnBr, Ag₂O, toluene; (d) TEMPO (catalytic), NaClO₂, NaClO, MeCN; (e) H₂, Pd/C, MeOH.

4 Ruthenium-promoted cyclisation

The use of ruthenium in the oxidative cyclisation of 1,5-dienes was first reported by Sharpless and colleagues (Scheme 9).⁴⁷a The focus of the study was to improve the catalytic conversion of primary alcohols to carboxylic acids using ruthenium and it was discovered that the oxidation of geranyl acetate 9 and neryl acetate 11 led to the formation of cis-THF adducts 10 and 12 respectively along with their trans-isomers 59 and 61 respectively (cis:trans ratio ~3:1), while cis-THF ketol 60 was obtained as a major by-product. Sica and co-workers also investigated the same transformation and attempted to enhance the cis-selectivity of the reaction but could not achieve a significant improvement.⁴⁷b The research group of Piccialli had some success with geranyl acetate 9 and their improved method minimised the formation of over oxidised product 60 as well.⁴⁷c
Scheme 9 Comparative report on RuO₄ promoted oxidative cyclisation of 1,5-dienes.

Reagents and conditions: (a) Sharpless conditions: RuCl₃•(H₂O)ₙ, (2.2 mol %), NaIO₄ (3.1 eq.), CCl₄:CH₂CN:H₂O (2:2:3), 0 °C, 15 min; Sica conditions: RuO₂•2H₂O, (5.0 mol %), NaIO₄ (2.5 eq.), EtOAc:(CH₃)₂CO:H₂O (2:1:1), 0 °C, 4 min; Piccialli conditions: RuO₂•2H₂O, (4 mol %), NaIO₄ (4.0 eq.), EtOAc:CH₂CN:H₂O (3:3:1), 0 °C, 4 min.

Investigative studies on RuO₄ catalysed polycyclisation of isoprenoid polyenes towards the syntheses of adjacently linked poly-THF rings have been described. Farnesyl acetate, geranylgeranylacetate and squalene underwent polycyclisation to afford bis-, tris- and penta-THF diols respectively (Scheme 10). In the case of tris-THF product and penta-THF product, the relative configuration was determined by NMR studies and confirmed by preparing the diols via reported methods. Also, polycyclisation of meso symmetric (Cs) tetraene, digeranyl has been carried out and the resultant stereochemical outcome is explained by NMR analysis and simulated three dimensional structures of the possible transition states.
Scheme 10 RuO₄ promoted polycyclisations of isoprenoid polyenes.

Reagents and conditions: (a) RuO₂•2H₂O (20 mol %), NaIO₄ (4.0 eq.), EtOAc:CH₃CN:H₂O (3:3:1), 0 °C, 30 min; (b) RuO₂•2H₂O (20 mol %), NaIO₄ (8.0 eq.), EtOAc:CH₃CN:H₂O (3:3:1), 0 °C, 30 min.

It is thought that the mechanism of this reaction is related to the proposal presented by Baldwin for the permanganate oxidative cyclisation of 1,5-dienes.¹⁵ It is believed that RuO₄ interacts with a double bond to form Ru(VI) diester, followed by an intramolecular [3+2] cycloaddition and subsequent hydrolysis to afford mono-cis-THF product (Fig. 8).³⁹ In order to achieve an active oxidation level, Ru(V) is oxidised to give Ru(VII) intermediate, which readily undergoes another [3+2] cyclisation to form Ru(V) ester. Hydrolysis of the resultant Ru(V) ester releases the bis-THF diol adduct, while oxidative cleavage leads to bis-THF ketol.
Fig. 8 Piccialli’s proposed mechanism for RuO₄ catalysed oxidative cyclisation of 1,5,9-trienes.

Origin of *cis-* and *trans*-selectivity in the incipient THFs resulting from RuO₄ cyclisations is also described with conformational models. After an initial attack of the Ru(VIII) species, diester 70 is formed which adopts a specific stereochemical arrangement 70a to ensure the correct positioning of the second double bond involved in THF ring formation (Fig. 9). Such a chair-like conformation 70a, on hydrolysis, leads to *cis*-THF ring 71. It is also proposed that hydrolysis of C(1)O–Ru bond would afford Ru(VIII) ester 72. The coordination of C(1)OH with Ru(VIII) would lead to a chair like conformation 70b, which is analogous to the reactive conformation 70a and provides *cis*-selectivity in the resulting THF ring 71 through chelation control mechanism.

Alternatively, if no coordination of C(1)OH takes place with Ru(VIII) diester 72, conformation 72a would be obtained which provides *trans*-THF product 73, based on the steric reasons. This form of Ru(VIII) intermediate 72a is similar to the perreheenate ester involved in the *trans*-diastereoselective oxidative cyclisation of the bishomoallylic alcohols.
Fig. 9 Origin of cis- and trans-selectivity in THFs resulting from RuO$_4$ catalysed oxidative cyclisation.

Stark and co-workers have reported a catalytic RuO$_4$ mediated oxidative cyclisation of several substituted 1,5-dienes 74-82 to afford THF diols 83-91 in good to excellent yields with high cis-stereoselectivity (dr >95:5, Scheme 11).$^{17e,f}$ The corresponding trans-THF diols were not observed except in the case of THF diols 86 and 89. Sodium periodate on wet silica was used as co-oxidant in a solvent mixture of THF and CH$_2$Cl$_2$ (9:1). The generality of this approach is described, in which a range of functional and protecting groups are tolerant to the reaction conditions and the cyclisation proceeds efficiently.
The mechanism proposed by Stark for the catalytic RuO$_4$ cyclisation is analogous to the KMnO$_4$$^{15d}$ and OsO$_4$$^{16b}$ mediated oxidative cyclisations. It is proposed that after the oxidation of pre-catalyst, an initial [3+2] cycloaddition takes place between RuO$_4$ and one of the double bond of 1,5-diene to afford Ru$^{(VI)}$ intermediate (Fig. 10).$^{17e,f}$ The intermediate undergoes another [3+2] intramolecular cyclisation to give Ru$^{(IV)}$ diester, which on subsequent hydrolysis furnishes a cis-THF diol and RuO$_2$, which is oxidised back to RuO$_4$. Computational studies based on density functional theory have also been conducted to understand the mechanistic pathway of the reaction and theoretical calculations are found to be in good agreement with the experimental results.$^{42}$ The transition state during the formation of cis-THF product is reported to have about 40 KJ/mol more stability than the corresponding trans-THF ring.

**Scheme 11** Catalytic RuO$_4$ mediated cyclisation of 1,5-dienes by Stark and co-workers.

*Reagents and conditions:* (a) RuCl$_3$ (0.2 mol %), NaIO$_4$ on wet silica (3.0 eq.), THF:CH$_2$Cl$_2$ (9:1).
RuO$_4$ catalysed monocyclisation of 1,5,9-trienes and polynes has also been performed, and shows good diastereoselectivity and regiocontrol. Farnesol derivatives $92-95$, bearing several protecting groups, were oxidised to corresponding cis-THF diols $96-99$ in good yields with high diastereoselectivity (dr $>95:5$, Scheme 12).$^{17g}$ Similarly, non-terpenoid 1,5,9-trienes $100-102$ were oxidised to cis-THF diols $103-105$ in moderate yields and with the same level of diastereoselectivity. The methodology was extended to various polynes including diester $106$ and a good level of regiocontrol and diastereoselectivity was observed along with moderate yield of the resultant cis-THF diol $107$. Interestingly, the cyclisation of polenes did not go to complete conversion using previously reported optimised conditions for 1,5-diene substrates.$^{17e}$ Changing the solvent from THF:CH$_2$Cl$_2$ (9:1) mixture to pure THF increased the reaction rates and yields. This may be due to faster hydrolysis in a more polar solvent.
Another discovery in the field of ruthenium based cyclisation is the use of perruthenate ion from tetrapropylammonium perruthenate (TPAP). In the presence of NMO as a co-oxidant and excess of TPAP (2.0 eq.), 1,5-diene 108 was cyclised to cis-THF diketone 109 in a good yield (Scheme 13). When TPAP was used alone as an oxidising agent in the absence of NMO, incomplete conversion to the desired THF compound was observed. The reaction was carried out under catalytic conditions of TPAP by changing the co-oxidant from NMO to tetrabutylammonium periodate (TBAPI) and the yield also increased from 59 to 68%. Oxidative cyclisation of diacetate 110 using catalytic TPAP with TBAPI afforded the THF ketol 111 in good yield. When the reaction was performed under acidic conditions using NMO, a mixture of cis-THF diol 112 and THF ketol 111 was obtained. By changing the co-oxidant and reaction conditions, the major product of the oxidative cyclisation can be controlled which is of significant synthetic importance.
Scheme 13 Perruthenate-promoted oxidative cyclisation of 1,5-dienes.

Reagents and conditions: (a) TPAP (2.0 eq.), NMO (25 eq.), 4 Å MS, CH₂Cl₂; (b) TPAP (10 mol %), TBAPI (5.0 eq.), CH₂Cl₂; (c) TPAP (5 mol %), TBAPI (5.0 eq.), CH₂Cl₂; (d) TPAP (2.0 eq.), NMO (3.0 eq.), AcOH, 4 Å MS, CH₂Cl₂.

Synthetic applications of catalytic RuO₄ mediated oxidative cyclisation has been investigated, which provide an elegant synthesis of cis-solamin (2)⁴⁴ and neodysiherbaine.⁴³ In addition to this, catalytic RuO₄ mediated oxidative cyclisation applied to 1,6- and 1,7-dienes provide a succinct route to trans-2,6-disubstituted tetrahydropyrans⁴⁴ and trans-2,7-disubstituted oxepanes⁴⁵ respectively, in good yield with high trans-diastereoselectivity (dr >95:5).

5 Conclusion

Natural products containing cis-2,5-disubstituted THF rings show remarkably wide range of pharmacological potential, particularly with regard to exhibiting potent cytotoxic activities against cancer cells, multidrug resistant tumors and significant bioactivities including antiparasitic, antimalarial and pesticidal. Given their distinctive structural features combined with remarkable cytotoxicity, these have attracted an unusually high level of interest from the synthetic community, spending a lot of time and efforts to establish new synthetic protocols and to obtain adequate quantities for expediting their biological evaluations. Several metal-oxo species have been reported to affect the oxidative cyclisation of 1,5-dienes towards cis-2,5-disubstituted THF moieties. Permanganate-induced cyclisation generally proceeds in a good yield and it is considered as an environmentally benign protocol in comparison with other counterpart metal–oxo species. In particular, chiral phase transfer catalyst and chiral auxiliaries have been incorporated to provide an effective control of absolute stereoselectivity. However, such a type of oxidative cyclisation of 1,5-dienes requires a stoichiometric amount of the transition metal oxidant. Osmium tetroxide, ruthenium tetroxide and perruthenate-mediated cyclisations can be achieved under catalytic conditions, though excesses of co-oxidants such as TMEDA, TMO, NMO, NaIO₄ and TBAPI are often required. Osmium tetroxide provides an efficient route, however does not allow direct
asymmetric oxidative cyclisation of 1,5-dienes. Application of internal stereodirecting to induce indirect enantioselective oxidative cyclisation has been devised. Ruthenium–oxo catalyst results in polycyclisation of multiple double bonds in an efficient manner. The synthetic protocols delineated in this review have been applied to numerous bioactive natural products with profound structural complexity and will continue the irresistible allure of fascinating natural products.

6 Abbreviations

Ac Acetyl
Ar aromatic
Bn benzyl
Bu butyl
Bz benzoyl
CSA camphorsulfonic acid
DFT density functional theory
DMF N,N'-dimethylformamide
dr diastereomeric ratio
eq. equivalent
Et ethyl
h hour
Me methyl
min minutes
mmol millimole
MS molecular sieves
NMO N-methylmorpholine-N-oxide
Ph phenyl
PTC phase-transfer catalyst
rt room temperature
TBAPI tetrabutylammonium periodate
TBDMs tert-butyldimethylsilyl
TBDDS tert-butyldiphenylsilyl
TEMPO (2,2,6,6,-tetramethylpiperidin-1-yl)oxyl
TFA trifluoroacetic acid
THF tetrahydrofuran
THP tetrahydropyran
TMEDA N,N,N',N'-tetramethylethylenediamine
TMO trimethylamine N-oxide
TPAP tetra-n-propylammonium perruthenate
Ts p-toluenesulfonyl

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8 References


