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Recent advances in the stereoselective synthesis of tetrahydrofurans

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1. Introduction

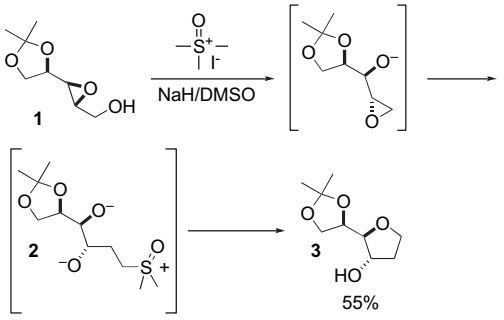
Substituted tetrahydrofurans are commonly occurring substructures found in a broad array of natural products and other biologically active molecules. For example, the annonaceous acetogenins are a large family of natural products bearing tetrahydrofuran cores.[1] Tetrahydrofuran moieties are also found in many other classes of natural products including lignans,[2] polyether ionophores[3] and macrodiolides.[4] These substances exhibit a diverse range of biological activities including antitumor, antihelmic, antimalarial, antimicrobial, and antiprotozoal.

Due to the importance of these molecules, considerable effort has been devoted toward the development of methods for the stereoselective construction of substituted tetrahydrofurans.[5] This review covers the important transformations that have been used in the stereoselective synthesis of tetrahydrofurans, with emphasis placed on literature published between 1993 and 2005. A broad array of new methods developed over the past 12 years as well as recent advances in older reactions that are widely used are described. The coverage of this review is limited to the synthesis of tetrahydrofurans; methods that generate furans, dihydrofurans, and benzofurans are not discussed.

2. Nucleophilic substitution processes

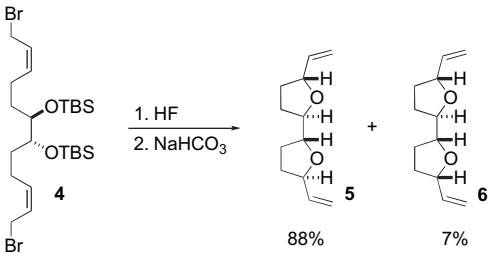
2.1. Intramolecular S_N2 and S_N1 reactions of hydroxyl nucleophiles with alkyl halides, sulfonates, or alcohols

Nucleophilic substitution chemistry has played a large role in tetrahydrofuran synthesis[5] and has been utilized in the construction of many natural products.[4,6] Many classical approaches to the formation of cyclic ethers employ intramolecular S_N2 reactions between a hydroxyl group and a tethered leaving group (e.g., halide or sulfonate). In general, the carbon bearing the leaving group is present in the starting material employed in the cyclization reaction. However, in recent studies Borhan has effected the ring expansion of 2,3-epoxyalcohols to tetrahydrofurans through a double S_N2 process in which the carbon atom bearing the second leaving group is installed in the first substitution. As shown below, treatment of **1** with trimethylsulfoxonium iodide under basic conditions results in Payne rearrangement of the epoxide followed by nucleophilic attack of a sulfoxonium ylide to yield **2**, which undergoes S_N2 ring-closure to afford hydroxytetrahydrofuran **3** (Eq. 1).[7] The best results are obtained with epoxides bearing ether substitution at C4, C5, or C6; epoxides bearing simple alkyl chains are transformed in low yield due to competing addition of the ylide to C3 instead of C1.



(1)

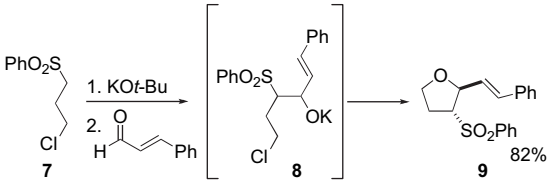
Most substrates used for the synthesis of tetrahydrofurans via intramolecular S_N2 reactions are prepared with all product stereocenters in place. As an alternative approach, several recent studies have been directed toward the development of nucleophilic substitution strategies that generate (rather than conserve) stereocenters. A method recently described by Zhao involves the use of S_N2' reactions to generate 2-vinyltetrahydrofurans with installation of a new stereocenter on each ring formed in the reaction.[8,9] For example, the double cyclization of **4** proceeded with 13:1 diastereoselectivity, and afforded the major isomer **5** in 88% isolated yield (Eq. 2).[10] The stereoselectivity of this reaction is highly dependent on alkene geometry, as the analogous *E*-alkene substrate was transformed to a 2:1 mixture of **5** and **6**. Although the origin of the high diastereoselectivity is unclear, the authors speculate that hydrogen bonding between the two hydroxyl groups (generated upon treatment of **4** with HF) may be important.



(2)

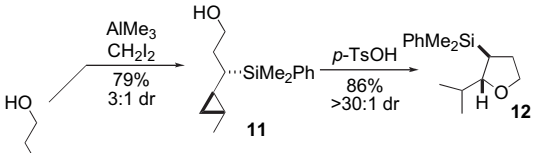
Another approach to the construction of tetrahydrofurans that generates two stereocenters and a carbon–carbon bond involves the nucleophilic addition of γ-chloroalkyl sulfones to aldehydes. For example, treatment of sulfone **7** with KO*t*-Bu followed by addition of cinnamaldehyde generates an intermediate potassium alkoxide (**8**), which undergoes subsequent ring-closure to provide tetrahydrofuran **9** as a single diastereomer (Eq. 3).[11] The product stereochemistry is believed to be thermodynamically controlled as the trans and cis tetrahydrofuran stereoisomers interconvert under the reaction conditions. Competing formation of cyclopropyl phenyl sulfone via deprotonation and cyclization of **7** is minimized by conducting the transformations at 0.5 M

concentrations. In general, acceptable yields are obtained with aromatic or unsaturated aldehydes, but reactions of aliphatic aldehydes proceed in modest yields. γ-Chloroalkyl esters and nitriles also serve as substrates for these reactions, although the yields and diastereoselectivities are highest with the sulfone derivatives. A related transformation of tin enolates derived from γ-chloroalkyl ketones has also been described.[12]



(3)

Cycloetherifications that generate new stereocenters have also been effected using S_N1 reactions.[5] For example, Panek has described a two-step route for the construction of tetrahydrofurans from β-hydroxy crotylsilanes.[13] As shown below, initial cyclopropanation of crotylsilane **10** followed by treatment of the resulting compound **11** with *p*-TsOH affords tetrahydrofuran **12** (Eq. 4). Interestingly, although the cyclopropanation of **10** to **11** proceeded with only 3:1 dr, this mixture of isomers was converted to the tetrahydrofuran product **12** with significantly enhanced (>30:1) diastereomeric purity. This result suggests that cyclization occurs via an S_N1 pathway, and the product stereochemistry is controlled by the adjacent silicon substituent. In a similar fashion, treatment of **10** with *m*-CPBA affords tetrahydrofuran **14** in 81% yield and 6:1 dr via intermediate epoxide **13** (Eq. 5). This strategy is also effective for the construction of 2,3,4-trisubstituted tetrahydrofurans from substrates bearing substituents at the homoallylic position.



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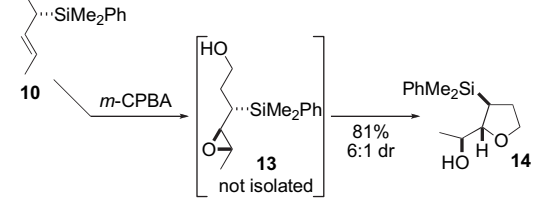
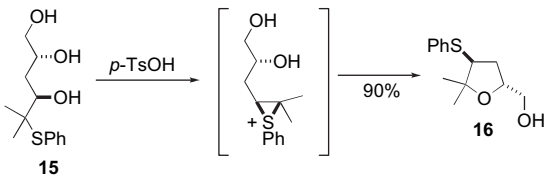


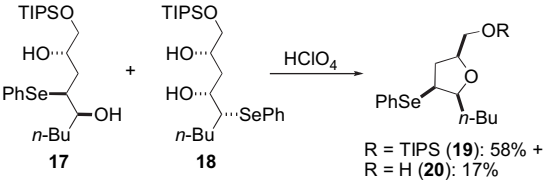
(5)

Warren has shown that *p*-TsOH mediated cyclizations of 2,4,5-triols containing a thiophenyl group at C1 provide tetrahydrofuran products via formation of an intermediate episulfonium ion followed by 5-*exo*/6-*endo*-cyclization.[14] For example, treatment of **15** with *p*-TsOH affords **16** in 90% yield as a single diastereomer (Eq. 6).[14d] The regioselectivity of this transformation is thermodynamically controlled, and reactions must be allowed to reach equilibrium to avoid the isolation of tetrahydropyran side products that derive from 6-*endo*-cyclization of the primary alcohol. These reactions are also amenable to the construction of spirocyclic products and tetrahydrofurans bearing substituents/stereocenters at C1′.



(6)

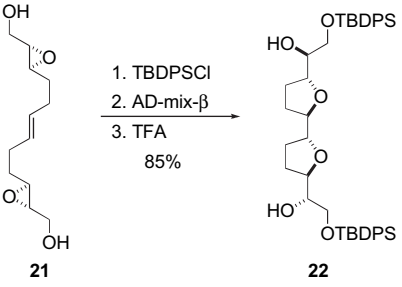
Gruttadauria[15] and Thomas[16] have developed an analogous $HClO_4$-catalyzed synthesis of 2,5-*cis*-disubstituted tetrahydrofurans from hydroxyselenide precursors. The starting regioisomeric selenides **17** and **18** were prepared as a mixture through epoxide ring-opening with PhSeNa. However, upon treatment with $HClO_4$ both regioisomers were converted to the same product diastereomer (**19**) in 58% yield along with 17% of the TIPS-deprotected tetrahydrofuran-2-yl-alcohol **20** (Eq. 7). This process is believed to proceed through a seleniranium ion intermediate analogous to the episulfonium ion species described above.



(7)

2.2. Intramolecular additions of alcohols to epoxides

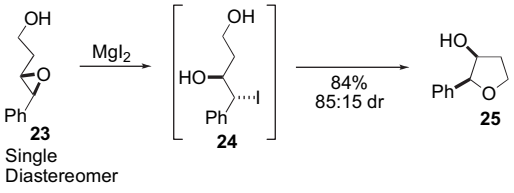
The synthesis of tetrahydrofurans via intramolecular additions of alcohols to epoxides was first described by Kishi in 1978[17] and is frequently utilized in the construction of complex molecules.[5] In situ generation of the epoxide followed by intramolecular cyclization has been achieved using a broad array of epoxidation methods including transition metal-catalyzed epoxidation,[18] biocatalytic epoxidation,[19] and S_N2 epoxide formation from 1,2-diol derivatives.[20] Cascade reactions have also been described in which an alkene bearing two pendant epoxides is subjected to dihydroxylation followed by cyclization.[21] For example, Hoye has prepared the bis-tetrahydrofuran core found in many acetogenin natural products via TBDPS-protection and Sharpless asymmetric dihydroxylation of **21** followed by addition of trifluoroacetic acid, which effects double cyclization to provide **22** in 85% yield as a single diastereomer (Eq. 8).[21a]



(8)

One key issue in the use of epoxide electrophiles for intramolecular cycloetherifications is the control of regiochemistry. In most cases *exo*-cyclization manifolds are favored over *endo*-cyclization pathways in these transformations, as the latter suffer from poor orbital overlap in the strained bicyclic transition state for cyclization.[22] In recent work Karikomi has developed a procedure that increases regioselectivity for the product of 5-*endo*-cyclization in reactions of 3,4-epoxybutanols through use of magnesium halide salt additives.[23] For example, treatment of **23** with catalytic MgI_2 affords **25** in

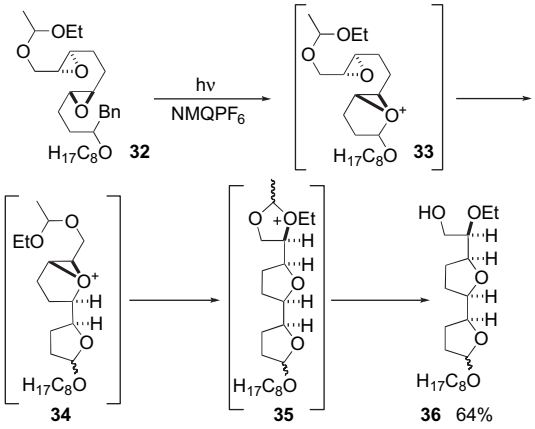
84% yield as an 85:15 mixture of diastereomers (Eq. 9). The magnesium salt mediates the conversion of the epoxide to halohydrin **24**, which undergoes cycloetherification to generate the 2,3-*cis*-disubstituted tetrahydrofuran product, albeit with slight loss of stereochemical purity.



(9)

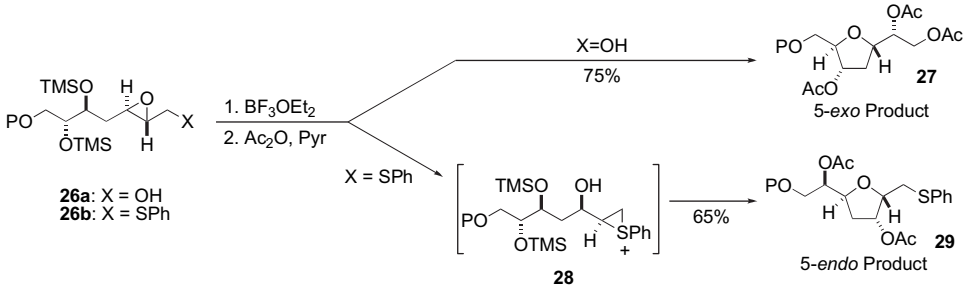
The structural factors that control regio- and stereoselectivity of Lewis-acid mediated cyclizations of protected epoxy diols have been examined by Borhan.[24] As shown below, substrate **26a** bearing a C1-hydroxyl group is converted to **27**, the product of 5-*exo*-cyclization, upon sequential treatment with $BF_3 \cdot OEt_2$ and Ac_2O (Eq. 10). However, this regioselectivity can be reversed through use of a substrate bearing a C1 thiophenyl substituent (**26b**, X=SPh) to provide **29**, the product of formal 5-*endo*-cyclization (Eq. 11). This change in selectivity is likely due to sulfur-induced epoxide opening to provide an intermediate episulfonium ion (**28**), which then undergoes stereoelectronically favorable 5-*exo*-cyclization to afford **29**. Products resulting from 5-*endo*-cyclization are also observed for substrates bearing a carbocation-stabilizing group (such as an alkene) adjacent to the epoxide.

initiated through photolysis of homobenzylic ethers.[26] As shown below, **32** undergoes photolytic cleavage of the benzyl group in the presence of $NMQPF_6$ (*N*-methylquinolinium hexafluorophosphate) to afford an oxonium ion that is engaged by a tethered epoxide to generate epoxonium ion **33**. Capture of this intermediate with a second epoxide affords **34**, which is trapped by the tethered ethyl ether group to give **35**. Upon workup, bis-tetrahydrofuran **36** is obtained in 64% yield as a single stereoisomer (Eq. 13).[27]



(13)

The conversion of 1-iodomethyl-1,5-bisepoxides to substituted tetrahydrofurans via a stereospecific elimination/cyclization sequence has recently been described by Marshall. As shown below, treatment of **37** with Zn/EtOH

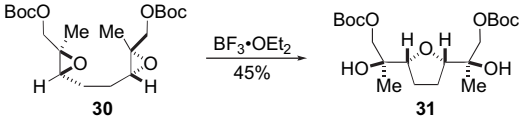


(10)

(11)

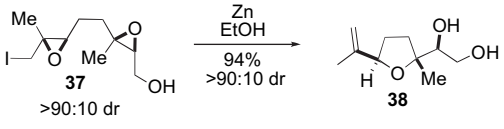
2.3. Substitutions involving other oxygen nucleophiles

A variety of oxygen-containing functional groups have been utilized as nucleophiles in tetrahydrofuran-forming reactions. For example, epoxides have been used in nucleophilic additions to tethered epoxides.[6,25] A representative transformation of this type is illustrated below, in which treatment of bis-epoxide **30** with $BF_3 \cdot OEt_2$ affords 2,5-*cis*-disubstituted tetrahydrofuran **31** (Eq. 12).[25b] Initial nucleophilic attack of one epoxide onto the other leads to generation of an epoxonium ion intermediate that is subsequently trapped by water upon quenching.



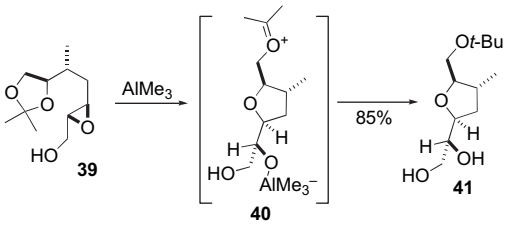
(12)

In recent work, Floreancig has demonstrated that transformations involving intermediate epoxonium ions can be induces ring-opening via elimination to generate an intermediate zinc alkoxide, which undergoes 5-*exo*-cyclization onto the pendant epoxide to afford **38** in 94% yield with complete preservation of diastereomeric purity (Eq. 14).[28]



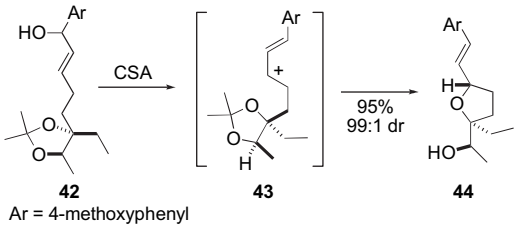
(14)

Acetonides have also been utilized as nucleophiles in tetrahydrofuran-forming reactions. For example, Still described the construction of a tetrahydrofuran ring via intramolecular alkylation of an acetonide oxygen atom with a tethered alkyl iodide in the context of a total synthesis of monensin.[29] In recent studies Parsons has noted that treatment of **39** with trimethylaluminum effects ring-opening of the epoxide with the tethered acetonide to generate oxonium ion **40**, which undergoes subsequent methylation to provide tetrahydrofuran **41** (Eq. 15).[30]



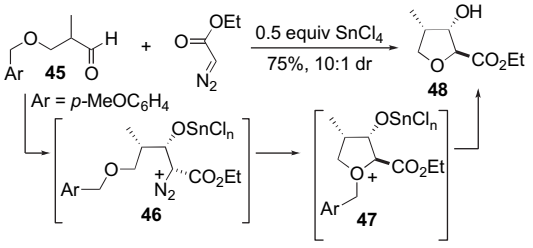
(15)

Acetonides have also been employed as nucleophiles in S_N1 reactions of 4-methoxyphenyl substituted allylic alcohols. For example, treatment of **42** with camphorsulfonic acid afforded a 95% yield of **44** with 99:1 diastereoselectivity via intermediate allyl cation **43** (Eq. 16).[31] These cyclizations can also be effected with Lewis acids, although use of Bronstead acids provides superior results.



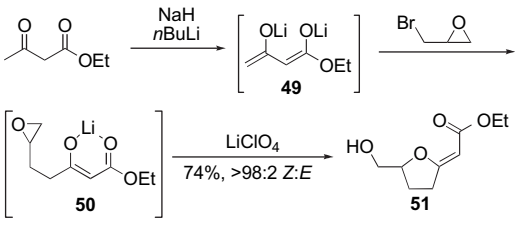
(16)

Ring-formation via intramolecular ether alkylation plays a key role in a Lewis-acid mediated synthesis of substituted tetrahydrofurans from α-diazoesters and β-benzyloxy carbonyl compounds developed by Angle.[32] As shown below, treatment of aldehyde **45** with ethyl diazoacetate and 0.5 equiv of $SnCl_4$ provided tetrahydrofuran **48** in 75% yield and 10:1 dr (Eq. 17).[32a] This reaction is believed to proceed via nucleophilic addition of the diazoester to the aldehyde followed by intramolecular alkylation of the resulting ether **46** and subsequent debenzylation of oxonium ion **47**. These transformations are also effective with β-silyloxy ketone and epoxide starting materials,[33] and aryldiazomethanes and tosyldiazomethanes can be used in place of the α-diazoester component.[34]



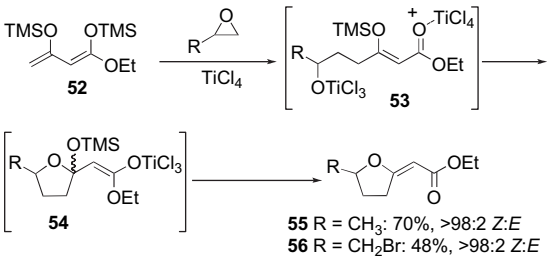
(17)

The synthesis of tetrahydrofurans via enolate O-alkylation has also been achieved. For example, dianions derived from 1,3-dicarbonyl compounds can be converted to 2-alkylidenetetrahydrofurans upon treatment with epibromohydrin derivatives or dihaloethanes.[35,36] As illustrated below (Eq. 18),[36a] generation of dianion **49** from ethyl acetoacetate followed by addition of epibromohydrin results in C-alkylation to provide enolate **50**. This intermediate then undergoes a $LiClO_4$-promoted intramolecular O-alkylation reaction with the tethered epoxide to afford tetrahydrofuran **51** as a single olefin isomer. Substitution on the β-ketoester component is tolerated, although the diastereoselectivities in these reactions are modest (ca. 1–2:1). The synthesis of tetrahydrofurans via alkylation of dicarbonyl dienolates with simple epoxides followed by acid-mediated carbonyl O-alkylation with the resulting alcohol has also been described.[37]



(18)

A similar transformation has been effected through Lewis-acid mediated reactions of 1,3-bis(trimethylsiloxy)-1,3-butadiene (**52**) with epoxides.[38] For example, treatment of **52** with 1,2-epoxypropane and $TiCl_4$ stereoselectively provided (*E*)-2-alkylidenetetrahydrofuran **55**.[38] This reaction is believed to proceed via initial epoxide opening by enolsilane **52** to afford **53**, which can undergo ring-closure to provide **54**. Elimination of TMSOH from **54** generates the observed product **55** in 70% yield (Eq. 19). Highly substituted products can be prepared in moderate to excellent diastereoselectivity through the use of 1,2-disubstituted epoxides or substituted enolsilane derivatives. This transformation is complementary to the related reactions of lithium dienolate **49** described above, as the opposite alkene stereoisomers are formed and halogen atoms are retained. For example, treatment of **52** with epibromohydrin in the presence of $TiCl_4$ afforded brominated tetrahydrofuran **56** in 48% yield.[38b]

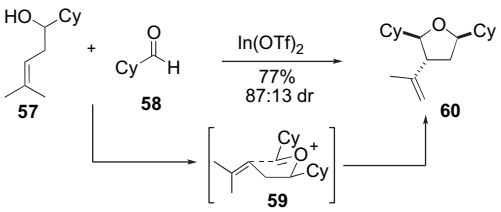


(19)

3. Nucleophilic capture of oxonium ions

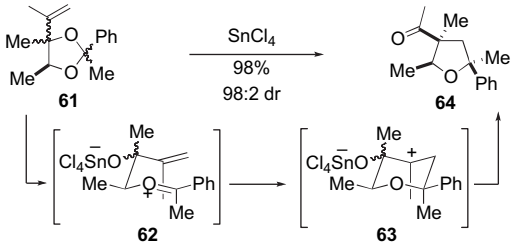
3.1. Intramolecular addition of nucleophilic alkenes to oxonium ions

A number of approaches to the stereoselective construction of tetrahydrofurans involve generation of reactive oxonium ion intermediates that undergo intramolecular capture by a tethered nucleophilic alkene.[39,40] For example, Loh has described the $In(OTf)_3$-mediated coupling of alcohol **57** and aldehyde **58** to generate tetrahydrofuran **60** in 77% yield with 87:13 dr via intermediate oxonium ion **59** (Eq. 20).[40a] The observed stereoselectivity is attributed to pseudoequatorial orientation of the substituents in the transition state for cyclization. Overman has developed very elegant methods for the construction of tetrahydrofurans that are also initiated



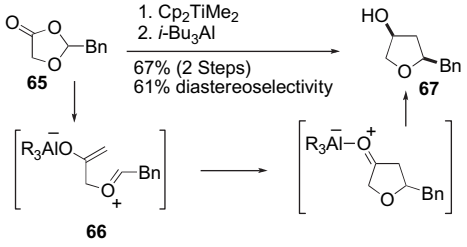
(20)

by the intramolecular cyclization of a nucleophilic alkene with an oxonium ion, but are terminated by a pinacol rearrangement.[41] For example, treatment of **61** with $SnCl_4$ affords **64** in 98% yield with 98:2 dr (Eq. 21).[42] As shown below, the transformation is initiated by Prins cyclization of oxonium ion **62** to generate carbocation **63**, which undergoes pinacol rearrangement to **64**. These reactions provide access to a wide array of 3-acyl tetrahydrofuran derivatives.



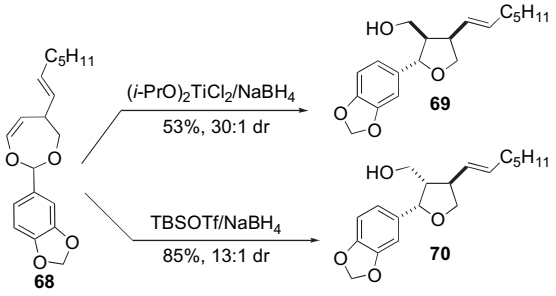
(21)

Petasis has described the conversion of substituted 1,3-dioxolan-4-ones to tetrahydrofuran products via methylenation and Lewis-acid mediated rearrangement.[43] For example, treatment of **65** with dimethyltitanocene followed by triisobutylaluminum affords disubstituted tetrahydrofuran **67** in 67% yield with modest stereoselectivity (Eq. 22). The reaction proceeds via rearrangement of oxonium ion **66** followed by in situ reduction of the resulting trialkylaluminum–ketone complex. Higher diastereoselectivities are obtained in transformations of substrates bearing a substituent adjacent to the carbonyl or disubstitution at the acetal carbon.



(22)

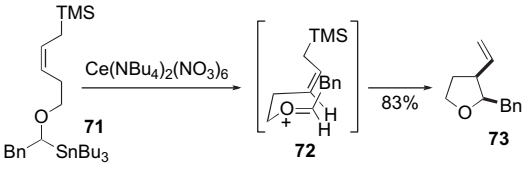
Takano has developed a Lewis-acid mediated ring contraction strategy for the synthesis of 2,3,4-trisubstituted tetrahydrofurans from 4,5-dihydro-1,3-dioxepin **68**.[44] Use of $(i\text{-PrO})_2TiCl_2$ as the Lewis-acid generated stereoisomer **69** in 53% yield with 30:1 dr (Eq. 23), whereas use of TBSOTf afforded a different diastereomer (**70**) in 85% yield and 13:1 dr (Eq. 24).[44a] Chelation is believed to play a significant role in controlling the stereochemical outcome of the titanium-mediated process.



(23)

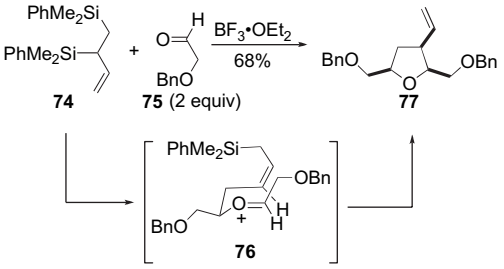
(24)

Allylsilanes and allylstannanes have frequently been employed as the nucleophilic alkene component in oxonium ion addition reactions that afford tetrahydrofuran products. For example, allylsilane tethered α-stannylethers have been transformed to substituted tetrahydrofuran products under oxidative conditions.[45] As shown below, treatment of *Z*-allylsilane derivative **71** with $Ce(NBu_4)_2(NO_3)_6$ generates intermediate oxonium ion **72**, which undergoes intramolecular reaction with the pendant allylsilane to afford 2,3-*cis*-disubstituted tetrahydrofuran **73** as a single diastereomer (Eq. 25).



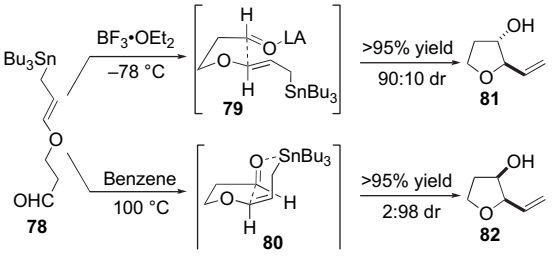
(25)

Sarkar has developed an alternative strategy for the generation of intermediates analogous to **72** that involves treatment of aldehydes with 1-silylmethyl allylic silane **74**. For example, tetrahydrofuran **77** was prepared from aldehyde **75** and allylsilane **74** in 68% yield as a single diastereomer via intermediate **76** (Eq. 26).[46]



(26)

Yamamoto has described the formation of 2-vinyl-3-hydroxytetrahydrofurans from γ-alkoxyallylstannanes bearing tethered aldehydes.[47] Either product stereoisomer can be obtained with good selectivity using the appropriate reaction conditions. For example, the $BF_3\cdot OEt_2$-catalyzed reaction of **78** provided 2,3-*trans*-disubstituted tetrahydrofuran **81**, which is believed to derive from a transition state in which the Lewis acid is oriented *anti* to the allylmetal reagent (**79**), in >95% yield with >90:10 dr (Eq. 27).[47b] In contrast, **78** is converted to 2,3-*cis*-disubstituted tetrahydrofuran **82** in >95% yield with 98:2 dr under thermal conditions (Eq. 28). The latter transformation is believed to proceed via a *cis*-decalin-like transition state **80**, in which the aldehyde is activated by intramolecular coordination with the stannyl moiety. A variant of this methodology has been developed that provides access to the analogous 2-vinyl-3-aminotetrahydrofurans.[48]

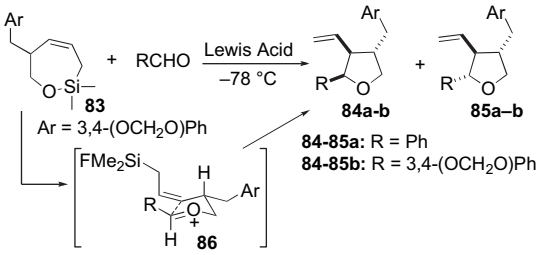


(27)

(28)

Marsden[49] and Cossy[50] have independently developed methodology for the construction of tetrahydrofurans via

a Lewis-acid mediated condensation of aldehydes with substituted 1-oxa-2-silacyclohept-4-enes. For example, treatment of oxasilacycloheptene **83** with benzaldehyde in the presence of $BF_3 \cdot OEt_2$ at −78 °C affords tetrahydrofuran product **84a** in 78% yield with 89:11 dr (Eq. 29). This product stereoisomer is believed to derive from a transition state in which the aldehyde substituent is oriented in a pseudoequatorial position (**86**).[49a] In contrast, reactions of electron-rich aldehydes fail to proceed at −78 °C, but upon warming generate a different tetrahydrofuran stereoisomer (**85b**). Marsden suggests that the latter reactions proceed via initial formation of **84b**, which then undergoes reversible ring-opening upon warming to generate the thermodynamically favored isomer **85b**. Use of the more reactive TMSOTf as Lewis acid promotes the reactions of electron-rich aldehydes at lower temperatures to generate the kinetic product **84b** with high diastereoselectivity. Enantioselective variants of this transformation have also been described,[51] along with a number of interesting applications.[52]

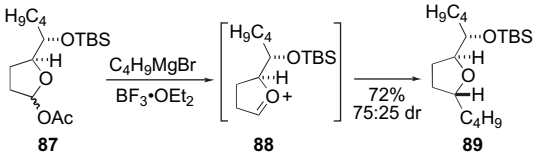


(29)

Lewis Acid	R	Major Product	Yield (dr)
BF_3OEt_2	Ph	**84a**	78% (89:11)
BF_3OEt_2	3,4-(OCH_2O)Ph	**85b**	58% (8:92)
TMSOTf	3,4-(OCH_2O)Ph	**84b**	73% (90:10)

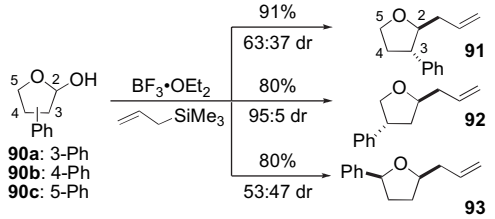
3.2. Nucleophilic addition to cyclic oxonium ions derived from γ-lactols

Addition of nucleophiles such as Grignard reagents,[53] organozinc reagents,[54] and titanium enolates[55] to oxocarbenium ions (e.g., **88**) derived from γ-lactol derivatives have been broadly employed in the stereoselective construction of tetrahydrofurans.[5c,56] In a representative example, acetoxytetrahydrofuran **87** was converted to substituted tetrahydrofuran **89** in 72% yield as a 75:25 mixture of diastereomers via treatment with $BF_3 \cdot OEt_2$ and butylmagnesium bromide (Eq. 30).[53]

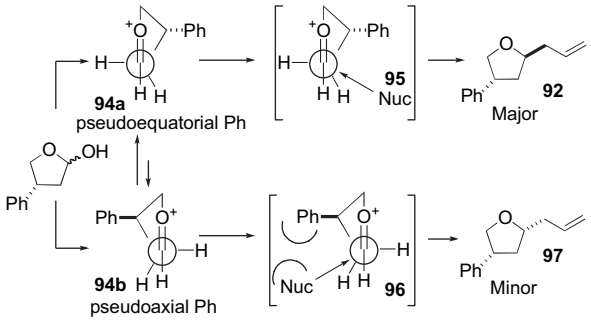


(30)

Many recent studies have led to the development of models to explain and predict the stereochemical outcome of nucleophilic additions to oxocarbenium ions. As shown below, Reiβig and co-workers have developed a transition state model that accounts for the stereochemical outcome of the addition of allylsilanes and silyl enol ethers to substituted γ-lactols (**90a–c**).[57,58] Interestingly, in a series of transformations involving addition of allyltrimethylsilane to phenyl substituted lactols, the conversion of the 4-phenyllactol substrate **90b** to 2,4-*trans*-disubstituted tetrahydrofuran **92** proceeds with the highest diastereoselectivity (95:5) (Scheme 1). The major product is believed to derive via reaction through transition state **95** (Scheme 2), in which developing 1,3-diaxial interactions between the nucleophile and the lactol ring substituent in the transition state are minimized. In this case the kinetic selectivity is complemented by the thermodynamic preference for pseudoequatorial orientation of the substituent in the ground state (**94a**>**94b**). A similar analysis has been used to account for the observed selectivities in reactions of lactols bearing substituents at the 3- or 5-positions.[57] Diastereoselectivities in these transformations are believed to be low due to the competing influence of kinetic and thermodynamic preferences for addition.

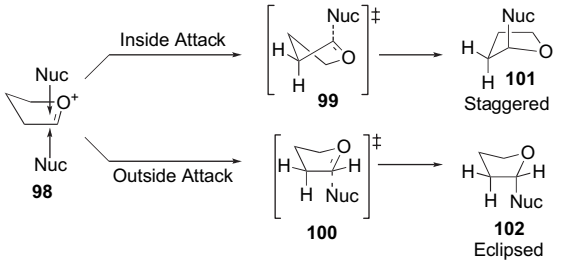


Scheme 1.



Scheme 2.

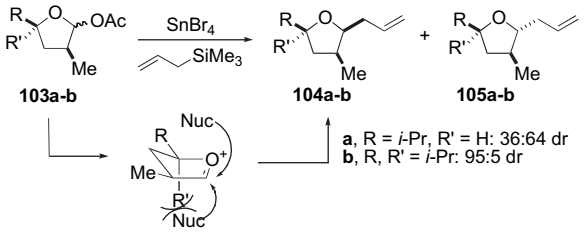
Woerpel has developed a complementary model for nucleophilic addition to 5-membered cyclic oxocarbenium ions that suggests addition preferentially occurs from the concave face of oxocarbenium ion **98**, which is postulated to react from an envelope conformation (Scheme 3).[59] The preference for 'inside attack' from the concave face is believed to result from a stereoelectronic effect. As shown below, if the allylations proceed through a late transition state, inside attack would result in a more stable staggered



Scheme 3.

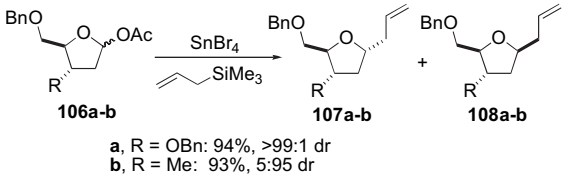
relationship between the partially formed C2–nucleophile bond and the C3–H bond (**99**→**101**). In contrast, outside attack would lead to a higher energy eclipsed relationship between the C2–nucleophile and the C3–H bond (**100**→**102**).[59a]

The size of the C2-substituent has a large impact on the diastereoselectivity of allylsilane additions to oxonium ions derived from 2,2,4-trisubstituted lactols. For example, treatment of **103a** with allyltrimethylsilane and $SnBr_4$ generates a 36:64 mixture of **104a** and **105a**; the selectivity is controlled by the C4-substituent when the axial C2-substituent is small. However, reaction of the related substrate **103b** bearing a second isopropyl group proceeds with 95:5 diastereoselectivity favoring the formation of **104b**. Developing 1,3-diaxial interactions in the transition state where R′=*i*-Pr further disfavor attack from the convex face of the envelope conformation, which results in improved selectivity (Eq. 31).[60]



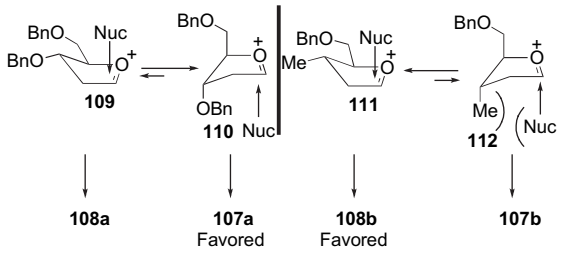
(31)

Woerpel has also observed that reactions of lactols bearing oxygen functionality at C4 proceed with unusual stereochemical outcomes. For example, the addition of allyltrimethylsilane to **106a** bearing a C4 benzyl ether substituent generated stereoisomer **107a**, whereas the analogous addition of allyltrimethylsilane to **106b** bearing a C4-methyl group afforded diastereomer **108b** (Eq. 32).[59c] These results have also been explained through the use of the inside attack model.



(32)

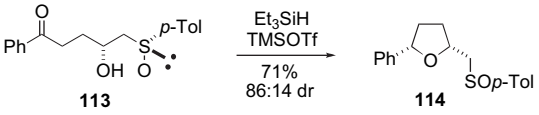
Woerpel suggests that the lower-energy oxonium ion envelope conformation (**110**) bears the C4-alkoxy group in a pseudoaxial orientation. This conformation is favored with an ether substituent, as the electron-rich oxygen atom is placed in relatively close proximity to the electron-poor cationic carbon atom. However, this stabilizing effect is not present with a C4 alkyl substituent, thus the lower-energy conformation (**111**) bears the alkyl group in a pseudoequatorial position to minimize nonbonding interactions. Inside attack of allyltrimethylsilane on alkoxy substituted intermediate **110** leads to stereoisomer **107a**, whereas inside attack on 4-alkyl intermediate **111** provides tetrahydrofuran **108b** (Scheme 4).



Scheme 4.

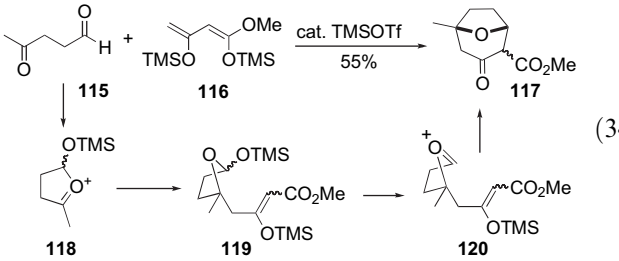
3.3. Nucleophilic addition to cyclic oxonium ions generated from acyclic precursors

Although the most common reactions for tetrahydrofuran synthesis via nucleophilic addition to cyclic oxonium ions involve generation of the reactive carbocation intermediate from a cyclic precursor, several interesting and useful transformations are initiated with acyclic substrates that are subsequently transformed to cyclic oxonium ions. For example, an asymmetric synthesis of 2,5-disubstituted tetrahydrofurans has recently been described that involves reduction of a lactol that is generated in situ from a γ-hydroxyketone bearing a chiral sulfoxide auxiliary.[61] As shown below, **113** is converted to 2,5-*cis*-disubstituted tetrahydrofuran **114** with 86:14 dr (Eq. 33).[61a] The starting material is generated as a single enantiomer via addition of the lithium anion derived from [(*S*)-*R*]-methyl-*p*-tolylsulfoxide to succinic anhydride followed by conversion of the resulting carboxylic acid to a ketone.



(33)

A stereoselective synthesis of substituted tetrahydrofurans via [4+3] annulation reactions between enol ethers derived from β-ketoesters and oxonium ions generated in situ from 1,4-dicarbonyl compounds has also been described.[62] As shown below, treatment of **115** and **116** with a catalytic amount of TMSOTf provided bicyclic tetrahydrofuran **117** in 55% yield (Eq. 34).[62a] These transformations proceed via initial generation of a cyclic oxonium ion (**118**), which undergoes intermolecular capture by the nucleophilic diene to provide **119**. A second ionization followed by intramolecular trapping of the resulting cation **120** affords the observed heterocycle **117**. The bicyclic products of these annulation reactions can be converted to highly substituted monocyclic tetrahydrofurans with further manipulation.



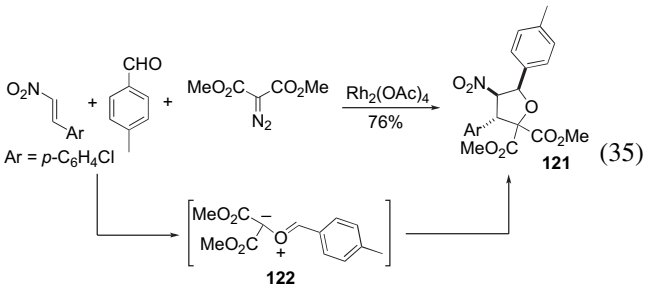
(34)

4. [3+2] Cycloaddition and annulation reactions

A very powerful strategy for the construction of tetrahydrofurans involves the use of [3+2] cycloaddition or annulation reactions. These transformations typically generate two to three bonds, two stereocenters, and a ring in a single step, thus providing a convergent and efficient route to highly substituted products. Many different methods have been developed that utilize various two- and three-atom components including epoxides, cyclopropanes, carbonyl ylides, and alkenes, although these strategies are often limited to certain classes of activated substrates.

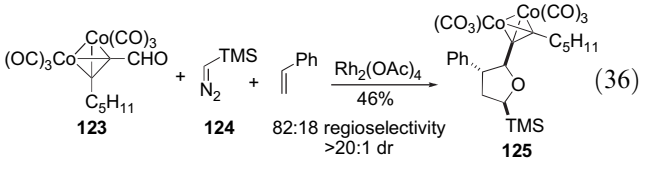
4.1. [3+2] Cycloadditions of carbonyl ylides

One common approach to the synthesis of tetrahydrofurans via [3+2] cycloaddition involves Rh-catalyzed reactions of diazo compounds with aldehydes and activated alkenes.[63] For example, the $Rh_2(OAc)_4$-catalyzed reaction of β-nitro-4-chlorostyrene with dimethyl diazomalonate and 4-methylbenzaldehyde generated tetrahydrofuran **121** in 76% yield as a single diastereomer (Eq. 35).[63c]



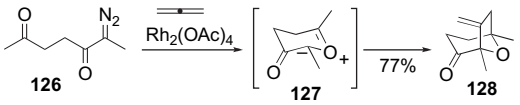
(35)

These transformations proceed via Rh-catalyzed generation of a carbonyl ylide (e.g., **122**) from the diazo compound and the aldehyde, which then undergoes a [3+2] dipolar cycloaddition with the alkene.[64] In general these transformations are only effective with electron-poor alkenes. However, Jamison has recently reported that use of aldehydes bearing cobalt carbonyl clusters leads to a broader range of reactivity in these transformations. As shown below, the coupling of aldehyde **123** (generated from 2-octynal and $Co_2(CO)_8$) with diazo compound **124** and styrene generates tetrahydrofuran **125** in 46% yield with 82:18 regioselectivity and >20:1 diastereoselectivity (Eq. 36).[63e]



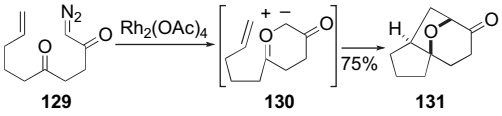
(36)

Intramolecular generation of carbonyl ylides from α-diazo ketones bearing tethered carbonyl groups followed by intermolecular [3+2] cycloaddition has also been described.[65] As shown below, **126** was converted to **128** in 77% yield upon treatment with allene in the presence of a $Rh_2(OAc)_4$ catalyst via carbonyl ylide **127** (Eq. 37).[65a]



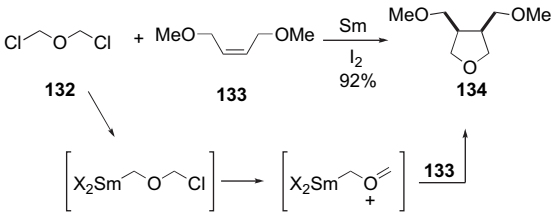
(37)

Padwa has developed tetrahydrofuran-forming reactions in which both generation and trapping of the carbonyl ylide are intramolecular events.[64] For example, treatment of **129** with a $Rh_2(OAc)_4$ catalyst generated **131** in 75% yield via intermediate **130** (Eq. 38).[66] These transformations have also been conducted asymmetrically using chiral rhodium complexes,[67] and have been utilized in the construction of a variety of interesting natural products.[64]



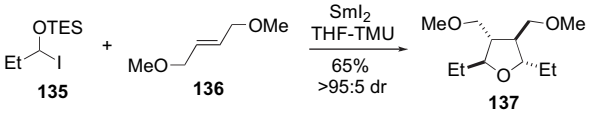
(38)

An alternative approach to the generation of carbonyl ylides that avoids use of diazo compounds involves treatment of bis(chloromethyl)ether derivatives with SmI_2 (generated in situ from Sm(0) and I_2) or Mn(0)/$PbCl_2$.[68] For example, the Sm-mediated reaction of **132** with **133** generated **134** in 92% yield as a single diastereomer (Eq. 39).[68a] Reactions of substituted bis(chloromethyl ethers) also proceed in excellent yield, although diastereoselectivities with these substrates are modest.



(39)

A related three-component synthesis of tetrahydrofurans via [3+2] cycloadditions of carbonyl ylides generated from α-iodo silylethers (e.g., **135**) in the presence of SmI_2 has also been described.[69] As shown below, this method is highly effective with unactivated alkene dipolarophiles such as **136**, affording product **137** in 65% yield and >95:5 dr (Eq. 40). However, the method is limited to the generation of tetrahydrofurans bearing identical substituents at C2 and C5, and the mechanism of this reaction is not well understood. A similar transformation using a combination of Mn/$PbCl_2$ in place of SmI_2 has also been reported.[70]

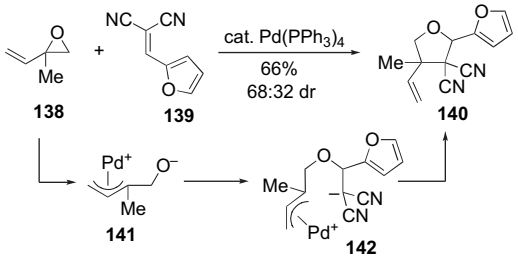


(40)

4.2. [3+2] Annulations involving strained-ring substrates

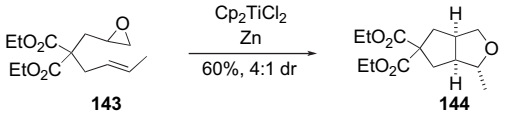
Several interesting [3+2] annulation strategies for the synthesis of tetrahydrofurans involve the use of strained-ring

substrates. For example, 2-vinylepoxides have been employed as starting materials in Pd-catalyzed [3+2] annulation reactions with activated alkenes[71] or enols derived from malonates.[72] As shown below, treatment of **138** with **139** in the presence of a Pd(0) catalyst afforded **140** with ~2:1 diastereoselectivity (Eq. 41). This transformation proceeds via oxidative addition of the epoxide to Pd(0) to generate **141**. Conjugate addition of the pendant alkoxide to the alkylidene malonate followed by intramolecular capture of the resulting allylpalladium complex **142** affords the observed product.



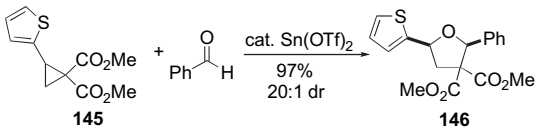
(41)

Epoxides have also been employed in transition metal mediated radical [3+2] annulation reactions.[73] As shown below (Eq. 42), treatment of **143** with Cp_2TiCl_2/Zn generates bicyclic product **144** in 60% yield with 4:1 dr via initial homolytic substitution of the C2–O bond with the Ti(III) complex to generate a radical that undergoes cyclization.[73a] Intermolecular reactions of alkenes with epoxides that proceed via radical intermediates have also been described.[74] Although the diastereoselectivities in many of these reactions are modest, the concept is attractive due to the broad availability of substituted epoxides, and further work in this area may lead to significant improvements.



(42)

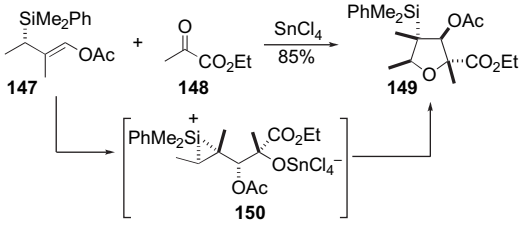
Cyclopropanes have also been employed as three-atom components in [3+2] annulation reactions that afford tetrahydrofuran products.[75] For example, treatment of **145** with benzaldehyde in the presence of a $Sn(OTf)_2$ catalyst provides tetrahydrofuran **146** in 97% yield with 20:1 diastereoselectivity (Eq. 43).[75a] These reactions are believed to proceed via Lewis-acid mediated cyclopropane opening to generate a stabilized carbocation, that is, trapped by the aldehyde. Thus, these transformations are typically limited to activated cyclopropanes bearing aryl substituents.



(43)

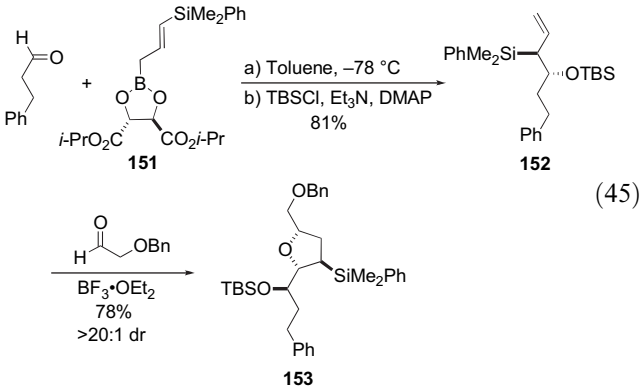
4.3. [3+2] Annulations involving allylsilane nucleophiles

[3+2] Annulation reactions between allylsilanes and aldehydes or other carbonyl derivatives, initially developed by Panek in 1991,[76] have been widely employed for the synthesis of tetrahydrofurans.[77] For example, in recent work Woerpel has effected the annulation of functionalized allylsilane **147** with α-ketoester **148** to provide tetrahydrofuran **149** in 85% yield as a single diastereomer (Eq. 44).[78] These reactions proceed through nucleophilic addition of the alkene to the Lewis-acid activated carbonyl group to generate a stabilized siliranium ion (**150**). This intermediate is then captured by the pendant alkoxide to afford the observed product.



(44)

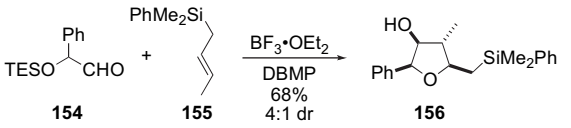
Roush has recently reported a multicomponent synthesis of tetrahydrofurans that is based on allylsilane [3+2] annulations.[79] This method effects the three-step coupling of two aldehydes with (*E*)-γ-(dimethylphenylsilyl)allylboronate **151**. As shown below, the reaction of **151** with hydrocinnamaldehyde followed by protection of the resulting alcohol product as a TBS-ether generates intermediate **152** in 81% yield.[79e] The subsequent reaction of **152** with α-benzyloxy acetaldehyde in the presence of $BF_3 \cdot OEt_2$ affords tetrahydrofuran **153** in 78% yield (63% yield over three steps) and >20:1 diastereoselectivity (Eq. 45). Ketones bearing α-carbonyl groups (e.g., 2,3-butanedione) can be used in place of aldehydes in the second step to provide more highly substituted products,[79e] and α,β-epoxyethers have also been employed as the electrophilic component in these transformations.[80]



(45)

In most Lewis-acid mediated [3+2] annulation reactions between allylsilanes and carbonyl derivatives the carbocation generated via addition to the carbonyl derivative is ultimately captured by the resulting Lewis-acid complexed alkoxide. However, in a few instances allylsilanes have been employed in [3+2] annulation reactions in which the carbocation intermediate is trapped by another pendant nucleophile to provide the tetrahydrofuran product. For example, Angle has reported that treatment of crotylsilane **155** with

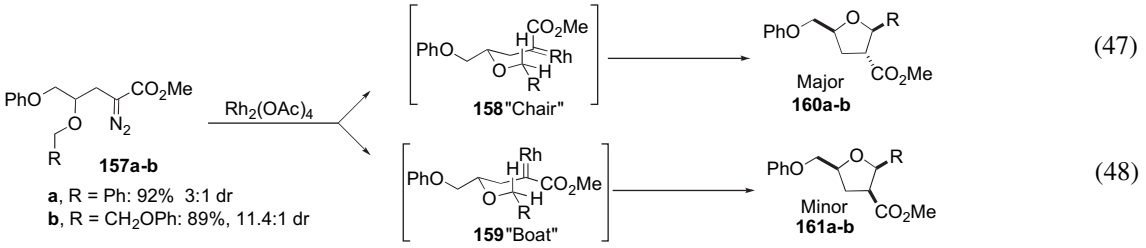
α-silyloxy aldehyde **154** affords tetrasubstituted tetrahydrofuran **156** in 68% yield and 4:1 diastereoselectivity (Eq. 46).[81] Similar transformations have been reported that involve aldehyde substrates bearing tethered acetonides,[82] and allylsilane nucleophiles that contain tethered silyl ethers.[83]



(46)

5. Metal-catalyzed addition or insertion reactions of diazo compounds

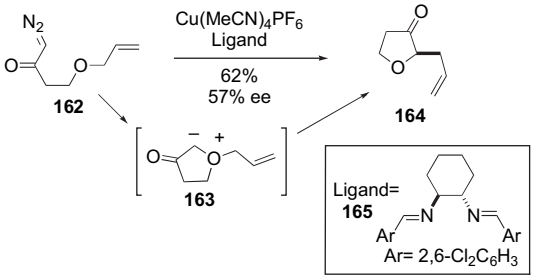
In addition to their utility in [3+2] cycloaddition reactions as described above, transition metal carbenoids generated from metal-catalyzed decomposition of diazo compounds have also been employed in C–H bond insertion processes that afford tetrahydrofuran products. For example, Taber has described the $Rh_2(OAc)_4$-catalyzed synthesis of 2,3,5-trisubstituted tetrahydrofurans from γ-alkoxy-α-diazoesters.[84] As shown below, treatment of **157a** with a catalytic amount of $Rh_2(OAc)_4$ affords tetrahydrofuran **160a** in 92% yield and 3:1 dr (Eq. 47).[84b] Taber suggests that the prominent reaction mechanistic pathway for these transformations involves insertion of the carbenoid into the C–H bond via a late, cyclic 'chair-like' transition state (**158**) in which the substituents are placed in pseudoequatorial positions. In contrast, the minor diastereomers are believed to derive from a boat-like transition state that occurs earlier on the reaction coordinate (Eq. 48, **159**). Stereoselectivities are observed to increase if an inductively electron withdrawing group is located adjacent to the site of C–H insertion, which decreases the reactivity of the C–H bond and leads to a more developed late transition state. For example, the oxygenated substrate **157b** was converted to **160b** in 89% yield and 11.4:1 dr. This methodology has been applied to the total synthesis of (−)-*trans*-cembranolide[85] and angularly substituted hydrindenes.[86]



(47)

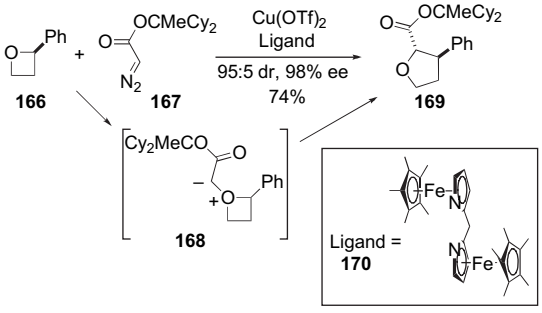
(48)

Transition metal carbenoids generated from α-diazocarbonyl compounds are also known to react with ethers to generate oxonium ylides that are useful intermediates in the construction of tetrahydrofurans. For example, [2,3]-sigmatropic rearrangements of oxonium ylides (e.g., **163**) generated in this manner have been employed for the construction of tetrahydrofuran-3-ones.[87,88] Asymmetric variants of this method have recently been developed that provide enantioenriched tetrahydrofuran-3-one products with modest selectivity.[89] As shown below, treatment of **162** with catalytic $Cu(MeCN)_4PF_6$ and chiral diimine ligand **165** provided **164** in 62% yield and 57% ee (Eq. 49).[89a]



(49)

Oxonium ylides generated via intermolecular Cu-catalyzed reactions of α-diazoesters with oxetanes (e.g., **168**) have been shown to undergo ring expansion to afford tetrahydrofuran products. Early studies in this area were conducted by Nozaki and Noyori, who demonstrated that 2-phenyloxetane is converted to 2-carbomethoxy-3-phenyltetrahydrofuran upon treatment with methyl diazoacetate and a copper catalyst.[90] In more recent years several highly selective chiral catalysts have been developed that effect the ring expansion of a broad range of oxetanes in good yield with high diastereoselectivity and enantioselectivity.[91] For example, treatment of **166** with diazoester **167** in the presence of a copper catalyst and chiral ligand **170** afforded tetrahydrofuran **169** in 74% yield with 95:5 diastereoselectivity and 98% ee (Eq. 50).[91c] Although high selectivities are obtained, this transformation is currently limited to oxetanes bearing a cation-stabilizing substituent.

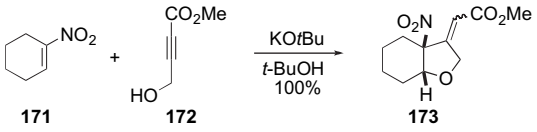


(50)

6. Conjugate addition/anion capture

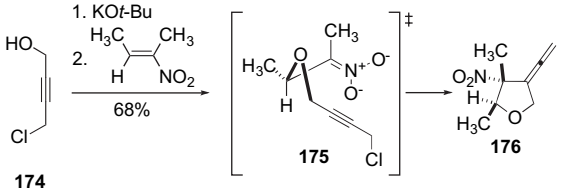
Several different methods for the stereoselective construction of tetrahydrofurans have been developed that involve tandem conjugate addition of an allylic or propargylic alcohol to a Michael acceptor followed by capture of the resulting anionic intermediate.[145a,92] Nitroalkenes have frequently been employed as the acceptor component in these transformations,[93] with subsequent trapping via a second conjugate

addition,[94] radical cyclization,[95] or dipolar cycloaddition.[96] For example, treatment of nitroalkene **171** with propargylic alcohol **172** in the presence of KO*t*-Bu generated tetrahydrofuran **173** in quantitative yield as a mixture of *E*/*Z* alkene isomers (Eq. 51).[94b] Double Michael addition reactions of γ-hydroxyenones that afford tetrahydrofuran products have also been described.[97]



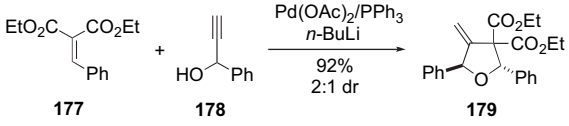
171 **172** **173** (51)

Dulcere has utilized a two-step protocol for the construction of tetrahydrofurans via oxy-Michael addition of propargyl alcohols to nitroalkenes followed by S_N2' ring-closure. This process is not stereospecific, but is highly diastereoselective.[94a,98] For example, **174** is converted to **176** in 68% yield as a single diastereomer upon treatment with KO*t*-Bu and (*E*)-2-nitro-2-butene (Eq. 52).[98] The major diastereomer is believed to derive from transition state **175**, in which $A^{(1,3)}$-strain is minimized.



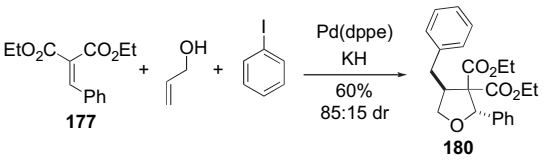
174 **175** **176** (52)

Alkylidene malonates have also been employed as Michael acceptors in tandem conjugate addition/anion capture reactions that are catalyzed by palladium[99,100] or zinc[101] complexes. For example, Balme has noted that the palladium-catalyzed reaction of propargyl alcohol **178** with alkylidene malonate derivative **177** generates 3-methylene tetrahydrofuran **179** in 92% yield with modest diastereoselectivity (Eq. 53).[99a] Balme has also described a related three-component synthesis of highly substituted tetrahydrofurans from alkylidene malonates, allylic alcohols, and aryl halides.[102]



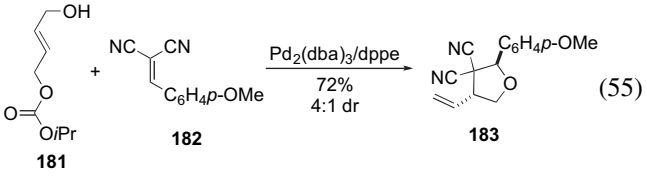
177 **178** **179** (53)

As shown below, treatment of alkylidene malonate **177** with iodobenzene and allyl alcohol in the presence of KH and a catalytic amount of Pd(dppe) affords tetrahydrofuran **180** in 60% isolated yield and 85:15 diastereoselectivity (Eq. 54). A number of aryl iodide coupling partners can be employed in these reactions, although the scope is limited to primary allylic alcohol nucleophiles. Related transformations involving propargylic alcohols have also been described in which both secondary and primary alcohols are effectively coupled, albeit with modest diastereoselectivity.[102b] A similar method involving the use of allyl chloride in place of the aryl bromide has also been recently reported by Lu.[103]



177 **180** (54)

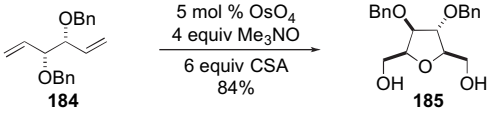
The Pd-catalyzed reaction of allylic alcohols bearing allylic carbonate functionality at C-4 with alkylidene malonate derivatives has been employed by Yamamoto for the construction of highly substituted 3-vinyltetrahydrofuran derivatives in good yield with moderate levels of stereocontrol.[104] For example, treatment of allylic alcohol **181** with **182** in the presence of a Pd/dppe catalyst provided **183** in 72% yield and 4:1 dr (Eq. 55). Use of catalysts bearing chiral phosphine ligands provides the 3-vinyltetrahydrofuran products in up to 92% ee.



181 **182** **183** (55)

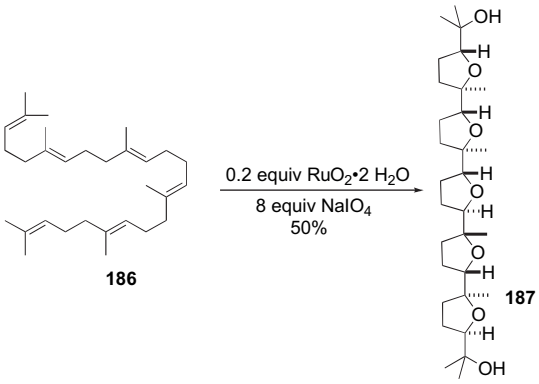
7. Oxidation of alkenes, dienes and polyenes

The oxidative cyclization of 1,5-dienes to hydroxylated tetrahydrofuran derivatives was initially reported over 40 years ago[105] and has been widely employed in the synthesis of complex molecules.[3,5a,c,106] Many of these transformations are limited by the need for stoichiometric amounts of oxidants such as $KMnO_4$ or OsO_4. However, recent efforts have been directed toward the development of catalytic versions of these reactions.[107] For example, Donohoe has effected the conversion of **184** to **185** in 84% yield as a single stereoisomer by treatment with catalytic OsO_4 and excess trimethylamine *N*-oxide under acidic conditions (Eq. 56).[107a]



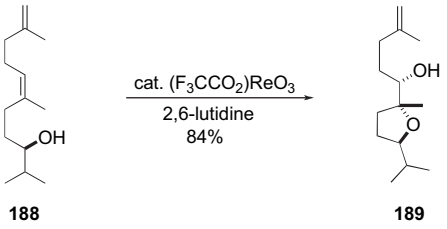
184 **185** (56)

Many early studies in oxidative diene cyclizations were focused on transformations that generate a single heterocyclic ring. However, more recent work has allowed for the stereoselective construction of bis-, tris-, and pentatetrahydrofurans from polyenes.[108] For example, RuO_4-catalyzed oxidation of squalene (**186**) afforded 50% of pentatetrahydrofuran **187** (Eq. 57).[108a] This impressive transformation generates 12 bonds and 10 stereocenters in one step. The oxidative cyclization of 1,4-dienes to 2,3,5-trisubstituted tetrahydrofurans has also been recently reported to occur with modest yields and regioselectivities.[109]



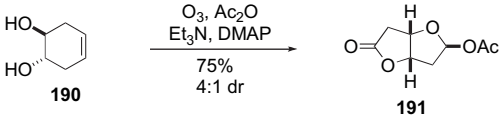
(57)

Oxidative cyclization reactions of γ-hydroxyalkenes and polyenes have also been broadly employed for the synthesis of tetrahydrofurans.[5a,c] For example, McDonald has described the Re-catalyzed oxidative cyclization of **188** to **189**, which proceeds in 84% yield to give a single product diastereomer (Eq. 58).[110] A number of other oxidants including Ti,[111] Cr,[110b,112] Tl,[113] and V[114]-based systems have been used for these transformations, and electrochemical oxidations of enol ethers bearing tethered hydroxyl groups have also been applied to the synthesis of tetrahydrofurans.[115]



(58)

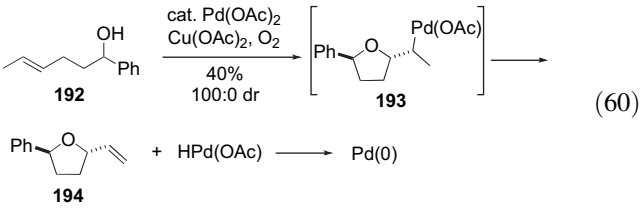
The oxidative cyclization of cyclohexene diol **190** was accomplished using a different strategy for oxidative cyclization. As shown below, use of modified Schreiber ozonolysis[116] conditions led to the efficient conversion of **190** to **191** in 75% yield and 4:1 dr (Eq. 59).[117] This compound was converted to a trisubstituted tetrahydrofuran via subsequent allylation and reduction.



(59)

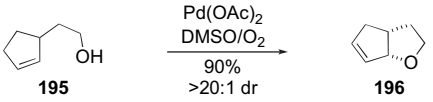
8. Oxidative cyclization of unsaturated alcohols

The palladium-catalyzed oxidative cyclization of unsaturated alcohols to 2-vinyltetrahydrofuran derivatives was initially described by Hosokawa et al. in 1976.[118] As shown below, treatment of **192** with a catalytic amount of $Pd(OAc)_2$ in the presence of stoichiometric $Cu(OAc)_2$ under an oxygen atmosphere afforded **194** in modest yield but with excellent diastereoselectivity (Eq. 60). These transformations are believed to proceed via oxypalladation of the alkene to generate **193**. This intermediate undergoes β-hydride elimination to provide tetrahydrofuran **194**, and the resulting Pd(H)(OAc) complex is reduced to Pd(0) with liberation of acetic acid. The stoichiometric copper additive serves to reoxidize Pd(0) to the catalytically active Pd(II) species. Historically the oxypalladation step has been postulated to occur via *anti*-addition of the oxygen atom and the metal across the double bond. However, recent mechanistic studies suggest that a *syn*-oxypalladation manifold is also accessible.[119]



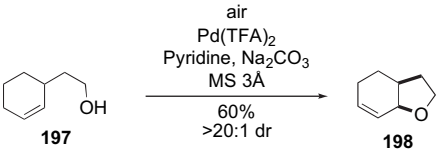
(60)

Recent studies in this area have been directed toward the development of catalysts and reaction conditions that do not require the use of added copper, which simplifies reaction workup and decreases the amount of waste generated in these transformations. One approach has been to utilize molecular oxygen in DMSO solvent to effect the Pd(0)–Pd(II) oxidation.[120] As shown below, these conditions effected the conversion of **195** to **196** in 90% yield and >20:1 diastereoselectivity.[120b] As an alternative strategy, Stoltz has developed an oxidative cyclization of γ-hydroxyalkenes that employs a $Pd(TFA)_2$/pyridine catalyst in the presence of atmospheric oxygen; use of DMSO as solvent is not required.[119a,b]



(61)

This transformation has afforded a variety of spirocyclic or fused bicyclic tetrahydrofuran products in 60–93% yield.[119] For example, these conditions effected the conversion of alcohol **197** to tetrahydrofuran **198** in 60% yield and >20:1 dr (Eq. 62).[119b] A number of groups have also been involved in the development of related enantioselective oxidative cyclization reactions that provide benzofuran derivatives, although these transformations are currently limited in scope.[119b,121]



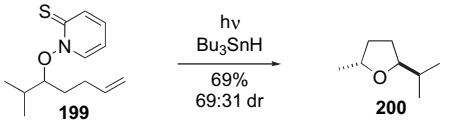
(62)

9. Alkene hydroetherification

9.1. Hydroetherification via oxygen radical cyclizations

The hydroetherification of alkenes via cyclization of oxygen-centered radicals is a useful method for the formation of tetrahydrofuran subunits. The oxygen radicals are typically generated through homolysis of a weak oxygen–heteroatom bond, and undergo rapid 5-*exo*-cyclization to afford tetrahydrofuran products.[122] For example, as shown in Eq. 63,

Hartung has described the conversion of *N*-alkoxypiperidinethione **199** to tetrahydrofuran **200** in 69% yield with moderate diastereoselectivity (69:31).[123] This methodology has been extended to the synthesis of 1′-bromo- and 1′-iodotetrahydrofurans through addition of a halogen source to the reaction mixture.[124] As shown below, photolysis of **201** in the presence of C_4F_9I provided **202** in 80% yield and 71:29 dr (Eq. 64).



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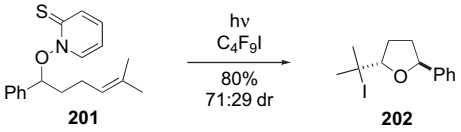
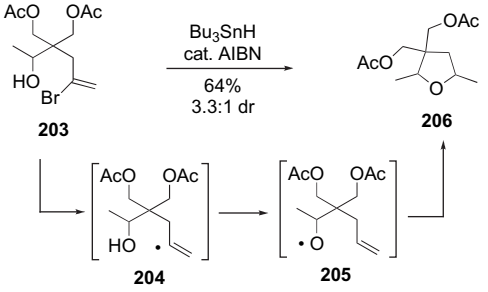


(64)

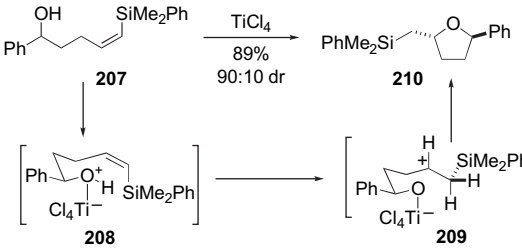
A recent study has demonstrated that substituted tetrahydrofurans can also be formed from 5-*exo*-cyclization reactions of alkoxy radicals generated via hydrogen atom abstraction.[125] For example, treatment of **203** with Bu_3SnH and AIBN provided **206** in 64% yield and 3.3:1 dr (Eq. 65). This transformation proceeds via generation of vinyl radical **204** followed by hydrogen atom abstraction from the alcohol group to provide **205**, which undergoes 5-*exo*-cyclization to generate the tetrahydrofuran product. This reaction is fundamentally interesting, as hydrogen atom abstraction from alcohols by carbon-centered radicals is rare. However, the scope is limited to substrates bearing *gem*-disubstitution in the tether between the reactive sites, and the relative stereochemistry of the products was not established.



(65)

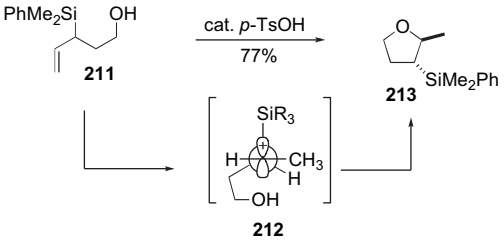
9.2. Hydroetherification via carbocation generation and capture

The acid-mediated intramolecular addition of O–H groups to unactivated alkenes is a straightforward approach to the synthesis of tetrahydrofurans. However, these transformations often are limited in scope. A related, alternative strategy has been developed by Hosomi that involves Bronstead or Lewis-acid mediated cyclization reactions of γ-hydroxyvinylsilanes.[126] For example, treatment of **207** with $TiCl_4$ affords 2,5-*trans*-disubstituted tetrahydrofuran **210** in 89% yield with 90:10 dr (Eq. 66).[127] These reactions are believed to proceed through initial protonation or Lewis-acid activation of the alcohol to generate **208**, which then effects intramolecular protonation of the vinylsilane moiety. The resulting β-silyl cation (**209**) is then captured by the tethered oxygen nucleophile to afford the cyclized product. Deuterium labeling studies indicate that the addition occurs with *syn*-selectivity, and these reactions are also effective for the construction of 2,5-*trans*-, 2,4-*cis*-, and 2,3-*trans*-disubstituted tetrahydrofurans from *Z*-vinylsilane substrates.[127]



(66)

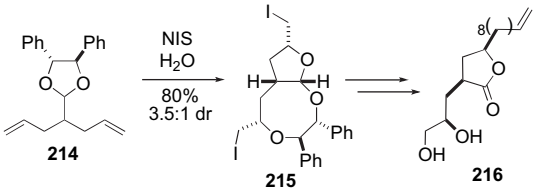
The Bronstead acid catalyzed annulation of 3-silyl-bishomoallylic alcohols has also been employed for the stereoselective construction of tetrahydrofurans.[128] For example, treatment of **211** with a catalytic amount of *p*-TsOH provided tetrahydrofuran **213** in 77% yield as a single diastereomer (Eq. 67).[128a] The silicon group plays a dual role in these reactions as it serves to stabilize the intermediate carbocation (**212**) via σ–π conjugation, and also facilitates torquoselective nucleophilic attack on the carbocation to generate a single product stereoisomer.



(67)

10. Alkene haloetherification, mercurioetherification, and selenoetherification

Haloetherification, mercurioetherification, and selenoetherification are among the most commonly employed methods for the construction of tetrahydrofurans, and are broadly employed in the synthesis of natural products. For example, a key step in Fujioka and Kita's synthesis of rubreanolide involved the double iodoetherification of acetal **214**, which generated bicyclic tetrahydrofuran **215** in 80% yield with 3.5:1 diastereoselectivity (Eq. 68).[129] Further elaboration of **215** afforded the natural product (**216**). Due to the broad utility of these transformations, this area has been extensively reviewed, and will not be discussed in detail.[5,130,131] However, a few recent developments of interest are described below.



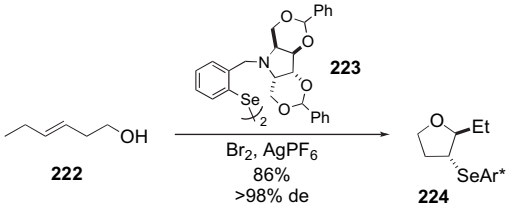
(68)

10.1. Reagent-based control of chemoselectivity/regioselectivity

Several recent studies have been focused on the issue of chemoselectivity or regioselectivity in electrophilic etherification reactions of substrates containing multiple nucleophilic groups.[132,133] For example, Castillon has demonstrated that the electrophilic cycloetherification of 4-penten-1,2,3-triol derivatives **217a–b** can be executed in either a 5-*exo*- or 5-*endo* manner with the appropriate choice of electrophile and primary alcohol protecting group.[133] As shown below (Scheme 5), 5-*exo*-cyclization is favored with a substrate bearing an unprotected primary alcohol (**217a**) under iodoetherification and selenoetherification conditions (NPSP=*N*-phenylselenophthalimide) to afford **218** and **219**, respectively. Cyclization of the dibenzyl ether substrate **217b** proceeded via 5-*exo*-cyclization under iodoetherification conditions to afford **221**, but the product of 5-*endo*-cyclization (**220**) was obtained upon treatment with NPSP. Related issues of *endo*- versus *exo*-cyclization manifolds have also been addressed computationally.[134]

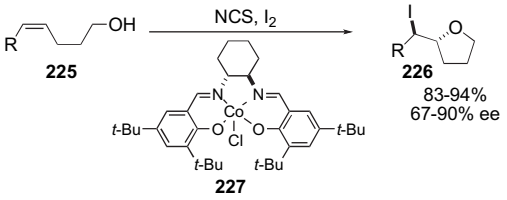
10.2. Asymmetric seleno- and haloetherifications

In recent years a considerable amount of effort has been devoted to the development of enantioselective seleno- and haloetherification reactions.[135] A number of different nonracemic selenium reagents have been prepared that derive their chirality from ferrocene derivatives,[136] C_2-symmetric aromatic groups,[137] chiral benzyl ethers or thioethers,[138] and camphor based moieties.[139] Reagents bearing chiral amines also effect asymmetric selenoetherifications with reasonably good generality and high enantioselectivity.[140] For example, treatment of **222** with a chiral arylselenyl hexafluorophosphate derived from the reaction of diselenide **223** with Br_2 and $AgPF_6$ provided tetrahydrofuran **224** in 86% yield with >98% de (Eq. 69).[140b]



(69)

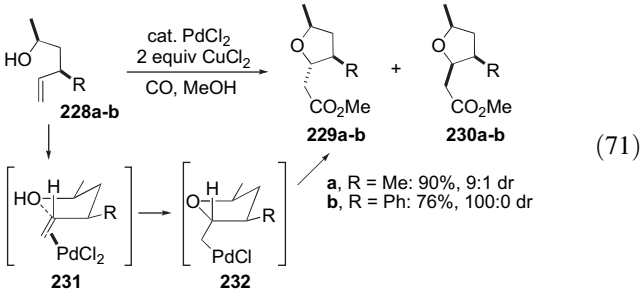
Although many reagents have been developed to effect asymmetric selenoetherification, asymmetric iodoetherification reactions remain quite rare. In recent studies Kang has described the synthesis of enantioenriched tetrahydrofurans via iodoetherifications conducted in the presence of a chiral Co(III)-salen catalyst (**227**) or a chiral BINOL-derived titanium catalyst.[141] For example, the Co(III)-catalyzed iodoetherifications of (*Z*)-4-pentenol derivatives (**225**) afford tetrahydrofuran products **226** in 83–94% yield with 64–90% ee (Eq. 70).[141a] Similar yields and enantioselectivities have been obtained in asymmetric mercuriocyclizations catalyzed by chiral Hg(II)–bisoxazoline complexes.[142]



(70)

11. Alkene carboetherification

As described in the preceding sections, a number of methods for tetrahydrofuran synthesis involve cyclization reactions of unsaturated alcohols or ethers that generate a carbon–heteroatom bond concomitant with the formation of the tetrahydrofuran C2–O bond. However, analogous reactions that generate both a carbon–oxygen bond and a carbon–carbon bond are much less common. Semmelhack has developed one strategy to effect this transformation that involves Pd-catalyzed Wacker-type carbonylation reactions of unsaturated alcohols.[143] For example, treatment of **228a** with a catalytic amount of $PdCl_2$ in the presence of excess $CuCl_2$ under a CO atmosphere in methanol affords a 9:1 mixture of **229a** and **230a** in 90% yield (Eq. 71).[143b] As shown below, these reactions lead to ring closure and installation of ester functionality at the C1′-position in one step via activation of the alkene by Pd(II) to provide **231** followed by nucleophilic attack of the tethered alcohol to generate **232**. This alkylpalladium complex then undergoes CO insertion, and reductive elimination to provide the tetrahydrofuran product.



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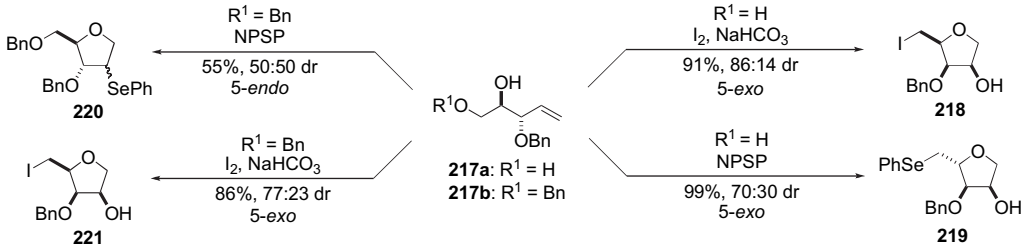
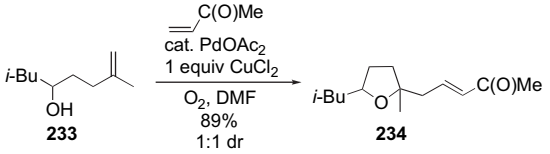


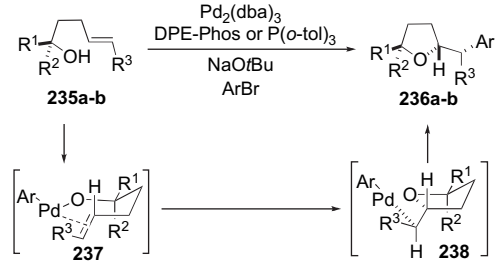
Scheme 5.

Diastereoselectivities and regioselectivities are typically dependent on substituent size and the degree of substitution. For example, the reaction of **228b**, which bears a bulky phenyl substituent, provides a 76% yield of **229b** as a single diastereomer.[143b] Substrates lacking a substituent in the allylic position cyclize with much lower selectivity.[143d] This method has been employed for the synthesis of a broad range of substituted tetrahydrofurans including fused bicyclic products.[144] Similar transformations of alkynyl and allenyl alcohols that afford 2-alkylidene- or 2-vinyltetrahydrofurans have also been described.[145] The capture of intermediates related to **232** with alkenes has also been reported. For example, the Pd-catalyzed reaction of **233** with methyl acrylate affords **234** in 89% yield, albeit as a 1:1 mixture of diastereomers (Eq. 72). However, this transformation is limited to alcohol substrates bearing 1,1-disubstituted alkenes due to the tendency of intermediates such as **232** to undergo competing β-hydride elimination side reactions.[146]



(72)

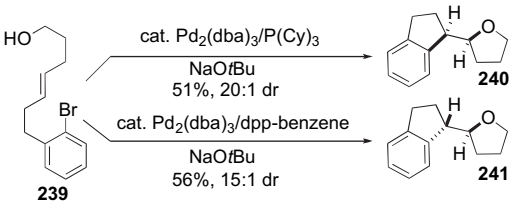
We have recently described palladium-catalyzed carboetherifications of alkenes with aryl bromides that afford 2-benzyltetrahydrofurans.[147] For example, the Pd-catalyzed reaction of **235a** with 1-bromo-4-*tert*-butylbenzene provides **236a** in 68% yield with >20:1 diastereoselectivity (Eq. 73).[147b] Substrates bearing acyclic internal alkenes are transformed with moderate to good diastereoselectivity. As shown below, the Pd-catalyzed reaction of **235b** with 4-bromobiphenyl provided **236b** in 73% yield with 5:1 dr.[147a] In contrast to the Wacker-type carbonylation reactions described above, these transformations proceed via very rare mechanistic pathways involving *syn*-insertion of an alkene into the Pd–O bond of intermediate **237**, which provides **238**.[147c] This intermediate undergoes C–C bond-forming reductive elimination to provide the tetrahydrofuran products.



(73)

Substrate	R^1	R^2	R^3	Ar	Yield	dr
235a	CH_2OTBS	H	H	4-(*t*Bu)C_6H_4	68%	>20:1
235b	Me	Me	Me	4-(Ph)C_6H_4	73%	5:1

The construction of tetrahydrofurans bearing attached carbocyclic rings via intramolecular versions of this transformation has also been described.[148] Interestingly, either product diastereomer can be selectively accessed from the same starting material with the appropriate choice of phosphine ligand. For example, treatment of **239** with catalytic Pd/PCy_3 provided **240** in 51% yield and >20:1 dr (Eq. 74), whereas use of catalytic Pd/dpp-benzene generated **241** in 56% yield and 15:1 dr (Eq. 75). The reversed diastereoselectivity is believed to be due to a change in reaction mechanism that is induced by variation of the catalyst structure. Palladium-catalyzed carboetherification reactions of allenes and alkynes with aryl bromides that afford 2-vinyltetrahydrofurans have also been reported.[145a,149]



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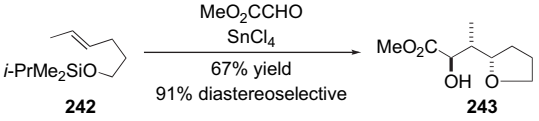
(75)

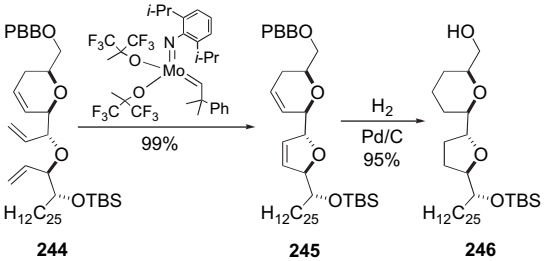
A Prins-cyclization strategy for carboetherification has been developed by Mikami that generates up to three stereocenters in a single step.[150] As shown below, treatment of bishomoallylic silyl ether **242** with methyl glyoxalate and $SnCl_4$ afforded tetrahydrofuran **243** in 67% yield with >91% stereoselectivity (Eq. 76). This method is currently limited to activated aldehyde substrates.



(76)

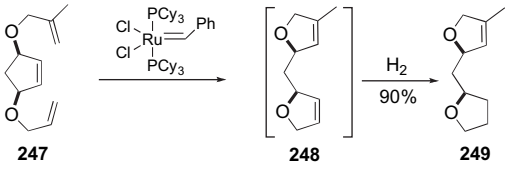
12. Olefin metathesis

In recent years olefin metathesis has become one of the most broadly employed reactions in organic synthesis.[151] This powerful transformation has provided a new strategic disconnection that allows for the construction of carbocycles and heterocycles through formation of bonds that would be difficult to construct with other methods. Not surprisingly, this technology has been applied to the stereoselective synthesis of tetrahydrofurans via two-pot procedures in which dihydrofurans are prepared via alkene metathesis and then converted to tetrahydrofurans via hydrogenation.[151] For example, in Jacobsen's synthesis of muconin the diallyl ether derivative **244** was treated with the Schrock metathesis catalyst to afford **245**, which was then hydrogenated to afford **246** (Eq. 77).[152] Other recent examples of this approach to tetrahydrofuran-containing natural products include Evans' synthesis of guar acid,[153] and Crimmins synthesis of mucocin.[154]



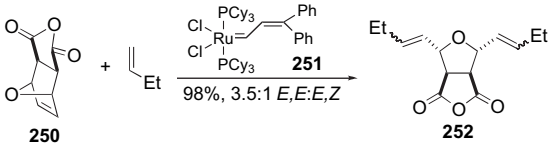
(77)

In recent studies Grubbs has demonstrated that ring closing olefin metathesis can be coupled with catalytic hydrogenation to afford tetrahydrofuran products in a one-pot process.[155] As shown below, triene **247** was treated with Grubbs' first-generation metathesis catalyst ($Cl_2(PCy_3)_2$-RuCHPh) to effect a ring-opening/ring-closing metathesis cascade that generated intermediate bis(dihydrofuran) **248**. Once complete conversion of **247** to **248** was achieved, the reaction vessel was charged with an atmosphere of H_2 to effect the reduction of the less sterically hindered double bond and provide **249** (Eq. 78). Under these conditions the olefin metathesis catalyst is converted to $RuHCl(H_2)(PCy_3)_2$, which catalyzes the hydrogenation step.



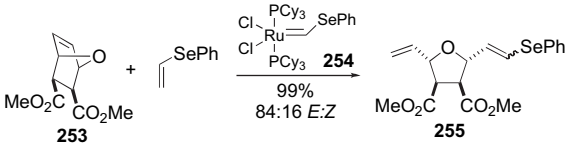
(78)

One popular alkene metathesis strategy for the synthesis of tetrahydrofurans developed by Blechert involves ring-opening of a strained alkene, such as a 7-oxanorbornene, followed by intermolecular cross metathesis with a second alkene.[156] This process is commonly referred to as ring-opening cross metathesis (ROCM).[157,158] In a representative example, 7-oxanorbornene **250** was treated with ruthenium carbene catalyst **251** in the presence of propene.[156a] Opening of the strained ring affords an intermediate carbene that undergoes cross metathesis with propene to afford bicyclic product **252** in 98% yield as a 3.5:1 mixture of olefin stereoisomers (Eq. 79). Competing ring-opening metathesis polymerization (ROMP) is minimized by carrying out the reaction under high dilution conditions. Although most of these transformations lead to incorporation of 2 equiv of the alkene coupling partner, Blechert has reported that the Ru-catalyzed reaction of a sterically bulky 7-oxanorbornene with a slight excess of the terminal alkene component afforded a tetrahydrofuran product that incorporates only one unit of the terminal alkene substrate.[156b]



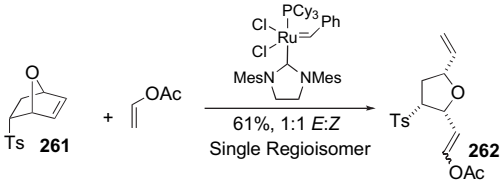
(79)

Ozawa has also noted that highly selective ROCM of norbornene derivatives can be effected using phenyl vinyl selenide as the acyclic olefin in the presence of selenoruthenium carbene **254**.[159] High yields were observed for the Ozawa process although *E*/*Z* isomer ratios were modest (55:45 to 84:16). For example, treatment of **253** with phenyl vinyl selenide in the presence of catalyst **254** provided **255** in near quantitative yield as an 84:16 mixture of olefin stereoisomers (Eq. 80).



(80)

Arjona and Plumet have demonstrated that ROCM of 2-substituted 7-oxanorbornenes provide substituted tetrahydrofuran products with good levels of regioselectivity when substrates bearing a bulky C2-*endo*-substituent are used.[160] As shown below (Scheme 6), treatment of **256** with allyl acetate in the presence of Grubbs' first-generation catalyst afforded an 81:19 ratio of **258**:**260** in 75% yield. The regioselectivity in this transformation is believed to arise from steric effects that favor formation of metallacycle **257** over **259**. In contrast, the analogous 2-hydroxy or 2-oxo substrates provided 1:1 mixtures of regioisomers. Rainer has also noted that regioselective ROCM reactions of 2-tosyl-7-oxanorbornenes proceed with high levels of regioselectivity provided the *endo*-tosyl isomer is used.[161] As shown below, *endo*-tosyl norbornene **261** was converted to **262** in 61% yield as a single regioisomer (Eq. 81), whereas *exo*-tosyl norbornene **263** was transformed to tetrahydrofuran **264** in 80% yield with 9:1 regioselectivity (Eq. 82).



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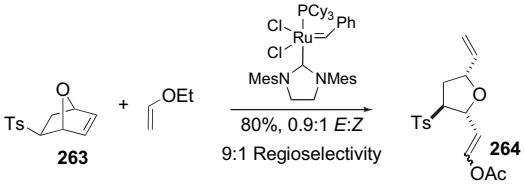

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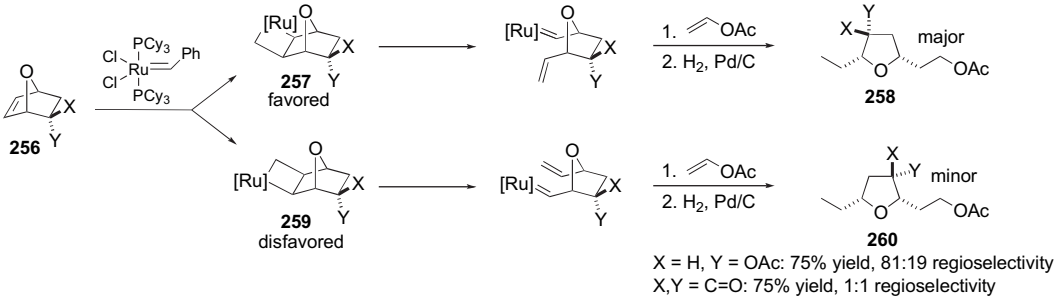
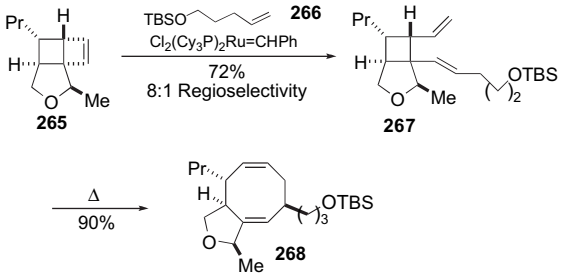


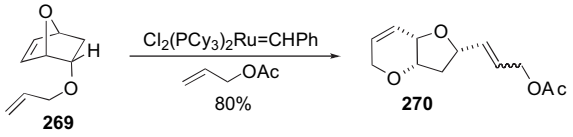
Scheme 6.

Snapper has demonstrated that ROCM reactions of highly strained tetrahydrofuranyl cyclobutenes provide 1,5-dienes that undergo [3,3]-sigmatropic rearrangement to give medium-ring products.[162] As shown below, treatment of **265** with alkene **266** in the presence of the Grubbs catalyst provides **267**, which is converted to **268** in 90% yield upon thermolysis (Eq. 83). The cyclobutene precursors are prepared via intramolecular [2+2] cycloaddition reactions of iron–cyclobutadiene complexes.



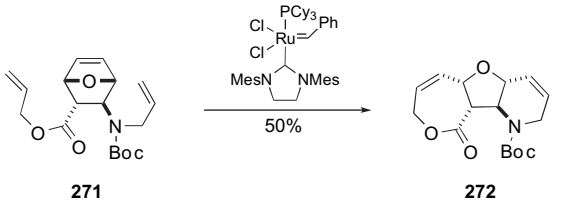
(83)

ROCM has been combined with other metathesis processes to provide facile access into more complex molecular architectures.[163] For example, the Ru-catalyzed reaction of **269** with allyl acetate provides bicyclic product **270**, which arises from a tandem ROCM/ring closing metathesis process (Eq. 84).



(84)

Ring-opening/ring-closing metathesis reactions have also been applied to the synthesis of complex tetrahydrofuran structures.[164] For example, Winkler has demonstrated the conversion of **271** to **272** in the presence of the second-generation Grubbs metathesis catalyst (Eq. 85).[164a]

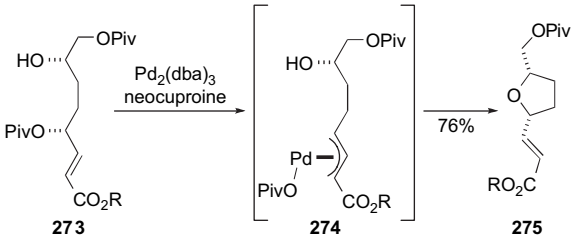


(85)

13. Ring-closure via allyl transition metal intermediates

13.1. Cyclizations that form C–O bonds

A number of stereoselective tetrahydrofuran syntheses employ a strategy that involves nucleophilic capture of intermediate allyl transition metal complexes. In general these reactions are highly diastereoselective, and enantioselective variants of these transformations have been achieved through the use of chiral transition metal catalysts.[165] In a representative example, Rein has described the construction of tetrahydrofuran **275** in 76% yield as a single diastereomer via the Pd-catalyzed intramolecular allylic alkylation of **273**, which proceeds through intermediate allylpalladium complex **274** (Eq. 86).[166] In contrast to S_N2 allylation reactions, the Pd-catalyzed allylations occur with overall retention of stereochemistry, as both the generation and trapping of the allylpalladium complex proceed with inversion of configuration. In some cases use of stannylethers in place of alcohol nucleophiles leads to superior results in these reactions, as the stannylethers are more nucleophilic toward the intermediate allylpalladium species than alcohols, and free alcohols are also prone to competing transesterification.[167] For example, treatment of **276** with Me_3SnCl and a Pd-catalyst provides **277**, which results from nucleophilic attack at the more substituted position, in 77% yield as an 8:1 mixture of diastereomers (Eq. 87).[168] Low yields (40–50%) were obtained under conditions in which significant amounts of the free alcohol were present in solution.



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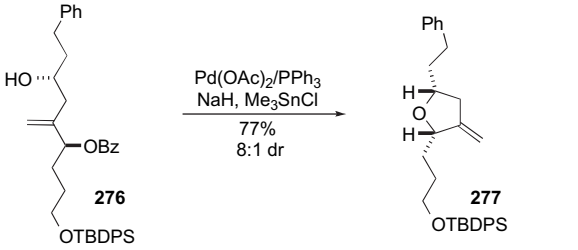
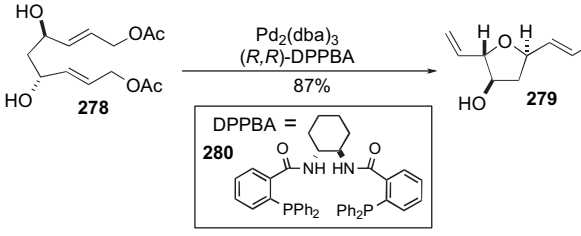


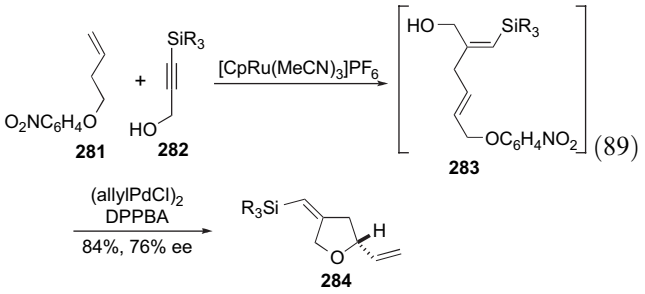
(87)

Burke has employed a desymmetrization strategy using Pd-catalyzed allylation reactions for the conversions of *meso*- or C_2-symmetric diols to highly substituted tetrahydrofuran products.[169] For example, treatment of diol **278** with a catalytic amount of $Pd_2(dba)_3$ and the chiral Trost ligand DPPBA (**280**) generated trisubstituted tetrahydrofuran **279**, a precursor to the F-ring of halichondrin B, in 87% yield as a single diastereomer (Eq. 88).[169a] This strategy has also been employed for the construction of members of the annonaceous acetogenin family of natural products.[169b]



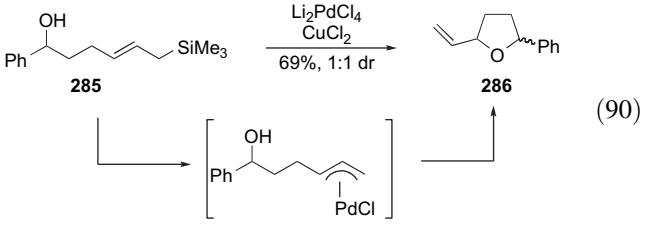
(88)

Trost has recently described an asymmetric synthesis of tetrahydrofuran **284** from alcohol **282** and alkene **281** that involves a one-pot sequence of two metal-catalyzed reactions.[170] As shown below, the Ru-catalyzed ene–yne coupling of **281** and **282** generates intermediate **283**, which is then converted to tetrahydrofuran **284** in 84% overall yield and 76% ee via an asymmetric allylpalladium cyclization reaction (Eq. 89).[170a]



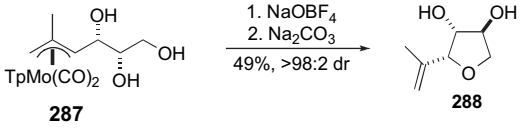
(89)

In most Pd-catalyzed allylation reactions the intermediate allylpalladium complex is generated through oxidative addition of an allylic acetate or related compound. However, the synthesis of tetrahydrofurans via allylpalladium intermediates that are generated through formal transmetalation reactions has also been achieved. For example, Szabo and co-workers have effected the Pd-catalyzed conversion of hydroxy-substituted allylsilane **285** to tetrahydrofuran **286** in 69% yield, albeit with poor (1:1) diastereoselectivity (Eq. 90).[171] These reactions require the use of stoichiometric amounts of Cu(II) salts, which serve to reoxidize Pd(0) to Pd(II) after the cyclization (formally a reductive elimination process), and provide an alternate strategy to access 2-vinyltetrahydrofurans.



(90)

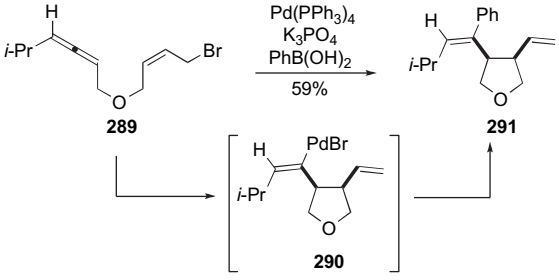
Although most reactions that afford tetrahydrofuran products via allylmetal intermediates employ palladium catalysts, a variety of other metals including Fe[172] and Mo[173] have been used to promote these transformations. For example, diastereomerically pure allylmolybdenum complex **287** has been transformed to tetrahydrofuran **288** with no loss of stereochemical purity (Eq. 91).



(91)

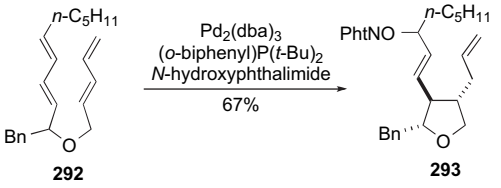
13.2. Cyclizations that form C–C bonds

Most syntheses of tetrahydrofurans that involve allylpalladium intermediates effect C–O bond formation to generate the heterocyclic ring. However, several examples of tetrahydrofuran formation via C–C bond construction have also been described that involve insertion of an unsaturated group into a Pd-allyl complex.[174] For example, treatment of ethereal 1,2,7-triene **289** with phenylboronic acid and a catalytic amount of $Pd(PPh_3)_4$ generated **291** in 59% yield as a single diastereomer (Eq. 92).[175] This reaction proceeds via allylpalladium formation followed by allene insertion to provide vinylpalladium intermediate **290**. This species can undergo transmetalation with the arylboronic acid followed by C–C bond-forming reductive elimination to give the observed product.



(92)

Takacs has developed a method for the conversion of bis-1,3-dienes to tetrahydrofuran products via palladium-catalyzed oxidative cyclization/nucleophilic trapping with excellent stereoselectivity.[176] As shown below, treatment of **292** with a Pd(0) catalyst and *N*-hydroxyphthalimide affords **293** in 67% yield as a single diastereomer (Eq. 93).[176]

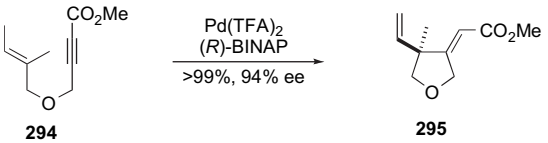


(93)

14. Metal-catalyzed cycloisomerization reactions

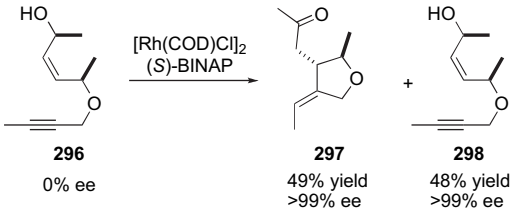
14.1. Enantioselective cycloisomerization reactions

Transition metal-catalyzed cycloisomerization has been widely employed as a convenient method for the formation of substituted tetrahydrofurans, as products are generally obtained in good yields and the allyl propargyl ether substrates are easily prepared. Considerable emphasis has been placed on the development of asymmetric versions of these reactions, and the details of this chemistry have been described in several reviews.[177] In a representative example, the cycloisomerization of **294** to **295** in quantitative yield and 94% ee was achieved by Mikami with a Pd/BINAP catalyst system (Eq. 94).[178] Zhang has reported several Rh-catalyst systems that effect these transformations with high levels of



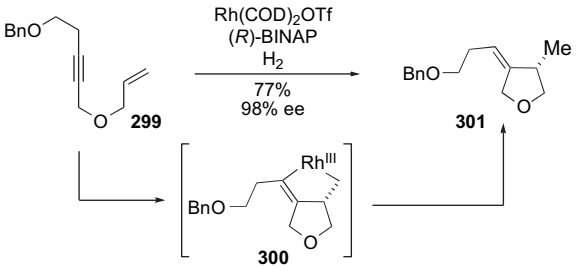
(94)

enantioselectivity (>99% ee),[179] and has also recently described a highly efficient kinetic resolution of racemic 1,6-enynes bearing alkyl substituents at both the allylic positions. As shown below, treatment of (±)-**296** with a catalyst comprised of $[Rh(COD)Cl]_2$/BINAP provided a 49% isolated yield of tetrahydrofuran **297** in >99% ee along with a 48% isolated yield of enyne **298** in >99% ee (Eq. 95).[180]



(95)

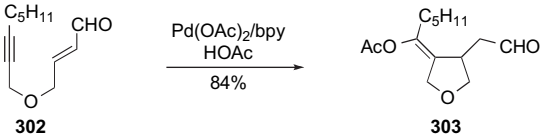
Krische has recently reported a simple, enantioselective reductive cyclization of 1,6-enynes that employs molecular hydrogen as the reducing agent. For example, treatment of **299** with a chiral rhodium catalyst under an atmosphere of hydrogen afforded **301** in 77% yield and 98% ee.[181] Mechanistic studies suggest that these reactions proceed via initial oxidative cyclization to generate intermediate **300**, which then undergoes hydrogenolysis to afford the observed product (Eq. 96).



(96)

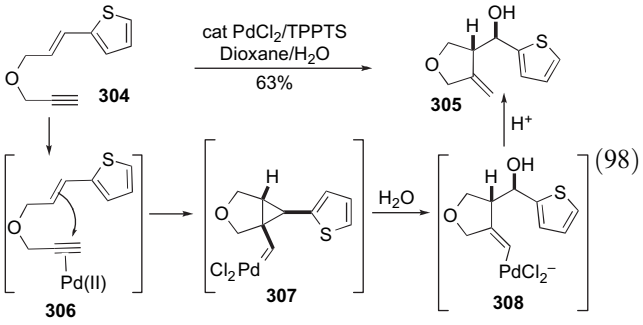
14.2. Cycloisomerization with concomitant generation of a C–O bond

As described above, carbon–carbon bond-forming cycloisomerization reactions have been thoroughly explored and documented in the literature.[177] However, related processes that generate a carbon–heteroatom bond during the cycloisomerization are relatively rare. In recent studies Lu has developed a cycloisomerization-type reaction of 1,6-enynes that effects acetoxylation of the alkyne to generate heterocycles bearing enol acetate functionality. For example, treatment of **302** with $Pd(OAc)_2$ and 2,2′-bipyridine (bpy) affords **303** in 84% yield as a single alkene stereoisomer (Eq. 97).[182]



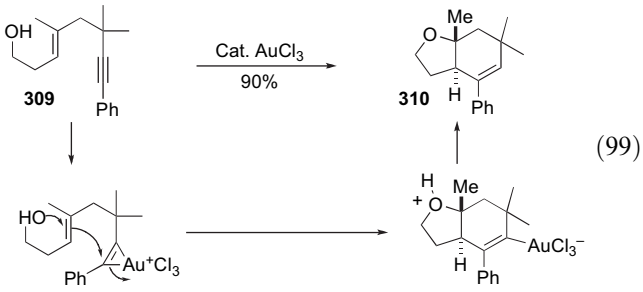
(97)

Genet has developed a cycloisomerization-type reaction of allyl propargyl ethers that leads to the incorporation of a hydroxyl group.[183] As shown below, the Pd-catalyzed cyclization of **304** under biphasic conditions generates tetrahydrofuran product **305**, which results from formal *syn*-carbohydroxylation, in 63% yield as a single diastereomer (Eq. 98).[183b] Mechanistic studies suggest that this transformation proceeds via alkyne complexation to give **306**, followed by alkene cyclization to afford a cyclopropyl palladium carbene (**307**). This intermediate then undergoes ring-opening with water to afford **308**, followed by protonolysis to generate the observed product.[184] An enantioselective version of this reaction that proceeds in up to 85% ee has also been described.[185]



(98)

Electrophilic gold catalysts have been employed in reactions of alcohol tethered 1,5-enynes that generate spirocyclic or fused bicyclic tetrahydrofuran products via cycloisomerization with intramolecular C–O bond formation.[186] For example, treatment of **309** with a catalytic amount of $AuCl_3$ provides bicyclic tetrahydrofuran **310** in 90% yield as a single diastereomer (Eq. 99). The authors suggest this transformation likely occurs via alkyne activation followed by concerted cyclization with subsequent proton transfer to afford the product.



(99)

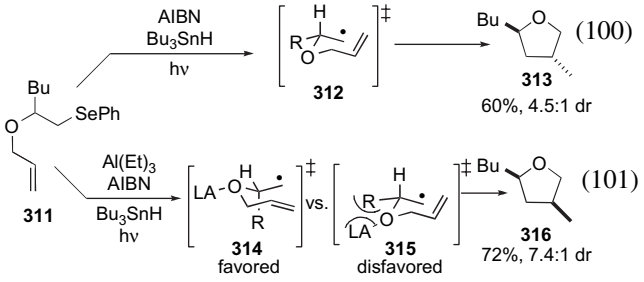
15. Radical C–C bond formation

Numerous methods for the generation of tetrahydrofurans involve ring-closure via radical-mediated C–C bond formation. These methods have been reviewed previously,[187] although this section will provide a brief overview of recent developments in this area.

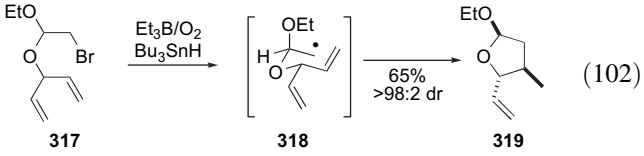
15.1. Cyclizations that form one bond

The stereochemical outcome of many tetrahydrofuran-forming radical cyclizations is often highly dependent on reaction

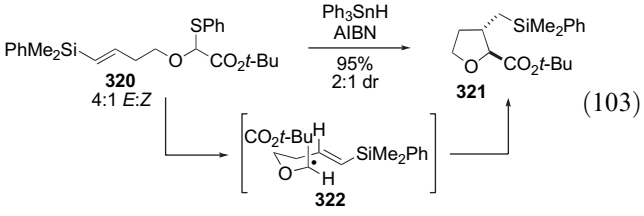
conditions. For example, Lewis-acid additives have a profound effect on the diastereoselectivity of these transformations.[188] As shown below, treatment of **311** with AIBN/Bu_3SnH afforded 2,4-*trans*-disubstituted tetrahydrofuran **313** in 60% yield with 4.5:1 dr (Eq. 100).[188b] The stereochemistry of the major product can be rationalized with the Beckwith transition state model, which suggests that the radical cyclization step proceeds via a chair-like transition state (**312**).[189] However, use of an $AlEt_3$ additive led to the generation of the 2,4-*cis*-disubstituted product **316** in 74% yield and 7.4:1 dr (Eq. 101). This effect is believed to derive from an unfavorable steric interaction between the Lewis acid and the adjacent pseudoequatorial R group in transition state **315** that can be relieved by relegating the substituent to an axial position (transition state **314**).



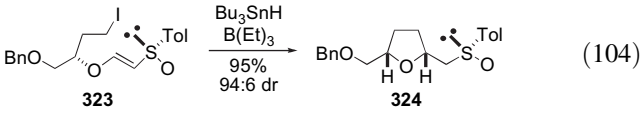
Radical cyclizations of haloacetal substrates are an efficient means of preparing 2-alkoxytetrahydrofurans with high diastereoselectivity.[190] For example, treatment of **317** with Et_3B/O_2 and Bu_3SnH provides tetrahydrofuran **319** in 65% yield with >98:2 dr (Eq. 102).[190c] These reactions are believed to proceed through a chair-like transition state in which the alkoxy substituent is placed in a pseudoaxial orientation to maximize anomeric stabilization (**318**).[190a] Analogous cyclizations involving propargyl ether substrates have also been described.[191]

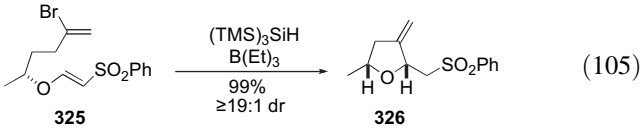


Burke has developed a method for the formation of 2,3-*trans*-disubstituted tetrahydrofurans via radical cyclizations of α-thioesters bearing tethered vinylsilane groups.[192] For example, treatment of **320** with AIBN and Ph_3SnH afforded **321** in 95% yield and 2:1 dr (Eq. 103). This reaction is believed to proceed via transition state **322**, which avoids eclipsing interactions between the *tert*-butyl ester group and the vinylsilane moiety.

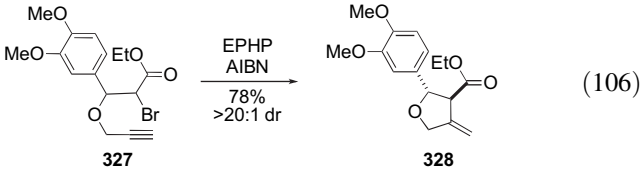


Radical cyclization reactions of enantiomerically pure β-alkoxyvinyl sulfoxides provide 2,5-*cis*-disubstituted tetrahydrofuran products in high yield and diastereoselectivity regardless of the substrate olefin geometry.[193] As shown below, treatment of iodide **323** with Bu_3SnH and Et_3B generates **324** in 95% yield with 94:6 dr (Eq. 104).[193a] A related cyclization of vinyl sulfones has been employed by Evans for the construction of 2,5-*cis*-disubstituted tetrahydrofurans. For example, **325** was converted to **326** in excellent yield and diastereoselectivity (Eq. 105).[194]

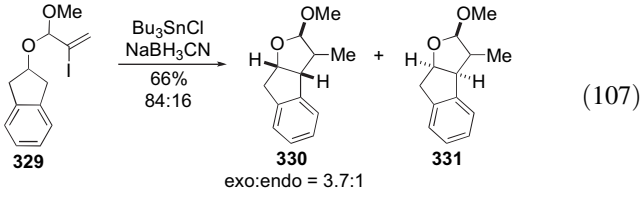




Radical-mediated cyclizations of β-bromoalkyl propargyl ether substrates have also been employed for the construction of tetrahydrofurans.[195] In contrast to the examples described above, these transformations lead to generation of a stereocenter at the radical-bearing carbon atom. For example, the conversion of **327** to **328** in the presence of AIBN and EPHP (1-ethylpiperidine hypophosphite) was achieved in 78% yield with >20:1 dr (Eq. 106).[195a] These conditions avoid the use of toxic tin hydride reagents and simplify product purification.

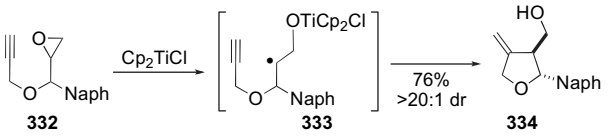


Radical-mediated hydrogen atom abstraction/cyclization processes have also been employed for the construction of tetrahydrofurans.[196] For example, treatment of vinyl iodide **329** with a catalytic amount of Bu_3SnCl and stoichiometric $NaBH_3CN$ afforded an 86:14 mixture of **330**:**331** (Eq. 107). Although mixtures of diastereomers are obtained, this method appears to have potential utility as the substrates for these transformations are simple to prepare.



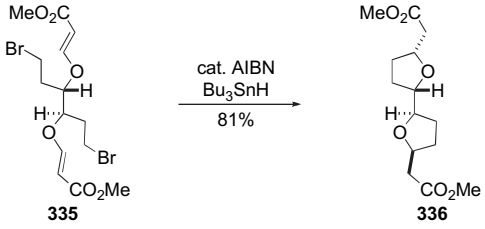
One electron reductions of epoxides mediated by Ti(III) have been used as an entry to carbon- centered radicals that can undergo cyclization to provide tetrahydrofuran

products.[197,198] As shown below, treatment of **332** with titanocene(III) chloride (generated in situ from commercially available titanocene(IV) chloride) provides **334** with >20:1 dr via intermediate radical **333** (Eq. 108).[198a]



(108)

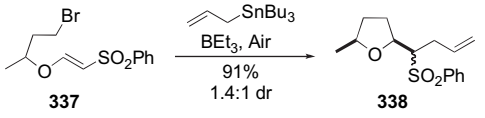
Radical-mediated cyclizations have also been employed for the stereoselective construction of bis(tetrahydrofurans) from acyclic precursors. For example, treatment of **335** with AIBN/Bu_3SnH generates **336** in 81% yield as a single diastereomer (Eq. 109).[199]



(109)

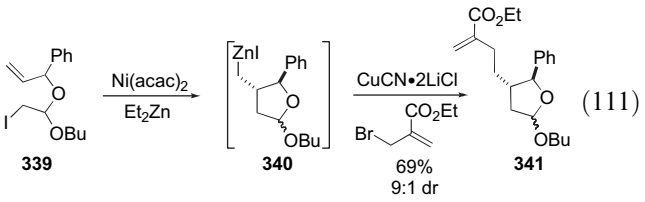
15.2. Cyclizations that form two bonds

Many radical cyclization reactions are terminated via capture of the final radical intermediate with a hydrogen atom that is donated by Bu_3SnH or a related reagent. However, use of other trapping agents allows for the formation of two bonds in a single process and facilitates the synthesis of more elaborate structures.[187] For example, Evans has reported that treatment of *E*-vinyl sulfone **337** with allyltributyltin, Et_3B, and air affords tetrahydrofuran product **338** in 91% yield as a 1.4:1 mixture of diastereomers (Eq. 110).[200] Excellent stereocontrol is observed for the formation of the 2,5-*cis*-disubstituted tetrahydrofuran, although modest stereoselectivity is obtained in the allylation step.



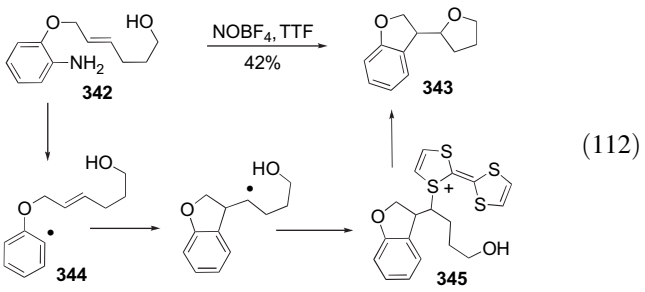
(110)

Knochel has developed a tandem radical cyclization–alkylation reaction that employs radical/polar crossover pathways for functionalization after the initial radical cyclization.[201] As shown below, treatment of haloallyl ether **339** with catalytic $Ni(acac)_2$ in the presence of Et_2Zn effects cyclization and generation of an alkylzinc reagent. The resulting intermediate (**340**) is converted to an organocuprate that is susceptible to electrophilic capture by an allylic bromide to provide **341** in 69% yield as a 9:1 mixture of diastereomers that are epimeric at C2 (Eq. 111).[201a] The observed product stereochemistry is in accordance with the Beckwith transition state model.[189]



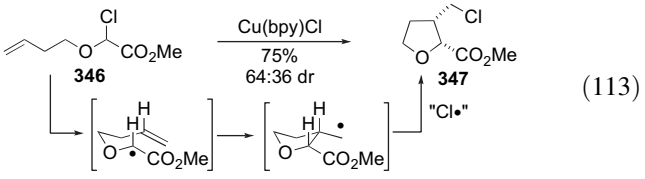
(111)

Another crossover process has been developed by Murphy and co-workers for the synthesis of bis-tetrahydrofuran or spirocyclic tetrahydrofuran products with C–O bond formation occurring after radical cyclization.[202] For example, treatment of aniline derivative **342** with $NOBF_4$ leads to the formation of radical **344** through an intermediate diazo derivative. 5-*exo*-Cyclization followed by one electron oxidation and trapping with tetrathiafulvalene (TTF) affords alkylsulfonium salt **345**, which undergoes intramolecular S_N1 substitution with the pendant alcohol to generate the tetrahydrofuran product **343** in 42% yield as a single diastereomer; the relative stereochemistry was not determined (Eq. 112).



(112)

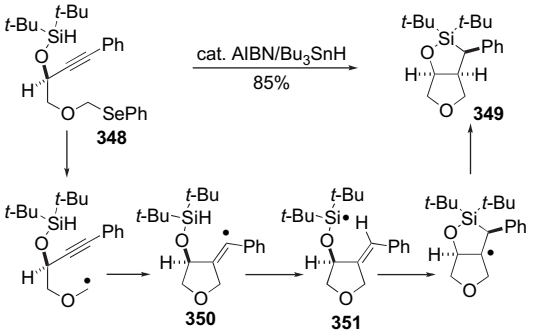
The installation of halogen atoms after cyclization has been effected using atom-transfer radical cyclizations.[187,203] For example, Hiemstra and Speckamp have reported an atom-transfer radical cyclization reaction of α-chloro esters that affords 2,3-disubstituted tetrahydrofurans containing a C3-chloroalkyl substituent.[204] As shown below, **346** was converted to **347** through the use of a copper-bipyridine reagent (Eq. 113). Chemical yields for these reactions are generally good, although highest diastereoselectivities are observed in reactions of substrates bearing internal cyclic olefins. Speckamp has also described a similar transformation involving xanthate group transfer.[205]



(113)

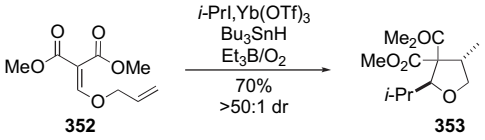
An interesting synthesis of fused bicyclic tetrahydrofuran **349** from ether **348** has been achieved using tandem a radical cyclization reaction that forms a carbon–carbon and a carbon–silicon bond (Eq. 114).[206] As shown below, homolysis of the C–Se bond in **348** with catalytic AIBN/$HSnBu_3$ followed by 5-*exo-dig* cyclization affords vinyl radical

350. An intramolecular hydrogen atom transfer generates silicon radical **351**, which undergoes 5-*endo*-*trig* cyclization and reduction to afford the fused bicyclic product **349** in 85% yield as a single diastereomer.



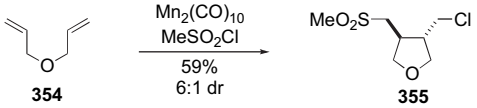
(114)

Most radical cyclization reactions are effected using substrates bearing functional groups such as halides, sulfides, or selenides that are employed as radical precursors. However, several other strategies initiate radical formation via addition to or oxidation of a double bond.[207] For example, Sibi has developed tandem radical addition–cyclization reactions for the stereoselective synthesis of 2,4-*trans*-disubstituted tetrahydrofurans from alkyl halides and alkylidene malonates that effect the formation of two C–C bonds.[208] As shown below, treatment of **352** with isopropyl iodide in the presence of Bu_3SnH, a radical initiator (Et_3B/O_2), and a Lewis acid [$Yb(OTf)_3$] affords tetrahydrofuran **353** in 70% yield with >50:1 dr (Eq. 115). This transformation is believed to proceed through chemoselective conjugate addition of the isopropyl radical to the alkylidene malonate followed by 5-*exo*-cyclization and hydrogen atom abstraction to afford the tetrahydrofuran product. Formation of the 2,4-*trans*-disubstituted tetrahydrofuran can be rationalized by applying the Beckwith transition state model as described above; the stereoselectivities of these reactions range from 1 to 50:1 and are dependent on alkene substitution.



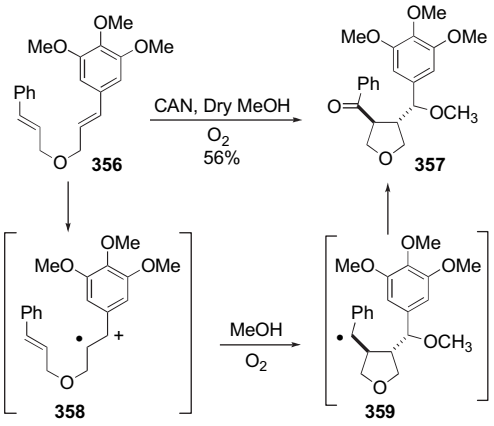
(115)

The construction of substituted tetrahydrofurans from diallyl ether derivatives has been accomplished via addition of a radical species to a C–C double bond followed by 5-*exo*-cyclization and trapping of the resulting intermediates. For example, treatment of diallyl ether (**354**) with $Mn_2(CO)_{10}$ and $MeSO_2Cl$ under photolytic conditions provides tetrahydrofuran **355** in 59% yield as a 6:1 mixture of diastereomers (Eq. 116).[209] Similar transformations have been effected using alternate initiators and traps.[210]



(116)

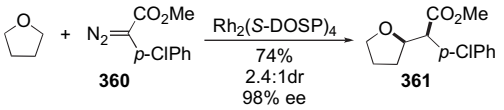
Oxidative cyclization has also been employed as a means of generating heterocyclic compounds from diallyl ethers.[211] For example, Nair has reported that treatment of **356** with CAN under an oxygen atmosphere affords 3,4-*trans*-disubstituted tetrahydrofuran **357** as a single diastereomer (Eq. 117).[210a] This reaction presumably proceeds via generation of a radical cation (**358**), which undergoes 5-*exo*-cyclization to afford **359**. Further oxidation of **359** leads to the observed product.



(117)

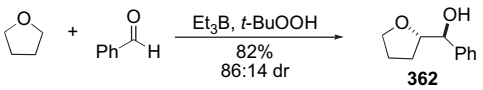
16. Miscellaneous strategies

Several approaches to the stereoselective construction of substituted tetrahydrofurans involve functionalization of tetrahydrofuran through the use of transformations that form a C–C bond and generate one or more stereocenters with control of absolute or relative stereochemistry. One such strategy involves the activation/functionalization of a C–H bond adjacent to the tetrahydrofuran oxygen atom using either radical[212] or carbenoid[213] methods. For example, Davies has developed an asymmetric Rh-catalyzed C–H bond functionalization reaction that generates a C–C bond and two stereocenters in one step. As shown below, treatment of tetrahydrofuran with diazoester **360** in the presence of a chiral rhodium catalyst provides **361** in 74% yield with 2.4:1 dr and 98% ee (Eq. 118).[214]



(118)

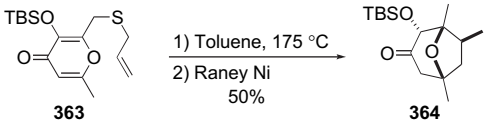
Generation of tetrahydrofuranyl radicals followed by addition to carbonyl compounds has also been employed for the stereoselective construction of tetrahydrofurans.[215] For example, treatment of tetrahydrofuran with Et_3B/*t*-BuOOH in the presence of benzaldehyde affords **362** in 82% yield with 86:14 dr (Eq. 119).[215a] The stereoselective trapping of tetrahydrofuranyl radicals with imines or activated alkenes has also been described.[216,217]



(119)

An interesting route for the stereoselective construction of highly substituted tetrahydrofurans that employs

pyrone–alkene cycloaddition reactions to effect [5+2] annulation has recently been described. For example, **363** was converted to **364** in a two-step sequence involving thermal cycloaddition followed by desulfurization with Raney nickel (Eq. 120).[218] The bicyclic products can be converted to highly substituted monocyclic tetrahydrofurans with further manipulation.



363 **364** (120)

17. Conclusion

Despite the myriad of transformations that have been employed in the construction of the tetrahydrofuran moiety, many possibilities remain for the development of new or improved reactions that provide stereoselective access to these important molecules. Methods that facilitate construction of two or more bonds and stereocenters in a single step will likely play an important role in future developments in this area, as will processes that lead to improved diastereoselectivity, enantioselectivity, or chemoselectivity.

Acknowledgements

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Biographical sketch

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Michael B. Hay was born in Rockwood, PA, and received a B.S. in chemistry from The Pennsylvania State University in 2002. During that time he performed undergraduate research under the guidance of Professor Blake R. Peterson, and participated in the cooperative education program at McNeil Consumer Healthcare and Johnson & Johnson Pharmaceutical Research and Development. He began his graduate studies at University of Michigan in August 2002, and is currently working with Professor John P. Wolfe. His research has focused on the synthetic and mechanistic aspects of palladium-catalyzed olefin carboetherification.